Physiological System Modelling and Clinical Simulation for Diagnosis

Vol. 1 Part I

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Declaration of Originality

This is to certify that the work presented in this thesis is original except where due reference is made in the text to all other material used. To the best of my knowledge, none of the work presented here has been previously published, presented or submitted for a higher degree.

This thesis less exclusions is less than 100 000 words in length.

Loh Kah Meng        April 2006
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Dedication

Dedicated to:
My wife: Chan Han Leng and
Supervisor Prof Dhanjoo Ghista
### Table of Contents

*(Volume 1 Thesis body, Volume 2 Appendices)*

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Declaration of Originality</td>
<td>ii</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>iii</td>
</tr>
<tr>
<td>Dedication</td>
<td>iv</td>
</tr>
<tr>
<td>Table of Contents</td>
<td>v</td>
</tr>
<tr>
<td>List of Figures</td>
<td>xi</td>
</tr>
<tr>
<td>List of Tables</td>
<td>xvii</td>
</tr>
<tr>
<td>Thesis Overview</td>
<td>xviii</td>
</tr>
<tr>
<td>Chapter 0 Introduction</td>
<td>xix</td>
</tr>
<tr>
<td>0.1 Use of NDPIs in Author’s Work</td>
<td>xx</td>
</tr>
<tr>
<td>0.2 Literature Review</td>
<td>xxi</td>
</tr>
<tr>
<td>0.3 Dimensional Analysis</td>
<td>xxii</td>
</tr>
<tr>
<td>0.3.1 Dimensional Homogeneity</td>
<td>xxiv</td>
</tr>
<tr>
<td>0.3.2 Buckingham $\pi$-Theorems</td>
<td>xxv</td>
</tr>
<tr>
<td>0.3.3 Application of Dimensional Analysis</td>
<td>xxvi</td>
</tr>
<tr>
<td>0.4 Non-Dimensional Analysis</td>
<td>xxix</td>
</tr>
<tr>
<td>0.5 Information Calculus</td>
<td>xxxii</td>
</tr>
<tr>
<td>0.5.1 Fundamentals of Information Calculus (Information Theory) [20-22]</td>
<td>xxxii</td>
</tr>
<tr>
<td>0.5.2 Information Calculus to select Relevant Variables if the</td>
<td>xxxii</td>
</tr>
<tr>
<td>variables are Independent</td>
<td>xxxii</td>
</tr>
<tr>
<td>0.5.3 Measure of Self-Importance</td>
<td>xxxiii</td>
</tr>
<tr>
<td>0.5.4 Self-Information, Conditional Information and Mutual Information</td>
<td>xxxiv</td>
</tr>
<tr>
<td>0.6 Information Calculus to select Relevant Variables if the</td>
<td>xxxvii</td>
</tr>
<tr>
<td>variables are not Independent</td>
<td></td>
</tr>
<tr>
<td>0.7 Summary of Author’s work on Non Dimensional Physiological Indices</td>
<td>xli</td>
</tr>
<tr>
<td>References On Non-Dimensional Physiological Indices</td>
<td>xlii</td>
</tr>
</tbody>
</table>

### Chapter 1 Glucose & Insulin Kinetics

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Motivation behind the Project</td>
<td>1</td>
</tr>
<tr>
<td>1.2 Background</td>
<td>1</td>
</tr>
<tr>
<td>1.2.1 Types of Diabetes Mellitus</td>
<td>5</td>
</tr>
<tr>
<td>1.2.2 Acute complications of Diabetes</td>
<td>6</td>
</tr>
<tr>
<td>1.3 Literature Review</td>
<td>12</td>
</tr>
<tr>
<td>1.3.1 Conventional Screening</td>
<td>12</td>
</tr>
<tr>
<td>1.3.2 Physiological Modeling Techniques</td>
<td>15</td>
</tr>
<tr>
<td>1.3.3 Why OGTT ?</td>
<td>16</td>
</tr>
<tr>
<td>1.3.4 OGTT Kinetic Modeling</td>
<td>19</td>
</tr>
<tr>
<td>1.3.5 Reproducibility</td>
<td>35</td>
</tr>
<tr>
<td>1.3.6 Fitting Results</td>
<td>36</td>
</tr>
<tr>
<td>1.3.7 The Oral Glucose Tolerance Testing Protocol Adopted</td>
<td>36</td>
</tr>
<tr>
<td>1.4 Author’s Work of Systems Engineering View of OGTT Blood Glucose &amp; Insulin Responses [10, 30]</td>
<td>42</td>
</tr>
</tbody>
</table>
1.4.1 Differential equation model of the Glucose-Insulin System ................................................................. 46
1.4.2 Solutions to the Governing Differential Equations and for Insulin Response to Glucose Bolus Ingestion ........................................................................................................ 56
1.5 Clinical Application of Model ................................................................................................................ 59
  1.5.1 Under-damped Category for Patients Clinically Designated to be Normal ........................................ 59
  1.5.2 Over-damped Category of Patients Clinically Designated as Diabetic .............................................. 62
1.6 Non-Dimensional Physiological Index (NDPI) ......................................................................................... 68
1.7 CONCLUSIONS ....................................................................................................................................... 75

References On Glucose & Insulin Kinetics .................................................................................................. 76

Chapter 2 Automated Insulin Infusion Regulation System for Lowering Blood Glucose After a Meal .......................................................................................................................... 83
  2.1 Motivation behind the Project ................................................................................................................ 83
  2.2 Functions of the Pancreas ..................................................................................................................... 84
    2.2.1 Glucose production ....................................................................................................................... 84
    2.2.2 Glucose Uptake ........................................................................................................................... 85
  2.3 Literature Review .................................................................................................................................. 86
    2.3.1 Glucose Measurement ................................................................................................................. 86
  2.4 Overview of Current Treatment and Monitoring Methods ................................................................ 88
    2.4.1 Intravenous Insulin Delivery Algorithms BiostatorTM and Nonlinear PID .................................... 99
    2.4.2 Advanced Control Algorithms .................................................................................................. 101
    2.4.3 Optimal Control Theory ............................................................................................................ 102
    2.4.4 Model-Based Predictive Control Under Patient Uncertainty ..................................................... 104
    2.4.5 Uncertainty Characterization .................................................................................................... 105
    2.4.6 Derivative Control ..................................................................................................................... 107
    2.4.7 Multi-Meal Tests ....................................................................................................................... 111
  2.5 Non-Invasive Insulin Deliver System .................................................................................................. 115
    2.5.1 Insulin Delivery by Ultrasound ................................................................................................. 116
    2.5.2 Insulin Delivery by Pulsation .................................................................................................... 117
    2.5.3 Glucose Responsive Insulin Release System and Techniques ..................................................... 120
    2.5.4 Inhale Insulin .............................................................................................................................. 125
  2.6 System Block Diagram ......................................................................................................................... 126
    2.6.1 Non-Invasive Blood Glucose Sensor ........................................................................................ 127
    2.6.2 Non-Invasive Insulin Sensor ..................................................................................................... 127
  2.7 Control System ....................................................................................................................................... 128
    2.7.1 Time-Domain Interpretation of Proportional-Derivative (PD) Control ......................................... 128
    2.7.2 Proportional-Integral (PI) Control ............................................................................................. 135
    2.7.3 Proportional-Integral-Derivative (PID) Control ........................................................................ 138
  2.8 Author’s work Type Controller selection ............................................................................................. 142
    2.8.1 Comparison of PD, PI and PID controllers ............................................................................... 142
    2.8.2 The Choice Controller: PD ........................................................................................................ 148
  2.9 Derivation of Insulin Response In Blood Pool ..................................................................................... 149
    2.9.1 Insulin Impulse .......................................................................................................................... 149
    2.9.2 Blood glucose Responses after Release of Insulin Pulse .......................................................... 151
Chapter 4 Lung Air Performance Analysis [1-4] .......................................................... 260
4.1 Motivation behind the Project ........................................................................... 260
4.2 Objectives ......................................................................................................... 260
4.3 Respiratory System ............................................................................................ 260
4.3.1 Exchange of Carbon Dioxide and Oxygen ............................................. 262
4.3.2 Blood-Gas Interface .................................................................................. 263
4.3.3 Airways and Air Flow ................................................................................. 267
4.3.4 Blood Vessels and Flow ............................................................................. 271
4.3.5 Ventilation ................................................................................................... 272
4.3.6 Anatomic Dead Space ................................................................................ 274
4.3.7 Diffusion ....................................................................................................... 274
4.3.8 Diffusion and Perfusion Limitations ......................................................... 275
4.3.9 Carbon Dioxide (CO₂) Transfer Along the Pulmonary Capillary ............ 277
4.4 Author’s work Lung Air Composition Analysis (and O₂ consumption and CO₂ production rates) [3-4] .......................................................... 279
4.4.1 Calculation of O₂ Consumption-Rate and CO₂ Production-Rate ......... 280
4.4.2 Dead Space Air Composition ..................................................................... 281
4.4.3 Alveolar Air Composition and Partial Pressures ..................................... 282
4.5 Lung Gas-Exchange Model & Parametric Analysis ........................................ 283
4.5.1 Expressions for O₂ and CO₂ ..................................................................... 283
4.5.2 Alveolar O₂ and CO₂ Partial Pressure Expressions .................................. 289
4.5.3 Arterial and Venous O₂ and CO₂ Partial Pressure Expressions ......... 292
4.5.4 Determining ΔP_{av}^{O₂} and ΔP_{av}^{CO₂} ......................................................... 295
4.5.5 Sequential procedure to compute D_{O₂} and D_{CO₂} ............................. 298
4.6. Case Studies .................................................................................................. 300
4.7 Non-Dimensional Physiological Index .............................................................. 305
4.8 Conclusion ........................................................................................................ 305

Reference on Lung Air Performance Analysis ...................................................... 306

Chapter 5 Modeling of Renal Obstructions ............................................................... 307
5.1 Purpose of Renal Scan ...................................................................................... 307
5.2 Evaluation of Renal Function by Radionuclide Methods ................................ 307
5.2.1 Radionuclide methods used in nephrology ............................................. 307
5.3 Diagnostic methods: In vivo – non-imaging methods .................................... 308
5.3.1 GFR and ERPF measurement ..................................................................... 308
5.3.2 Radionuclide nephrography ..................................................................... 309
5.3.3 Imaging methods ....................................................................................... 309
5.3.4 Static imaging ............................................................................................. 309
5.3.5 Dynamic imaging ....................................................................................... 309
5.4 Patient positioning ............................................................................................ 310
5.5 The renogram curve ........................................................................................ 310
5.6 Clinical applications ........................................................................................ 311
5.6.1 Renal function: ......................................................................................... 311
5.6.2 Scrotal imaging ................................................................. 315
5.7 RENOGRAPHY ................................................................. 315
  5.7.1 QUANTITATION OF RENAL FUNCTION ......................... 318
5.8 SCINTIGRAPHIC PROCEDURE ........................................... 320
  5.8.1 Patient positioning ....................................................... 320
  5.8.2 Data acquisition in standard renography ....................... 322
  5.8.3 Sequential and delayed images .................................... 322
5.9 PROCESSING AND ANALYSIS OF THE STUDY .................... 323
  5.9.1 Relative renal function ............................................... 323
  5.9.2 ROI assignment ......................................................... 324
  5.9.3 Background correction ............................................... 324
  5.9.4 Renal depth correction ............................................... 325
  5.9.5 Excretory function ...................................................... 326
5.10 RENAL CORTICAL SCINTIGRAPHY CLINICAL INDICATIONS ................................................................. 335
5.11 Literature Review on Measurement of Glomerular Filtration Rates (GFRs) ...................................................... 338
  5.11.1 Effective Renal Plasma Flow (ERPF) ............................ 344
  5.11.2 Differential Function ................................................... 349
5.12 Author’s work RENOGRAPHY MODELLING [25-26] ............. 352
  5.12.1 Control volume around the renal pelvis ....................... 355
5.13 CLINICAL DATA & EVALUATION ..................................... 364
  5.13.1 Model Application: ..................................................... 364
5.14 Non-Dimensional Indices for Kidney Obstructions .................. 370
5.15 Conclusions ....................................................................... 371
Reference on Modeling of Renal Obstructions ............................ 372

Chapter 6 Non-dimensional Physiological Indices for Clinical Assessment ................................................................. 380
  6.1 Summary of Author’s work Non Dimensional Physiological
  Indices ................................................................. 381
  6.2 Conclusions ....................................................................... 383
References On Non-Dimensional Physiological Indices ................................. 385
Volume 2 Appendices

Appendix A  Underdamp Responses for Subjects N01-N20
Appendix B  Overdamp Responses for Subjects N01-N20
Appendix C  Critical Damp Responses for Subjects N01-N20
Appendix D  Non-dimensional plots
Appendix E  Tables
Appendix F  Results of the Insulin Infusion System based on PD controller
Appendix G  Renogram Simulations Results
Appendix H  Clinical Renogram
Appendix I  Published Papers and Book Chapters
Appendix J  System and Method for Detecting Pulmonary Diseases
List of Figures

1.1 The organs of the digestive system. The pancreas is the organ responsible for regulating the blood glucose concentration by release of insulin. [Prof Gunther H, Bodyworlds] .................................................................................................................. 4
1.2 Pictures illustrating haemorrhages and exudates. The basic anatomy of human eye ball is shown above [SGH, Endocrine Lab] ................................................................. 8
1.3 Normal retinas versus abnormal retina [SGH, Endocrine Lab] ............................ 9
1.4 Retina after treatment [SGH, Endocrine Lab]. .................................................... 9
1.5 Blood glucose response to oral and intravenous glucose [45]. Each point is the mean value (for 10 patients) above the fasting level during and following a 60-min constant infusion of glucose ......................................................... 16
1.6 Plasma insulin responses to oral and intravenous glucose [45]. Each point is the mean value (for 10 patients) above the fasting level during and following a 60-min constant infusion of glucose ......................................................... 17
1.7 Blood glucose and plasma insulin concentrations in the fasting state and following oral administration of glucose in adult subjects [53]. Criteria employed: Non-diabetic peak <160 mg/dl and 2-hour glucose < 120 mg/dl; frank diabetes peak glucose > 180 mg/dl and 2-hour glucose > 120 mg/dl; impaired glucose tolerance – glucose curves not satisfying either of above criteria ................................................................................................................. 18
1.8 Block-diagram representation of feedback loop involved in glucose tolerance test. Question marks indicate uncertain reactions. Diagram is vastly oversimplified in that there is a different rate of metabolic utilization of glucose for each tissue [46]. ............................................................................................................ 21
1.9 A normal glucose-tolerance curve (example A of Table 2). Points show measured values, whereas solid curve shows computed best fit [46] ........................................ 22
1.10 An abnormal glucose-tolerance curve (example C of Table 2). Note high, slow response [46] .................................................................................................................. 23
1.11 A normal glucose-tolerance curve (example B of Table 2). Note difference between this critically damped curve and the more usual normal curve of Figure 1.9 [46] ......................................................................................... 24
1.12 The three-compartment basal glucose model with the mean population values for masses and exchange constants (n=6). Rate constants are in units/min; mean±SD. [3] ........................................................................................................ 26
1.13 Three proposed insulin-independent models of glucose metabolism. Left panel: proposed structure; middle panel: mathematical representation when parameters are defined as shown on the right panel. Values of k represent fractional turnover rates (min⁻¹); P, hepatic glucose production; V, glucose space, and Iₘₚ and Kₘ, Michaelis-Menten parameters. G(0) is glucose concentration that would obtain immediately after injection assuming no dynamics of mixing in glucose space [4] ........................................................................ 28
1.14 Four proposed insulin-dependent models of glucose metabolism. I(t), time course of plasma insulin supplied to model; I, concentration of insulin in a compartment remote from plasma. B₀, extrapolated hepatic glucose production at 0 glucose concentration [4] ................................................................................... 29
1.15 When glucose bolus is administered to a normal person, a typical response of blood glucose and insulin correlation (normalised) ............................................... 42
1.16 When glucose bolus is administered to a diabetic patient, a typical response of blood glucose and insulin correlation (normalized) ........................................... 43

1.17 Blood Glucose-Insulin Control System (BGIRS). Block diagram of (i) insulin level & rate-of-change of insulin $x(t)$ governs blood-glucose concentration $y(t)$, and (ii) rate-of-change of glucose $y(t)$ is influenced by insulin concentration $x(t)$ & ingested glucose input rate $q(t)$................................. 47

1.18 Effect of substrate and enzyme concentrations on the rate of enzyme-catalyzed reaction. The general form of Michaelis-Menten equation for active transport is: .......................................................................................................................... 52

1.19 LaPlace Transform format of the GI tract and Blood Pool system of governing equation (5), to simulate the monitored OGTT glucose response curve (adapted from 33 & 38).............................................................................................................. 54

1.20 The Glucose-Insulin response of N02 is a good example of a normal response e.g. no-diabetic. This result correlates very well with clinically diagnosis. .............................................................................................................................. 60

1.21 The Glucose-Insulin response of D02 is a good example of a wrong clinical diagnosis. The subject may be subjected to unnecessary medication and procedures which are physiologically and morally depressing. .......... 61

1.22 The Glucose-Insulin response of N01 is another good example of a wrong clinical diagnosis. The subject may not be given the required medical attention and the consequences can be very depressing. .................................................... 63

1.23 The Glucose-Insulin response of D01 is a good example of an overdamp response e.g. diabetic. This result correlates very well with clinically diagnosis. D01 will undergo immediate medical attention................................................. 64

1.24 The Glucose-Insulin response of N03 is a good example of a missed clinical diagnosis or a good example of pre-emptive treatment beneficial. Even though the subject is diagnosed as normal clinically e.g. non-diabetic, the subject in fact is at-risk e.g. preventive medical attention is required to prevent the current health conditions to deteriorate. N03 requires prevent medical measures immediately.................................................................................... 66

1.25 The Glucose-Insulin response of D05 is a good example of a wrong clinical diagnosis. The subject may be subjected to unnecessary medication and procedures which are physiologically and morally depressing. D05 only requires only preventive medical attention to prevent the current health conditions to deteriorate and not diabetic medical procedures which can be health hazardous. ......................................................................................................... 67

1.26 Non-dimensional plot of Tables 1.10-12 Non-dimensional plot of

$$\frac{G_{\text{NDI}}}{I_{\text{NDI}}} = \left(\frac{y_{\text{max}} \times y_{\text{max}} \times T_{\text{d}} \times T_{\text{max}}}{G \times A \times 32 \times 10^6}\right) \cdot \left(\frac{\beta \gamma \delta}{\alpha}\right).$$

...................................................... 73

2.1 Components of the integumentary system .......................................................................................................................... 89

2.2 Shows a typical absorbance spectrum measurement from the forearm of a human subject [33].................................................................................................................. 91

2.3 A closed-loop glucose control system ....................................................................................................................... 99

2.4 Graphical sensitivity analysis ................................................................................................................................. 107
2.5 Glucose input model of OGTT curve used in the simulations by Geoffrey Chase, et al. [80-81] ......................................................................................................................... 109
2.6 Glucose response for an OGTT [81] ........................................................................ 109
2.7 Insulin infusion rate for an OGTT [80-81] ............................................................... 110
2.8 Multi-meal glucose input profile [81] ....................................................................... 111
2.9 Glucose level of a normal human and controlled diabetic individual with 1-min sampling period for each controller type ......................................................... 112
2.10 Multi-meal glucose level for controllers at different sampling periods .......... 113
2.11 Infusion rate for controllers at different sampling periods for the multi-meal test .............................................................................................................................. 113
2.12 The cymbal transducer made of piezoelectric material PZT-4 operated at a frequency of 20kHz ................................................................................................. 116
2.13 The lightweight, low-profile array was constructed using 4 cymbal transducers connected in parallel and encased in URALITE polymer ........................................... 117
2.14 Over a period of 90 minutes, the blood glucose level of the rats decreased from the insulin with ultrasound (US) exposure ( ) using the cymbal array................................. 118
2.15 Profile of the pulsed current simulation used to enhance transdermal penetration of insulin [85] ....................................................................................................... 119
2.16 Release rate of insulin from nanoshell-composite hydrogels in response to cyclic irradiation of 821 nm (1.7 W/cm2) .............................................................. 120
2.17 Schematic [87] representation of the glucose-sensitive release principle of microcapsules with a porous membrane and functional gates ...................................... 122
2.18 Schematic [86] illustration of the preparation process route and the principle of glucose-responsive control of the permeation through the gating membrane .......... 124
2.19 Glucose-responsive diffusional permeation of insulin through the proposed gating membrane with PAAC grafting yield of 1.55% [86] ........................................... 125
2.20 Block diagram of a insulin infusion system without insulin sensor ..................... 126
2.21 Responses of controllers based on patient D18 data ............................................. 126
2.22 Overview of the Insulin Release System .............................................................. 127
2.23 Waveforms of y(t), e(t), and de(t)/dt ...................................................................... 129
2.24 Bode diagram of 1 + k_D/k_P, k_p =1 [78] .............................................................. 132
2.25 Unit-step responses of the attitude control system with and without PD control [78] ......................................................................................................................... 133
2.26 The plot of versus parameter plane for a PD control system with
\[ \xi = \frac{0.2 + 451.46k_p}{\sqrt{k_p}} \] [78] .................................................................................. 134
2.27 Pole-zero configuration of a PI controller [78] ....................................................... 136
2.28 Bode plot of the PI controller \( G_c = k_p \frac{k_i}{s} \) [78] .................................................. 137
2.29 Unit responses of systems with PI and PD controllers [78] .............................. 138
2.30 Unit-step responses of system with PI and PD controllers [78] .......................... 139
2.31 Step responses of a system with PD, PI and PID controllers [78] ..................... 140
2.32 Bode plots of a system with PD and PID controllers [78] ................................. 141
2.33 PD, PI and PID controller responses for subject D01 ...................................... 143
2.34 PD, PI and PID controller responses for subject D04 ...................................... 144
2.35 PD, PI and PID controller responses for subject D09 ..................................... 145
2.36 PD, PI and PID controller responses for subject N01 ...................................... 146
2.37 PD, PI and PID controller responses for subject N17 ...................................... 147
2.38 Response of blood glucose concentration after the insulin impulse infused into the GI ................................................................. 151
2.39 Flow chart of the workings of the insulin infusion system .......... 152
2.40 The final block diagram of the insulin infusion system ........... 153

3.1 The Respiratory System .............................................................. 170
3.2 Lungs with main bronchi, windpipe and larynx ......................... 171
3.3 The eight gas volume components ........................................... 172
3.4 Dynamics of a normal Tidal Volume breadth ............................... 173
3.5 Airflow pattern of the lungs ....................................................... 175
3.6 Body plethysmography method .................................................. 178
3.7 Changes in (a) airways resistance (R_{aw}), and (b) conductance (G_{aw}) with changes in lung volume in a normal individual ................................. 180
3.8 Esophageal-mouth pressure (\Delta P) versus time ....................... 182
3.9 Esophageal-mouth pressure versus volume ............................... 182
3.10 Typical changes in total respiratory resistance at different applied oscillation quencies .......................................................... 185
3.11 Forced oscillation method for measuring input impedance during tidal breathing .............................................................. 186
3.12 Airflow Interruption Apparatus .................................................. 187
3.13 Analysis of P_{mouth} versus time record .................................... 188
3.14 The Resistance to airflow profile along the airways ................. 190
3.15 Resistance against Volume profile ............................................ 191
3.16 Statistic PV curve of respiratory system with maximal pressures generated by respiratory muscles .............................................. 193
3.17 Static PV curves of respiratory system, lungs and chest wall .... 194
3.18 Measurement of lung PV curve and compliance ....................... 196
3.19 Volume-Pressure profile for different lung diseases ................. 198
3.20 Lung Pressure Volume curve .................................................... 199
3.21 Model of an alveolus at the end of an airway .............................. 200
3.22 Dynamics of soap bubbles [9] ................................................... 202
3.23 Regular airway branching model [9] .......................................... 206
3.24 Single component and multi-component models of the lung ... 209
3.25 The flow rates in the total lung model ....................................... 211
3.26 Pressure-Volume curve of a volume control breath (without patient effort) [24] ................................................................. 212
3.27 Multi component model of lung reduced to two components .... 218
3.28 Lung compliance and resistance as functions of breathing frequency for models of a normal lung and of a lung with obstructed airways [W. R. Powell] ................................................................. 220
3.29 Two-compartmental model of the lung ...................................... 223
3.30 The flow rates in the total lung model ...................................... 224
3.31 Alveolar model .......................................................................... 229
3.32 Lung ventilatory model and lung-volume & pleural-pressure data .................................................. 229
3.33 A The pressure curve represented by equation (3) matched against the pressure data (represented by dots). B The volume curve represented by equation (6) .................................................. 237
3.34 Plot of Pressure versus Volume ................................................... 243
3.35 Results of Single Compartmental Model based on differentiate equation formulation, compared with the First Order differential equation model .......... 246
5.8 (A) Six consecutive reoriented sagittal sections and (B) three-dimensional display showing a linear area of absent tracer uptake from the left renal hilum into the parenchyma ................................................................. 335
5.9 (A) Non-reoriented corona slices and (B) reoriented corona tomographic section .......................................................................................................................................................... 336
5.10 (A) Normal planar views. (B) Two consecutive non-reoriented coronal slices; the left kidney is on the right side of the image. (C) Reoriented coronal topographic section; (D) three-dimensional display ........................................ 337
5.11 The dual-compartment elimination curve of a glomerular filtration rate agent ................................................................................................................................................. 340
5.12 Compartmental Model .................................................................................................................................................................................. 353
5.13 Human Kidney ........................................................................................................................................................................................................... 354
5.14 Renogram showing the normal versus obstructed at the renal pelvis .................................................................................................................................................... 355
5.15 The derived two-compartmental renal model .................................................................................................................................................. 355
5.16 Clinical renograms of volunteer coded Patient 7 ..................................................................................................................................................... 364
5.17 Simulated results based on the clinical data of Patient 7 in Figure 5.15 ............... 365
5.18 Clinical renograms of volunteer coded Patient 19 ..................................................................................................................................................... 366
5.19 Simulated results based on the clinical data of Patient 19 in Figure 5.17 .............. 367
5.20 Clinical renograms of volunteer coded Patient 11 ..................................................................................................................................................... 368
5.21 Simulated results based on the clinical data of Patient 11 in Figure 5.19 .............. 369
5.22 Ranges for indicating the left or right or both kidneys and normal ranges ......... 370
List of Tables

0.1 Dimensions of some common physical quantities. The following table lists dimensions and SI units of some commonly physical quantities. xiii

1.1 Tentative Arbitrary Criteria Employed at the Mayo Clinic in the Diagnosis of Diabetes Mellitus [32] 14
1.2 Diagnostic values for the OGTT for diabetes mellitus 14
1.3 Glucose-tolerance test 24
1.4 Summary of Minimal Model selections and behaviours 34
1.5 Subjects Classified as Normal Clinically 38
1.6 Subjects Classified as Diabetic Clinically 40
1.7 Subjects that were well fitted by underdamped characteristic model equation 59
1.8 Subjects that were well fitted by overdamped characteristic model equation 62
1.9 Subjects that were well fitted by critically damped characteristic model equation 65
1.10 Results of the patients who were classified as normal (non-diabetic) and having underdamp response from the OGTT 70
1.11 Results of the patients who were classified as at-risk and having critical damp response from the OGTT 71
1.12 Results of the patients who were classified as diabetic and having overdamp response from the OGTT 72

3.1 Model projections of the prevalence of moderate to severe COPD in those 30 years and older for 12 countries in the Asia-Pacific region [Respiratory, 8, 192-198] 166
3.2 Direct and indirect costs of lung diseases, 1993 (US $ Billions) 167
3.3 WHO projection of total social burden world-wide. Leading causes of Disability-Adjusted Life Years (DALYs) lost world-wide, 1990 & 2020 (projected) [GOLD workshop report 2003 update] 168
3.4 Abbreviations 177
3.5 Data 240

4.1: Inspired air composition and partial pressures 279
4.2 The alveolar air composition 282

5.1 MAG3 renogram parameters obtained in healthy Volunteer 329
5.2 Comparison of clinical and calculated results of Patient 7 365
5.3 Comparison of clinical and calculated results of Patient 19 367
5.4 Comparison of clinical and calculated results of Patient 11 369
Thesis Overview

Chapter 0  Contains the thesis introduction thesis and concepts of NDIs, derivations and applications. It also summarizes the PNDIs that are derived in the subsequent chapters.

Chapter 1  Introduces the concept of using Physiological Non-Dimensional Indexes (PNDI) for distinguishing or classifying patients who were diabetic from non-diabetic and those who are the risk of becoming diabetic. In the authors work, he has also demonstrated that those who were diabetic were actually at-risk and those who were normal were in fact at the rim of becoming diabetic. All the works were verified against with clinical data by parametric identification techniques.

Chapter 2  Using the findings of the above chapter, the author conceptualized, and design and simulated a dynamic activity-based insulin infusion system. He has used the clinical data of diabetic patients in the above chapter for demonstrating the operations of the system. He has even demonstrated the stability of the system by having continual simulations till 4-hour.

Chapter 3  In this chapter, the author has derived a series of system equations for identification of pulmonary diseases based in the inhale and exhale gas mixtures concentrations and volume space.

Chapter 4  In this chapter, the author has derived a series of system equations for identification of diseased lungs based of the lungs’ pressure-volume graphs. He has even demonstrated the techniques of obtaining the Cardiac Output (CO) non-invasively

Chapter 5  The author has demonstrated how to obtain the relative urine outflow non-invasively for normal kidneys.

Chapter 6  The author has described the significance and derivation background of PNDI.
Chapter 0 Introduction

In physiological medicine, the use of Non-Dimensional Physiological Indices (NDPI) or numbers can provide a generalized approach by which unification or integration of a number of isolated but related events into one non-dimensional physiological index (NDPI) can help to characterize an abnormal state associated with a particular physiological system. The evaluation of the distribution of the values of such NDPI(s), in a big patient-population, can then enable us to designate normal and disordered ranges of NDPI, with a critical value of NDPI separating these two ranges, illustrated in figure 1. Herein, we have formulated several such new NDPIs.

The concept of Non-Dimensional Physiological Index is quite new, and has been adopted from Engineering, wherein non-dimensional numbers (made up of several parameters) are employed to characterize a regime or strata disturbance phenomena. For example, in a cardiovascular fluid-flow regime, the Reynolds number.

\[
\text{Re} = \frac{\rho V D}{\mu} \tag{1}
\]

The Reynolds number for the flow of a fluid of density \(\rho\) and viscosity \(\mu\) through a pipe of inside diameter \(D\) and \(V\) is the velocity. The Reynolds factor represents a complex dimensionless factor that characterized a complex property of a physical situation, i.e. its susceptibility to turbulence.

Similarly, we can construct other such physiological numbers is employed to characterize the conditions when \(\text{Re}\) exceeds 2000, at which laminar flow changes to turbulent flow, which can occur in the ascending aorta when either the aortic valve is stenotic (giving rise to mururs) or in the case of anaemia (decrease blood viscosity).
0.1 Use of NDPIs in Author’s Work

The author’s work focuses on systematic application of dimensional analysis in human physiology, in which use is made of parameters of functional second order linear differential equations of physiological systems, to develop non-dimensional physiological indexes (NDPIs) to qualify patient health and diseases status as well as patient improvement. NDPIs have been developed for several physiological phenomena and systems (Chapters 1, 3 through 5), and indicated as to how they can be employed diagnostically. In this chapter, we will describe the principles behind the NDPIs formulations. We have formulated NDPIs for:

(i) Chapter 0, Introduction, contains the theoretical details how the NDIs in this thesis are formed.

(ii) In Chapter 1, we have use Oral Glucose Tolerance Test, to classify the patients into non-diabetic, diabetic or at-risk. The NDPIs can also distinguish the patients who are at-risk from non-diabetic and diabetic. Then they can undergo pre-emptive medications.

(iii) Chapter 3, Lung Ventilatory function, to enable us to diagnose lung diseases in terms of just one non-dimensional lung-ventilatory index ($VTI$) number, incorporating the lung parameters resistance ($R$) and compliance ($C$) as well as the lung breathing rate.

(iv) Chapter 4, Lung Gases Metabolism, to enable us to determine the lung efficiency in oxygen consumption and carbon dioxide rates, by one NDPI incorporating oxygen diffusion coefficient $D_{O_2}$ and carbon dioxide diffusion coefficient $D_{CO_2}$.

(v) Chapter 5, Kidney Renal Dysfunctions, to enable us to quantify the severity of renal obstructions of both the patient’s kidneys by a NDPI.

(vi) Chapter 6, Non-dimensional Physiological Indices for Clinical Assessment, contains the summary of Author’s work.
0.2 Literature Review

Dimensional Analysis is not just a systematic method for checking the consistency of equations and converting systems of units. In fact, it is a complex and interesting branch of algebraic theory, with a very broad range of applications [6, 8, 15].

One of the most important applications of dimensional analysis is Reynolds number (\(Re\)) as shown in (1). Reynolds number was discovered by Osborne Reynolds of the University of Manchester in 1883. Reynolds number is dimensionless quantity associated with the smoothness of flow of a fluid. It is an important quantity used in aerodynamics and hydraulics. At low velocities fluid flow is smooth, or laminar, and the fluid can be pictured as a series of parallel layers, or lamina, moving at different velocities. The fluid friction between these layers gives rise to viscosity. As the fluid flows more rapidly, it reaches a velocity, known as the critical velocity, at which the motion changes from laminar to turbulent, with the formation of eddy currents and vortices that disturb the flow.

Walter had claimed that his paper [15] was the first published article on dimensional analysis in biology making use of dimensionless number and functional dimensional equations. But this paper had not published any of his mathematical and experimental works. It had consolidated many important works based on dimensional analysis such as:

(a) Dimensional considerations were used by Gunther & Guerra in 1955 [6] for analysis of heart and respiratory rate as a function of animal weight.
(b) Felix Klein in 1939 [7] used dimensional equations and dimensionless numbers to get solutions for the general affine space motion group.
(c) Works had been done by Rashevsky [25] and Reiner [26] on dimensional analysis for cellular physiochemical problems and proliferation of biomass.
(d) The technique was applied by Brillouin [28], Yockey [29], Luce [30] and Cherry [31] for dimensions in information based on basic mathematical function suggested by Boltzmann.

Walter [15] had also mentioned that the use of characteristic ratios such as \(C/C^*\) and \(T/T^*\), in which the starred value is some convenient reference point in biological system was published by Thun [27] in 1960. In which Thun had emphasized that any dimensional identity could be converted into a dimensionless form by making a quotient of left and right sides. He used this technique for classifying biomathematical identities and equations.
In Walter’s second paper [16], he had further illustrated the application of dimensional analysis in biology by using functional equations of dimensionless numbers dealing with renal physiology, lung physiology and leaf shape. In his paper, he had presented twelve dimensional tables for general fundamental biological applications.

Even though Langhaar in 1951 [8] reveals that modeling is rarely possible for more than two dimensionless numbers at a time, and these must be chosen on the basis of experimental capability and basic goals of the particular model. Our work has shown that this is possible by careful compartmental modeling.

The ability to get dimensional and dimensionless relationships from differential equations is of great importance when the latter too complex for analytic solution. Derivation of suitable dimensionless terms yields terms yields major insights into physical nature of particular problem [12-15].

Dimensional analysis has contribution to make to almost any problem and especially those where analytic methods fail [12-15].

Dimensional analysis has contribution to make to almost any problem and especially those where analytic methods fail [12-15].

### 0.3. Dimensional Analysis

Dimensional analysis is a mathematical tool often applied in physics, chemistry, and engineering to simplify a problem by reducing the number of variables to the smallest number of "essential" parameters and how they should be presented for analysis. This process is based on the Buckingham \(\pi\)-Theorem [1-5]. Systems which share these essential parameters are called similar and do not have to be studied separately [1-5, 10].

The dimension of a physical quantity is the type of unit needed to express it. For instance, the dimension of a speed is distance/time and the dimension of a force is mass×distance/time. In mechanics, every dimension can be expressed in terms of distance (which physicists often call "length"), time, and mass, or alternatively in terms of force, length and mass. Depending on the problem, it may be advantageous
to choose one or the other set of fundamental units. Every unit is a product of (possibly fractional) powers of the fundamental units, and the units form a group under multiplication.

In the most primitive form, dimensional analysis is used to check the correctness of algebraic derivations as described in the previous section. In every physically meaningful expression, only quantities of the same dimension can be added or subtracted. The two sides of any equation must have the same dimensions (Dimension Homogeneity). Furthermore, the arguments to exponential, trigonometric and logarithmic functions must be dimensionless numbers, which is often achieved by multiplying a certain physical quantity by a suitable constant of the inverse dimension.

**Table 0.1** Dimensions of some common physical quantities. The following table lists dimensions and SI units of some commonly physical quantities.

<table>
<thead>
<tr>
<th>Physical Quantities</th>
<th>SI Units</th>
<th>Dimension Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length</td>
<td>m</td>
<td>L</td>
</tr>
<tr>
<td>Mass</td>
<td>kg</td>
<td>M</td>
</tr>
<tr>
<td>Time</td>
<td>s</td>
<td>T</td>
</tr>
<tr>
<td>Force</td>
<td>N</td>
<td>MLT⁻²</td>
</tr>
<tr>
<td>Electric Charge</td>
<td>C</td>
<td>Q</td>
</tr>
<tr>
<td>Velocity</td>
<td>ms⁻¹</td>
<td>LT⁻¹</td>
</tr>
<tr>
<td>Acceleration</td>
<td>ms⁻²</td>
<td>LT⁻²</td>
</tr>
<tr>
<td>Energy</td>
<td>J</td>
<td>ML² T⁻²</td>
</tr>
<tr>
<td>Power</td>
<td>W</td>
<td>ML² T⁻³</td>
</tr>
<tr>
<td>Pressure</td>
<td>Nm⁻²</td>
<td>ML⁻¹ T⁻²</td>
</tr>
<tr>
<td>Density</td>
<td>kgm⁻³</td>
<td>ML⁻³</td>
</tr>
<tr>
<td>Viscosity</td>
<td>Nsm⁻²</td>
<td>ML⁻¹ T⁻¹</td>
</tr>
<tr>
<td>Surface Tension</td>
<td>Nm⁻¹</td>
<td>MT⁻²</td>
</tr>
</tbody>
</table>
0.3.1. Dimensional Homogeneity

Any equation describing a physical system will only be valid if both sides have identical dimensions. This is known as dimensional homogeneity.

Before further discussing about Non-Dimensional Analysis, let’s understand the importance of Dimensional Analysis.

- Dimensional analysis is used in numerical calculations, and in converting units
- Dimensional analysis can help identify whether an equation is set up correctly (i.e. the resulting units should be expected)
- Units are treated similarly to the associated numerical values, i.e. if a variable in an equation is supposed to be square, then the associated dimensions are squared, etc

Units are a critical part of describing every measurement. Before we can work with units mathematically, we frequently must convert from one unit to another.

An equation in which each term has the same dimensions is said to be dimensionally correct. All equations used in any science should be dimensionally correct. The only time we will encounter one which is not is if there is an error in the equation. So dimensional analysis is a valuable tool in helping you to detect an equation in which you made an error in algebra, for example.

Consider Einstein’s well-known equation $E = mc^2$. Dimension Analysis requires both sides of the equations to have the same dimensions.

$E$ is energy, which has units of $mass \times length^2 / time^2 \left(ML^2 / T^2\right)$. (This is because energy = force $\times$ length, and force = mass $\times$ acceleration, and acceleration = $length / time^2$.)

$m$ is mass, which is $M$.
$c$ is speed, which has units $L/T$.

The left-hand side, $E$, therefore has units of $ML^2 / T^2$.
The right-hand side, $mc^2$, has units $ML^2 / T^2$. 
The two sides therefore have the same dimensions.

0.3.2 Buckingham $\pi$-Theorems

Buckingham $\pi$-Theorems [1-5] states that if a system has $k$ physical quantities of relevance that depend on $r$ independent dimensions, then there are a total of $k-r$ independent dimensionless products $\pi_1, \pi_2, \ldots, \pi_{k-r}$. The behavior of the system is describable by a dimensionless equation:

$$\theta(\pi_1, \pi_2, \ldots, \pi_{k-r}) = 0$$

(2)

There are two theorems accredited to Buckingham $\pi$-Theorem, and known as his $\pi$-Theorems.

0.3.2.1 First $\pi$-Theorem

This theorem describes how every physically meaningful equation involving $k$ variables can be equivalently rewritten as an equation of $k-r$ dimensionless parameters, where $r$ is the number of fundamental units used. Furthermore, and most importantly, it provides a method for computing these dimensionless parameters from the given variables, even if the form of the equation is still unknown.

0.3.2.2 Second $\pi$-Theorem

Each $\pi$ group is a function of $r$ governing or repeating variables plus one of the remaining variables. The repeating variables are those which we think will appear in all or most of the $\pi$ groups. As the $\pi$ groups are all dimensionless, we can use the principle of Dimensional Homogeneity (in previous section) to equate the dimensions for each $\pi$ group.

It is very important that the initial choice of variables is carried out with great care. If extra unimportant variables are introduced, then extra $\pi$ groups will be formed. They will play very little role influencing the physical behaviour of the problem concerned. If an important variable was missed, then a $\pi$ group would be missing.
0.3.3 Application of Dimensional Analysis

Based on the Buckingham $\pi$-Theorems, we have derived the following dimensional analysis method:

(a) List all variables and their dimensions.
(b) Count the number of variables $k$ and the number of independent dimensional constraints $r$.
(c) Based on Buckingham $\pi$-Theorem, find $k-r$ independent dimensionless groups $\pi_1, \pi_2, \pi_3, \ldots$, by multiplying variables.

The following is an example of Dimensional Analysis.

A stationary sphere in water moving at a velocity of 1.6m/s experiences a drag of 4N. Another sphere of twice the diameter is placed in a wind tunnel. Find the velocity of the air and the drag which will give dynamically similar conditions. The ratio of kinematics viscosities of air and water is 13, and the density of air 1.28kg/m$^3$.

(a) List all variables and their dimensions.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Water</th>
<th>Air</th>
<th>Dimension</th>
</tr>
</thead>
<tbody>
<tr>
<td>$u$</td>
<td>1.6m/s</td>
<td>$u_{air}$</td>
<td>LT$^{-1}$</td>
</tr>
<tr>
<td>Drag</td>
<td>4N</td>
<td>$D_{air}$</td>
<td>MLT$^{-2}$</td>
</tr>
<tr>
<td>$\nu$</td>
<td>$\nu$</td>
<td>13 $\nu$</td>
<td>LT$^{-1}$</td>
</tr>
<tr>
<td>$\rho$</td>
<td>1000 kgm$^{-3}$</td>
<td>1.28 kgm$^{-3}$</td>
<td>ML$^{-3}$</td>
</tr>
<tr>
<td>$d$</td>
<td>$d$</td>
<td>2$d$</td>
<td>L</td>
</tr>
</tbody>
</table>

(b) Count the number of variables $k$ and the number of independent dimensional constraints $r$.

Kinematic viscosity is dynamic viscosity over density = $\nu = \mu/\rho$.

The Reynolds number: $Re = \frac{\rho ud}{\mu} = \frac{ud}{\nu}$

From Buckingham $\pi$-Theorem we have $k-r = 5 - 3 = 2$, non-dimensional groups.
(c) Based on Buckingham $\pi$-Theorem, find $k-r$ independent dimensionless groups $\pi_1, \pi_2, \pi_3, \ldots$, by multiplying variables.

$$\theta(\mu, d, \rho, D, \nu) = 0$$  
$$\theta(\pi_1, \pi_2) = 0$$  
$$\pi_1 = \mu^{a_1} d^{b_1} \rho^{c_1} D$$  
$$\pi_2 = \mu^{a_2} d^{b_2} \rho^{c_2} \nu$$

Each $\pi$ group is dimensionless.

Considering $\pi_1$:

$$M^0 L^0 T^0 = (LT^{-1})^{a_1} (L)^{b_1} (ML^{-3})^{c_1} MLT^{-2}$$

$M \equiv 0 = c_j + 1$

$\quad c_j = -1$

$L \equiv 0 = a_j + b_j - 3 c_j + 1$

$\quad -4 = a_j + b_j$

$T \equiv 0 = a_j - 2$

$\quad a_j = -2$

$\quad b_j = -2$

$$\pi_1 = \mu^{2} d^{-2} \rho^{-1} D$$

$$\quad = \frac{D}{\mu^{2} d^{-2} \rho}$$

Considering $\pi_2$:

$$M^0 L^0 T^0 = (LT^{-1})^{a_2} (L)^{b_2} (ML^{-3})^{c_2} \frac{L^2 T^{-1}}{}$$

$M \equiv 0 = c_2$

$\quad c_2 = 0$

$L \equiv 0 = a_j + b_j - 3 c_j + 2$

$\quad -2 = a_j + b_j$
\[ T \] 0 = -a_2 - 1  
\[ a_i = -1 \]

\[ b_i = -1 \]

\[ \pi_2 = \mu^{-1} d^{-1} \rho^0 \nu \]

\[ = \frac{\nu}{\mu d} \]

So the physical situation is described by this function of non-dimensional numbers,

\[ \theta(\pi_1, \pi_2) = \theta \left( \frac{D}{\mu^2 d^2 \rho}, \frac{\nu}{\mu d} \right) = 0 \]

For dynamic similarity these of non-dimensional numbers are the same for both the sphere in water and in the wind tunnel i.e.

\[ \pi_{1\text{air}} = \pi_{1\text{water}} \]
\[ \pi_{2\text{air}} = \pi_{2\text{water}} \]

For \( \pi_2 \):

\[ \left( \frac{\nu}{\mu d} \right)_{\text{air}} = \left( \frac{\nu}{\mu d} \right)_{\text{water}} \]

\[ \frac{\nu}{\mu_{\text{air}} \times 2d} = \frac{\nu}{1.6 \times d} \]

\[ \mu_{\text{air}} = 10.4 \text{ms}^{-1} \]

For \( \pi_1 \):

\[ \left( \frac{D}{\mu^2 d^2 \rho} \right)_{\text{air}} = \left( \frac{D}{\mu^2 d^2 \rho} \right)_{\text{water}} \]

\[ \frac{D_{\text{air}}}{10.4^2 \times (2d)^2} \frac{1.28}{1.6^2 \times d^2 \times 1000} = \frac{4}{D_{\text{air}}} = 0.865N \]
0.4 Non-Dimensional Analysis

In the physical sciences, dimensionless number is a quantity which describes a certain physical system and which is a pure number without any physical units. Such a number is typically defined as a product or ratio of quantities which do have units, in such a way that all units cancel.

For example: "one out of every 10 apples I gather is rotten." The rotten-to-gathered ratio is \([1 \text{ apple}] / [10 \text{ apples}] = 0.1\), which is a dimensionless quantity.

Dimensionless numbers are widely applied in the field of mechanical and chemical engineering. According to the Buckingham \(\pi\)-theorem [1-5] of dimensional analysis, the functional dependence between a certain number of variables; \(k\) can be reduced by the number of independent; \(r\) dimensions occurring in those variables to give a set of \(p = k - r\) independent, dimensionless numbers. For the purposes of the experimenter, different systems which share the same description by dimensionless numbers are equivalent. When plotting graphs, the quantities plotted are also dimensionless - the notation \(x (/s)\), for example, serves to divide the data (time in seconds) by the unit vector \(t\), and produces a dimensionless value for plotting.

A dimensionless group \(\theta\) formed from variables \(a, b, c, d\) is a product of the variables raised to powers \(\alpha, \beta, \gamma, \delta\), such that:

- \(\theta = a^\alpha b^\beta c^\gamma d^\delta\)
- \((\alpha, \beta, \gamma, \delta) \neq (0, 0, 0, 0)\)

The constraint that \(\theta\) be dimensionless implies linear relationships among \(\alpha, \beta, \gamma, \delta\). For the relativistic mass example, the constraint that \(\theta \equiv m^\alpha m^\beta v^\gamma c^\delta\) has no mass (M) dimension gives:

\[
\alpha + \beta = 0 \quad (3)
\]

The constraint that \(\theta\) has no length (L) dimension gives:

\[
\gamma + \delta = 0 \quad (4)
\]

The third dimensional constraint on \(\theta\) (no time \(T\)) reproduces constraint (2), so the number of independent constraints is just 2.
A set of dimensionless groups $\theta_1, \theta_2, \theta_3$, are independent if there is no relationship of the form:

$$\theta_j = \theta_m^p \theta_n^q$$

(5)

between them. Equivalently, if we think of the numbers $(\alpha, \beta, \gamma, \delta)$ associated with each group as defining vectors, the groups are independent if the vectors $(\alpha, \beta, \gamma, \delta)_1$, $(\alpha, \beta, \gamma, \delta)_2$, $(\alpha, \beta, \gamma, \delta)_3$ are linearly independent.

If there’s more than one dimensionless group, then there are indeed many choices for the set of independent groups. For example, the triangle problem

<table>
<thead>
<tr>
<th>Physical parameters</th>
<th>Symbol</th>
<th>Dimension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area</td>
<td>$A$</td>
<td>$L^2$</td>
</tr>
<tr>
<td>Base</td>
<td>$a$</td>
<td>$L$</td>
</tr>
<tr>
<td>Height</td>
<td>$b$</td>
<td>$L$</td>
</tr>
<tr>
<td>No. of constraints</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

can yield the dimensionless groups

\[
\left( \frac{A}{a^2} \right) \text{ and } \left( \frac{a}{b} \right); \\
\text{or} \hspace{1cm} \left( \frac{A}{ab} \right) \text{ and } \left( \frac{b}{a} \right); \\
\text{or} \hspace{1cm} \left( \frac{Aa}{b^3} \right) \text{ and } \left( \frac{Ab^2}{a^4} \right);
\]

But the answer from dimensional analysis,

\[
\text{(one group)} = F(\text{all the groups}),
\]

is always correct, and this answer is equivalent for any choice of the independent groups. All the changes is the meaning and form of the dimensionless function $F$. For example, for the first two choices of groups listed above, $F_1(x) = \frac{1}{2x}$ and $F_2(x) = \frac{1}{2}$ respectively. If we wish to express the answer from dimensional analysis in the form (one variable) = $f$(the others), for example $A = f(a, b)$ then we should
ensure that the chosen variable appears in only one of the groups. So the choice of groups

$$\left( \frac{A}{ab} \right) \text{ and } \left( \frac{A}{a^2} \right);$$

are valid, but not useful when we are trying to write $A = f(a,b)$. 
0.5 Information Calculus

Claude E. Shannon (1960-2001) has been called "the father of information theory". His theory for the first time considered communication as a rigorously stated mathematical problem in statistics and gave communications engineers a way to determine the capacity of a communication channel in terms of the common currency of bits. The transmission part of the theory is not concerned with the meaning (semantics) of the message conveyed, though complementary wing of information theory concerns itself with content through lossy compression of messages subject to a fidelity criterion.

On the early 1940’s, Shannon developed a mathematical theory [32], called information theory, for dealing with the most fundamental aspect of communication systems. Since then, researchers, engineers and scientists have been applying the theory in many areas of their own expertise for analyzing collected results such as [11, 17, 20-22, 29].

0.5.1 Fundamentals of Information Calculus (Information Theory) [20-22]

Information comes in the form of data collected by researchers, engineers and scientists from which they derive conclusions and make conjectures. The modern computerized technologies in data acquisitions have enabled many parameters in an experiment to be collected at simultaneously ease. This naturally makes researchers, engineers and scientists to collect data any time they think; it might be potentially important.

As a result, they have included more data that might be irrelevant than to exclude them. As a result, it is easy to collect data and often difficult to analyze them. It was obviously, not all of the collected information is relevant to their research works. Hence, it will be necessary for them to be able systematically to single out variables that are important and discard those that are not.

0.5.2 Information Calculus to select Relevant Variables if the variables are Independent

Intuitively, we assume that a variable is important if it is highly related to our problem and not important if it has nothing to do with our problem. For example, if the
percentage of diabetic patients is the same for every race (Chinese, Indians, Malays and minority races) is not important for diabetic-insulin kinetics research. On the other hand, if diabetic is much more prevalent among over-weight than normal-weight subjects, then we say that over-weight is important for diabetic-insulin kinetics research.

But how do we measure the degree of importance? Assume that we have two variables Y and X where Y is a dependent variable and X is an independent variable. Then the relevance of X with respect to Y is reflected by the statistical dependence between X and Y. X is absolutely irrelevant to Y if X is statistically independent of Y.

Besides, a variable might not be important for its sake. If everyone on this world is diabetic, then diabetic cannot be very interesting for diabetic-insulin kinetics research. (In fact diabetic cannot be interesting for any research, in this case). For either everyone gets diabetic or only some get it. In the case where only some become diabetic, over-weight obviously cannot be used to predict diabetics. In those cases where everyone get diabetic, although over-weight might cause diabetic, we cannot conclude anything because we do not have any data on non-diabetic.

0.5.3 Measure of Self-Importance

As pointed in the previous section, a variable cannot be important if it does not vary much; for example, it assumes only one value in all situations. Therefore, a reasonable way to measure self-importance of a variable is to measure its “randomness”.

Let us denote a measure of the importance of an independent variable X with respect to a dependent variable Y by $M(Y,X)$ and it should meet the following requirements:

(a) $M(Y,X)$ takes into account both the self-importance of $X$ and its relevance with respect to $Y$.
(b) $M(Y,X)$ assumes the minimum value iff $Y$ and $X$ are statistically independent.
(c) $M(Y,X_i) > M(Y,X_j)$ iff $X_i$ is more relevant to $Y$ than $X_j$ is.

In our work of glucose-insulin kinetics modeling, we work intensely with mutual information. The concept of mutual information actually consists of two concepts: self-importance and conditional self-importance. The former corresponds to self-importance and the latter corresponds to our concept of relevance.
0.5.4 Self-Information, Conditional Information and Mutual Information

**Definition 1**: The self-information of an event $E$ is defined as

$$ I(E) = \log \frac{1}{P(E)} \quad (6) $$

**Definition 2**: If random variable $X$ assumes the values $x_1, x_2, \ldots, x_n$, then the average self-information of $X$, $H(x)$, is defined by

$$ H(X) = \sum_{i=1}^{n} P(x_i) I(x_i) \quad (7) $$

or

$$ H(X) = \sum_{i=1}^{n} P(x_i) \log \frac{1}{P(x_i)} \quad (8) $$

and $H(X)$ is called the entropy of $X$.

Similarly, the conditional entropy,

**Definition 3**: For events $E$ and $F$, the conditional self-informations are

$$ I(E \mid F) = \log \frac{1}{P(E \mid F)} \quad (9) $$

and

$$ I(F \mid E) = \log \frac{1}{P(F \mid E)} \quad (10) $$

**Definition 4**: For random variables $Y$ and $X$ assuming values $y_1, y_2, \ldots, y_m$ and $x_1, x_2, \ldots, x_n$ respectively, the conditional entropies are

$$ H(Y \mid X) = \sum_{i=1}^{m} \sum_{j=1}^{n} P(y_i \mid x_j) I(y_i \mid x_j) \quad (11) $$

and

$$ = \sum_{i=1}^{m} \sum_{j=1}^{n} P(y_i \mid x_j) \log \frac{1}{P(y_i \mid x_j)} $$
\[ H(X \mid Y) = \sum_{i=1}^{m} \sum_{j=1}^{n} P(x_j \mid y_i) I(x_j \mid y_i) \]
\[ = \sum_{i=1}^{m} \sum_{j=1}^{n} P(x_j \mid y_i) \log \frac{1}{P(x_j \mid y_i)} \]  

(12)

In the above, we have defined self-information and conditional self-information, we are going to define the final important concept, the mutual information \( I(Y,X) \).

**Definition 5**: Let \( E \) and \( F \) be two events. The amount of information provided by the occurrence of event \( F \) about the occurrence of event \( E \) is defined as

\[ I(E, F) = \log \frac{P(E \mid F)}{P(E)} \]  

(13)

The following function is defined because the information provided by \( F \) about \( E \) is indicated, in some way, by the change of the probability \( P(E) \) to \( P(E \mid F) \). The equation (8) can be expressed as:

\[ I(E, F) = \log \frac{P(E \mid F)P(F)}{P(E)P(F)} \]  

(14)

\[ = \log \frac{P(E \mid F)}{P(E)} \]  

(15)

\[ = \log \frac{P(F \mid E)}{P(F)} \]  

(16)

If \( E \) and \( F \) are statistically independent, then \( P(E,F)=P(E)P(F) \). In this case, as can be seen from (10), \( I(A,B) \) reduces to zero \( \log 1 = 0 \).

**Definition 6**:

Let \( X \) and \( Y \) be two random variables where \( Y \) assumes values \( y_1, y_2, \ldots, y_n \), and \( X \) assumes values \( x_1, x_2, \ldots, x_n \). Then the expected value of information between \( Y \) and \( X \) is:

\[ I(Y, X) = \sum_{i=1}^{m} \sum_{j=1}^{n} P(y_i, x_j) I(y_i, x_j) \]

\[ = \sum_{i=1}^{m} \sum_{j=1}^{n} P(y_i, x_j) \log \frac{P(y_i, x_j)}{P(y_i)P(x_j)} \]  

(17)
\( I(Y, X) \) is called the mutual information between \( Y \) and \( X \). An important property of \( I(Y, X) \) can be expressed by the following two equations.

\[
I(Y, X) = H(X) - H(X \mid Y) \quad (18)
\]

and

\[
I(Y, X) = H(Y) - H(Y \mid X) \quad (19)
\]

In information theory, \( I(Y, X) \) is interpreted as the average information received by \( Y \) transmitted from \( X \); \( H(X) \) is interpreted as the average information transmitted by \( X \); and \( H(X \mid Y) \) is the loss.

In data analysis, we interpret \( (Y, X) \) as the relative importance of \( X \) with respect to \( Y \), \( H(Y) \) as the self-importance of \( X \), and \( H(X \mid Y) \) as the irrelevance of \( X \) with respect to \( Y \).

We can conclude that \( I(Y, X) \) does meet the requirements of the measurement \( M(Y, X) \):

(a) \( I(Y, X) \) takes into account the self-importance of \( X \) and the relevance of \( X \) with respect to \( Y \) (13).

(b) \( I(Y, X) \) is always nonnegative and \( I(Y, X) \) is zero iff \( Y \) and \( X \) are statistically independent of each other.

(c) From (14), we obtain the relation \( I(Y, X_1) > I(Y, X_2) \) iff \( H(Y \mid X_1) < H(Y \mid X_2) \). Since \( H(Y \mid X) \) is a measure of independence between \( Y \) and \( X \), \( H(Y \mid X_1) < H(Y \mid X_2) \) means that \( Y \) depends on \( X_1 \) more than it depends \( X_2 \). This justifies our claim that variable \( X_1 \) is better than variable \( X_2 \).
0.6 Information Calculus to select Relevant Variables if the variables are not Independent

In section 0.5.2, we have presented Information Calculus to select variables if they are independent. In this section, we will discuss how to use Information Calculus to analyze medical data where the variables are not exclusive. The reduction of number of symptoms needed for characterization of patient’s state, diagnosis and prognosis.

In the paper [18], Lee proposed that arranging the variables $X_1, X_2, ..., X_m$ in decreasing order of mutual information shared with a variable $Y$. Once this has been done, one may set a maximum loss of information about $Y$ which must not be exceeded. Then we may progressively discard those variables which tell us the least about $Y$ from the bottom of this list until our threshold is reached.

In his analysis, Lee decided to retain only the assumption of statistical independence of the $X_i$. We now restate briefly his selection method. He derives the ranking $X_{s1}, X_{s2}, ..., X_{sn}$ by requiring that:

$$I(Y, X_{s1}) \geq I(Y, X_{s2}) \geq \cdots \geq I(Y, X_{sm}) \quad (20)$$

because, when the $X_i$ are statistically independent,

$$I(y; X_{s1}, X_{s2}, ..., X_{sn}) = I(Y, X_{s1}) + I(Y, X_{s2}) + \cdots + I(y, X_{sn}), \quad n \leq m,$$

where

$$I(Y, X_{si}) = H(Y) + H(X_{si}) - H(Y, X_{si}) \quad (21)$$

By substituting (2) into (1), we derive (3), which is found in the paper [11]

$$I(Y; X_{s1}, X_{s2}, ..., X_{sn}) = nH(Y) + \sum_{i=1}^{n} H(X_{si}) - \sum_{i=1}^{n} H(Y, X_{si}), \quad n \leq m \quad (22)$$

Lee comments that the problem becomes much more complicated without this assumption of independence. Such a supposition is, however, seldom justified in the analysis of medical data for the variables are often highly correlated. Thus, the following more general solution is proposed. It will be shown that the extra work involved in dropping Lee's assumption need not be prohibitive [17].

The desired ranking may be achieved by using the formula
\[ I(Y; X_{s1}, X_{s2}, \ldots, X_{sn}) = H(Y) + H(X_{s1}, X_{s2}, \ldots, X_{sn}) \]
\[ - H(Y; X_{s1}, X_{s2}, \ldots, X_{sn}), \quad n \leq m \] (23)

The complications to which Lee refers arise because instead of performing only \( m \) calculations using (2) of the mutual information \( I(Y, X_i) \) of two variables and then substituting these to get (3), we now have to use (4), which requires \( 2^m - 1 \) evaluations of the mutual information of up to \( m \) variables jointly. These complications can, however, be greatly reduced by retaining the \( X_{s_i} \) found from maximizing \( I(Y; X_i = X_{si}), j = 1, 2, \ldots, m \) and then using it in the selection test for \( X_{s_i} \): maximization with respect to \( j \) of \( I(Y; X_{s_i} = X_{s_i}), j = 1, 2, \ldots, m \) and \( s_2 \neq s_1, \ldots \). Similarly, succeeding variables are found from

\[ \max I(Y; X_{s1}, X_{s2}, \ldots, X_{si} = X_j), j = 1, 2, \ldots, m; s_i \neq s_1, s_2, \ldots, s_{i-1} \] (24)

This retention of each previously generated \( X_{si} \) necessitates only \( + (m - 1) + (m - 2) + \ldots + 2 + 1 = m(m - 1)/2 \) calculations with (4) of mutual information as opposed to the previously mentioned

\[ \binom{m}{1} + \binom{m}{2} + \ldots + \binom{m}{m-1} + \binom{m}{m} = 2^m - 1 \]

needed for reevaluation of all the \( X_{s_i} \) whenever (4) is used to determine the next one in the ranking.

The large reduction in computer time obtained by this slight sacrifice in rigor is obvious and the results we obtained by this technique [18, 19].

Now, the maximum knowledge we possess about \( Y \) is contained in all our \( m \) variables and is \( I(Y; X_{s1}, X_{s2}, \ldots, X_{sn}) \). So if we desire to reduce the size of our data base while maintaining most of this information content, we may use the maximization procedure (5) to tell us which of the \( X_i \) may be neglected without falling below a desired threshold

\[ (1 - \varepsilon) \cdot I(Y; X_1, X_2, \ldots, X_m), \]

where \( \varepsilon \ll 1 \). Iteration proceeds \( n \) times until we first achieve
\[ I(Y; X_{s1}, X_{s2}, \ldots, X_{sm}) \geq (1 - \varepsilon) \cdot I(Y; X_1, X_2, \ldots, X_m) \] (25)

If, say, \( \varepsilon = 0.05 \), then the "minimal subset" \( X_{s1}, X_{s2}, \ldots, X_{sm} \) gives us 95% of the information about \( Y \) which is contained in all \( m \) members \( X_1, X_2, \ldots, X_m \) of the complete data base.

It is useful to normalize the information \( I \) which is shared with \( Y \) by dividing into it the total information which \( Y \) possesses, \( H(Y) \), in order to get an explicit index of the amount of information known about \( Y \) relative to the total amount \( H(Y) \) which can ideally be known. This quotient has been defined by Nikl and Perez as the "information influence coefficient \( Z \)" [21] and can be readily seen to act as an index of the efficiency of our iteration procedure and thus of our ability to predict \( Y \) from the \( X_s \). So, restating (6), iteration will proceed \( n \) times until we first achieve

\[ Z(Y; X_{s1}, X_{s2}, \ldots, X_{sm}) \geq (1 - \varepsilon) \cdot I(Y; X_1, X_2, \ldots, X_m) \] (26)

From the theory and discussion so far, it can be observed that Information Calculus relies on probability and statistics to determine the health conditions, treatment improvement and diseases classification. Even with high probability, there still a chance of false classification. Our modeling techniques that we are proposing will ensure the classification to be as accurate as the acquired data for our models.
0.7 Summary of Author’s work on Non Dimensional Physiological Indices

In the following chapters (1 to 5), we have realized that dimensional analysis has contribution to make to almost any problem and especially those where analytic methods fail. The ability to get dimensional and dimensionless relationships from differential equations is of great importance when the later too complex for analytic solution. Derivation of suitable dimensionless terms yields major insights into physical nature of particular problem. We have developed NDPIs for:

(i) Oral Glucose Tolerance Test, to classify the patients into non-diabetic, diabetic or at-risk. The NDPIs can also distinguish the patients who are at-risk from non-diabetic and diabetic. Then they can undergo pre-emptive medications [41-42].

\[
G_{NDI} = \frac{y_{max} \times y_{1}}{G^2} \times \frac{T_d}{A} \times \frac{T_{max}}{T_2} \times 10^6
\]

\[
I_{NDI} = \frac{\beta \gamma \delta}{\alpha}
\]

\[
NDI = G_{NDI} \times I_{NDI}
\]

\[
= \frac{y_{max} \times y_{2}}{G^2} \times \frac{T_d}{A} \times \frac{T_{max}}{T_2} \times 10^6 \times \frac{\beta \gamma \delta}{\alpha}
\]

\(\alpha\) : increases means insulin removed
\(\beta\) : increases means insulin responsive to glucose concentration
\(\gamma\) : decreases means blood glucose increases and not enough glucose absorbed by tissues.
\(\delta\) : decreases means blood glucose increases and inadequate tissue glucose utilization.

(ii) Lung Ventilatory function, to enable us to diagnose lung diseases in terms of just one non-dimensional lung-ventilatory index (VTI) number, incorporating the lung parameters resistance (R) and compliance (C) as well as the lung breathing rate [9, 45, 48].
\[ NDPI = \frac{D_{CO_2}}{D_{O_2}} \times \frac{\text{O}_2 \text{ consumption rate}}{\text{CO}_2 \text{ production rate}} \]

Checking dimensions:

\[ NDPI = \frac{D_{CO_2}}{D_{O_2}} \times \frac{\text{mlCO}_2/\text{min}/\text{mmHg}}{\text{mlO}_2/\text{min}/\text{mmHg}} \times \frac{\text{mlO}_2/\text{min}}{\text{mlCO}_2/\text{min}} \]

Example:

\[ NDPI = \frac{417.68 \text{mlCO}_2/\text{min}/\text{mmHg}}{21.90 \text{mlO}_2/\text{min}/\text{mmHg}} \times \frac{283.2 \text{ml/min}}{226.8 \text{ml/min}} = 23.8 \]

(iii) Lung Gases Metabolism, to enable us to determine the lung efficiency in oxygen consumption and carbon dioxide rates, by one NDPI incorporating oxygen diffusion coefficient \( D_{O_2} \) and carbon dioxide diffusion coefficient \( D_{CO_2} \) [44,46-47, 49-51].

\[ \text{VTI}_1 = [ (R_a \text{ Ca})(\text{Ventilatory rate in s}^{-1}) 60 ]^2 = \tau_a^2 (\text{BR})^2 60^2 \]

where BR is the breathing rate.

\[ \text{VTI}_2 = \frac{(BR)R[TV]^2}{[P_1C]P_2C[P_3C]} = \frac{(BR)R[TV]^2}{[P_1P_2P_3C]^2} \]

(iv) Kidney Renal Dysfunctions, to enable us to quantify the severity of renal obstructions of both the patient’s kidneys by a NDPI [52-53].

\[ \text{NDI} = \frac{\text{Area under the curve between 60 sec and 120 sec for left kidney}}{\text{Area under the curve between 60 sec and 120 sec for right kidney}} \]

In the paper by Naoki et. al [40], the team has developed a set of physiological indices based on electroencephalogram (EEG), electrocardiogram (ECG) and skin potential response (SPR) to reflect human condition related to comfortable aspect. These set of indices will be used as control parameters by the system to bring the user to the state of relaxation through audio-visual means. The system works based on the binary values of “low” or “high”. The scales of differentiation are determined through a series of experiments. But the team has not able to combine these qualitative ranges into quantitative values or a single non-dimensional physiological index. The significance of the above PNDIs will be discussed in the respective proceeding chapters.
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Chapter 1 Glucose & Insulin Kinetics

1.1 Motivation behind the Project

Currently, there is no existing automated quantitative system to diagnose the endocrinological conditions of diabetic or diabetic prone patients. The diagnostic results are mainly based on qualitative analysis [14, 43, 57-58] by qualified clinicians.

The desirability of maintaining an equivocal category of test results is supported in the interest of avoiding overdiagnosis of diabetes. → pre-emptative, prevention

1.2 Background

Diabetes is a group of disorders resulting from insulin deficiency, impaired effectiveness of insulin action or both [27]. Insulin impairment leads to high levels of glucose in the blood as the body cannot break down this basic sugar. Diabetes mellitus is a serious condition in itself, but is also a risk factor for other conditions including blindness, renal failure, macro-vascular diseases, such as stroke, and ischaemic heart disease. There are four different types of diabetes based on aetiology and clinical presentation. These are type 1 diabetes, type 2 diabetes, gestational diabetes and other specific types of diabetes. Our work focuses on type 2 diabetes, which is characterized by insulin resistance and relative insulin deficiency [27].

The prevalence of diabetes mellitus in Singapore has increased from 1.9% in 1975 to 8.6% in 1992. The prevalence among Singaporeans aged 30 to 69 is 12%. Diabetes mellitus in Singapore is mainly of the non-insulin dependent type. Diabetes mellitus has been identified as a priority health program in the Singapore Government's National Health Agenda for the 1990s [12-15]. The Ministry of Health appointed the National Diabetes Commission (NDC) as an expert panel to review and provide advice on measures to prevent and control diabetes in Singapore. The NDC, in
consultation with a large number of physicians and health care professionals in Singapore and in reference to established guidelines from developed centres around the world, has drawn up the Singapore Practice Guidelines. These are mainly aimed at primary health physicians and members of the Diabetes Health Care Team who manage diabetics in Singapore.

Type 2 diabetes mellitus is a complex metabolic disorder which leads to a variety of complications that include nephropathy, retinopathy and cerebrovascular and cardiovascular disease. The rapid economic development and the associated lifestyles changes in Singapore have resulted in significant increases in the prevalence of coronary heart disease (CHD), which is now among top three leading causes of death among Singaporean [12]. Singapore is similar to other industrialized nations in that diabetes is an important risk factor for the development of CHD. In the Singapore Cardiovascular Cohort Study [16], one-third of patients who developed CHD had type 2 diabetes at baseline. Individuals with type 2 diabetes are also at increased risk of mortality compared with non-diabetics, with heart disease contributing to about three out of every four deaths among persons diabetes [17].

According to the 1988 National Healthy Survey (NHS) [18], among Singaporeans aged 18-64 years of age, the prevalence of diabetes and impaired glucose was approximately 9% and 15%, respectively. In this survey, 62% of patients diagnosed with diabetes were previously undiagnosed. Globally, this places Singapore among countries with a high rate of diabetes [19]. There are marked ethnic differences in the prevalence of diabetes in Singapore. The highest rate is seen among Indians (15.8%), followed by Malays (11.3%), and is lowest in Chinese (8.0%) [18]. The rate of increase in the prevalence of diabetes is occurring in both sexes and is particularly marked among the Chinese, with prevalence doubling from 4.7% in 1984 to 8% in 1998 [12, 20, 21]. Singaporean Indians (15.8%) and Chinese (8.0%) are also at higher risk of developing diabetes than their counterparts from rural India (2.7%) and China (1.6%) [20].

Several factors may account for the higher prevalence of diabetes in Singapore. Although the molecular basis for type 2 diabetes is still poorly understood, both insulin resistance and beta-cell dysfunction are well documented [22, 23] and is likely
a result of both environmental influences and genetic factors [24, 25]. The ageing population in Singapore, increasing prevalence of obesity and a sedentary lifestyle parallel the rise in diabetes, and are likely contributors to this metabolic abnormality [12].
Figure 1.1 The organs of the digestive system. The pancreas is the organ responsible for regulating the blood glucose concentration by release of insulin. [Prof Gunther H, Bodyworlds]
Diabetes mellitus, named by Aretaeus of Cappadocia (AD 81-138), has been diagnosed since roughly 1500 BC. Nevertheless it is only recently that its treatment has been made possible, due to the discovery of insulin by Banting and Best in 1921. Diabetes has by the increased thirst and frequent urination experienced by the person with diabetes. Often, this person also feels a generalised weakness. Later in 1679 the discovery that the urine of a diabetic person had a sweet taste, gave the condition its name. The term "diabetes mellitus" was derived from 2 terms:

(a) The Greek word Diabetes = to Siphon /pass through
(b) The Latin word mellitus = sweet as honey

Diabetes mellitus is a condition in which patients have high blood sugar. It is a common condition and affects 8.6% of the population in Singapore [12]. This is an increase from 4.7% in 1984. It is an important condition because there are many complications that can occur as a result of diabetes mellitus. These can be divided broadly into those that occur in the short term (the acute complications) and those that occur over a long time (the chronic complications).

1.2.1 Types of Diabetes Mellitus

There are 2 major types of diabetes mellitus [12, 18, 22, 23]:

(i) Type 1 diabetes mellitus has also been known as juvenile-onset diabetes mellitus or insulin dependant diabetes mellitus. This is the less common type and usually occurs in young persons below the age of 35. In this condition, the body is unable to produce insulin. Insulin is a hormone produced by the pancreas, a gland that is in the abdomen. Insulin is a hormone that controls the use of different fuels for energy. It is especially important because it allows the body to use glucose (simple sugar) instead of fats. When there is no insulin, the body cannot use or store the glucose that comes from food and this causes the blood sugars to become very high. Instead, the body uses fat as a source of fuel giving rise to some of the acute complications of diabetes mellitus.
(ii) Type 2 (adult-onset or non-insulin requiring) diabetes mellitus is much more common and is the type of diabetes that affects most Singaporeans. In this type of diabetes, there is no shortage of insulin (at least at the start of the disease). Instead, the cells and tissues of the body are unable to respond to the insulin produced by the pancreas. This type of diabetes commonly occurs in persons who are overweight and have high blood pressure. There are often other family members who also have the disease.

1.2.2 Acute complications of Diabetes

Acute complications of diabetes include those in which the blood sugar is high (hyperglycaemia) and those in which the blood sugar is low (hypoglycaemia). These include diabetic ketoacidosis and hyperosmolar non-ketotic coma.

1.2.2.1 Diabetic ketoacidosis

Diabetic ketoacidosis occurs when there is insufficient insulin to deal with the amount of sugar in the blood stream. When this occurs, the body uses fat as an energy source and this resulted in the production of ketones that accumulate in the body. These ketones also appear in the urine and can be detected with a simple urine labstix test.

Diabetic ketoacidosis often occurs in type 1 diabetes mellitus when the patient does not give him/herself insulin injections. In type 2 diabetes mellitus, it usually occurs when a patient has some other illness at the same time. This would include all types of infections or fever such as urine infection or chest infections. Other types of stressful events can also lead to diabetic ketoacidosis such as a heart attack.

The symptoms of diabetic ketoacidosis include thirst, passing large volumes of urine, feeling very tired, nausea, vomiting and abdominal pain. Others may notice very deep, rapid breathing and a fruity smell on the breath. In severe cases, patients can become drowsy and become unconscious. This is an emergency and you must be seen immediately in a hospital.

Diabetic ketoacidosis could be prevented by taking insulin and medication regularly,
especially when one is sick. When one is unwell, one should monitor one’s blood sugar frequently and give additional insulin when the blood sugar is high.

1.2.2.2 Hyperosmolar Non Ketotic Coma

Compared to diabetic ketoacidosis, which can occur very quickly, hyperosmolar non ketotic coma occurs more gradually. One may feel thirst and pass large volumes of urine. This will result in one becoming more and more dehydrated. One will feel tired and may lose weight. Usually the urine ketones are negative or present only in small quantities. Patients may become more and more drowsy and become unconscious. This condition is more common in type 2 diabetes mellitus and may occur because of insufficient medication. More commonly, it occurs due to some other illness or injury such as infection. Once again, if the blood sugar is very high and you feel very unwell, it is important to consult one’s doctor quickly as this is also a diabetic emergency.

1.2.2.3 Chronic complications of diabetes mellitus

Apart from the acute diabetic emergencies, high blood sugar does not cause death or disability in itself. Most of the disability from diabetes mellitus results from the chronic complications of diabetes mellitus and we stress again, these are preventable. The complications of diabetes mellitus affect many organs in the body and these include the eyes, heart, feet, kidneys, and the nervous system.

1.2.2.4 Eye disease in Diabetes mellitus

Diabetes mellitus can affect the eye in many ways. Cataracts and glaucoma are more common in patients with diabetes mellitus. In addition, it can affect the part of the eye at the back which is responsible for sensing light and colour, the retina. In the retina, small vessels become "leaky" resulting in the formation of exudates, which are the yellow areas seen in the picture below. If these exudates are too close to the most sensitive area of the retina, the macula, this can impair one’s vision.
Diabetes mellitus also causes weakness in the blood vessel walls causing them to bulge and form microaneurysms. Generally, all persons with diabetes mellitus develop some of these microaneurysms or exudates if they have diabetes for a sufficient length of time. Unless the exudates are very close to the macula, they and the microaneurysms are harmless and will not impair one’s vision. We call this "background retinopathy." In fact, almost all persons who have diabetes mellitus for 20 years have changes that are due to background retinopathy.
Patients who have diabetes mellitus can also develop "proliferative retinopathy". In these cases, new blood vessels grow on the retina. These new blood vessels are fragile and can bleed giving rise to haemorrhage in the eye and this can lead to blindness.

It is important to pick up the changes due to maculopathy and proliferative retinopathy early as laser therapy can reduce the likelihood of loss of vision. In order to make sure that this is carried out at the right time, you need to go for regular eye screening. It is recommended that one have one’s eyes screened when one first find out one have type 2 diabetes mellitus. If they are normal, one should continue to have screening once a year. If there are any abnormalities that require attention, one’s doctor will refer one to an ophthalmologist (eye specialist) for treatment. Patients with type 1 diabetes mellitus do not require eye screening until 3 years after the diagnosis has been made and then once a year thereafter.
Screening can take 2 forms. Many centres can carry out fundal photography where a photograph is taken of the back of your eye allowing a doctor to look for any changes on the retina. The photograph will serve as a permanent record. In Singapore, the polyclinics have this service available. Contact your nearest polyclinic to find out when they have this service available as there are 2 cameras that move to various polyclinics at various times of the year. When a fundal camera is not available, your doctor can look at the retina directly using an instrument called an ophthalmoscope. Most doctors who manage diabetes will have an ophthalmoscope that can be used to examine the eyes carefully. Remember that your doctor has many patients to look after and make it a point to remind him or her of the time to examine your eyes.

Diabetic eye disease is one of the reasons we must try to keep the blood sugar under strict control, the Diabetes Control and Complications Trial (DCCT) has shown us that good control of blood sugar results in less eye disease and even if you already have eye disease, it can prevent it from getting worse.

The Diabetes Control and Complications Trial or DCCT was a large multi centre study conducted in the US which showed convincingly that tight glucose control prevented complications in type 1 diabetes mellitus.

This was a large study that followed up 1441 patients with type 1 diabetes mellitus. The results showed that tight control of blood sugar reduced the development of diabetic eye disease by 76%. If patients already had eye disease, it prevented the worsening of the eye disease by 54%. There was also a reduction in kidney disease by 50% and nerve disease by 60%. It is for this reason that we say that the chronic complications of diabetes mellitus are preventable. However, this requires effort on your part and also that of your health care team to maintain this kind of control. In addition, the treatment given results in an increase in the rate of hypoglycaemia (low blood sugar) and this must be carefully monitored.

1.2.2.5 Diabetes mellitus and the heart [12, 19, 20]

Coronary artery disease or blockage of the arteries supplying the heart is the major cause of death in patients with diabetes mellitus. It can result in heart attacks, heart
failure or angina. The risk of developing coronary artery disease in diabetic patients is known to be several times higher at every level of cholesterol. The multiple risk factor intervention trial (MRFIT) found that coronary artery disease risk in diabetic subjects at any given plasma cholesterol level was approximately four times greater than in non-diabetic patients. This is especially true in women who lose their "natural" protection against heart disease.

With respect to heart disease, diabetes mellitus is more than just a problem of high blood sugar. In contrast to eye and kidney disease, good blood sugar control alone is not enough to prevent the development of heart disease. Diabetes mellitus is associated with widespread abnormalities in the blood. Of particular importance to heart disease are the blood lipids, which includes cholesterol and triglyceride. High triglyceride and low HDL cholesterol (the good cholesterol) is often seen in diabetic patients. In addition, the LDL cholesterol (the bad cholesterol) in diabetics may be 10-15% higher than in non-diabetics.

1.2.2.6 Kidney disease in diabetes mellitus [12, 19, 20]

30-50% of patients with diabetes mellitus may develop kidney disease. Diabetes mellitus is now the more common cause of kidney failure requiring dialysis in Singapore.

Kidney disease in diabetes mellitus usually follows a set pattern. It begins with the appearance of small amounts of a protein called albumin in the urine. This is called microalbuminuria and can be detected using specialised tests. It is important to screen for this stage of diabetic kidney disease because aggressive treatment can normalise the kidney function at this time. Speak to your doctor about a test for urine microalbumin. As with eye disease, this stage of kidney disease produces no symptoms and you will not know you have it unless you test for it. This should be done at the time of diagnosis for type 2 diabetes mellitus and yearly thereafter. Those with type 1 diabetes mellitus can wait 3 years before doing their first test.

Later on, the amount of protein increases and patients reach a stage called nephrotic syndrome. This stage may be associated with swelling of the ankles or abdomen. As
the disease progresses, the patient can eventually develop kidney failure. These later stages of kidney disease are not reversible, i.e. Your kidneys cannot return to normal. However, treatment at this time can still slow down the progression of kidney disease. This is important as it will delay your requirement for dialysis, sometimes as much as 5-10 years.

The regulation of carbohydrate metabolism is a complicated process in which the anterior pituitary, the pancreas, the thyroid, the adrenal cortex and medulla, and the central nervous system are all involved. The mode of action of the hormones of the anterior pituitary on the blood sugar has not been fully elucidated, whereas the pancreas is known to produce glucagons as well as insulin. [18] on chromium (III) and the so-called “glucose tolerance factor” suggests that yet another biochemical mechanism may be involved in the regulation of glucose tolerance. There is consequently a large number of possible pathways through which carbohydrate metabolism can be influenced by the environment. The possibility of disturbances in the regulation of carbohydrate metabolism on the day following a glucose tolerance test does not seem to have been taken account by [19], although such disturbances may be less marked if the subject’s diets are standardized before the test. In such circumstances, comparison of the results of glucose and galactose tolerance tests, performed on subsequent days, might not distinguish quantitatively between changes in glucose absorption and changes in glucose tolerance.

1.3 Literature Review

1.3.1 Conventional Screening

From the paper [32], the differentiation between normality and very mild diabetes requires a somewhat arbitrary definition of criteria. Determination of the concentration of blood glucose 2 hours after a high-carbohydrate meal will often yield diagnostic information.

Determination of the concentration of fasting blood glucose as an initial screening procedure in patients who are suspected of having diabetes because of such reasons
as obesity, family history of diabetes, previous glycosuria, or a history of large babies.

The purpose of the study in [14] was to determine what correlation exists between the level of the blood glucose before the administration of a test dose of glucose and the frequency of significant abnormality, arbitrarily defined, of the subsequent glucose tolerance curve [2, 10, 12, 31, 26].

1.3.1.1 Methods

For at least a day before the test [32], the patients were instructed to eat a diet high in carbohydrates. The tests were done in the morning after an overnight fast. The dose of glucose was 1gm per 1 kg of the actual body weight. Samples of venous blood for determination of glucose were obtained before and at hourly intervals for 3 hours after administration of the test dose.

1.3.1.2 Analysis

For a variety of reasons, overdiagnosis of diabetes should be avoided [32, 63], and an equivocal category such as we have employed seems justifiable. In this category the results of the tests are neither normal nor sufficiently abnormal to warrant a firm diagnosis of diabetes. In our experience, an appreciable number of patients with such tests eventually prove to have diabetes.

In the definition of normality or abnormality [32] of the glucose tolerance curve, one must avoid, insofar as possible, the pitfall of “circular reasoning”, in which the persons subjected to the test are classified as nondiabetic or diabetic on the basis of the test under study.

Even so, some circulatory of reasoning will be inescapable, for any large group of supposedly normal subjects is certain to include some mild diabetes.

The above issues will be addressed and solutions will be proposed by our [2, 41, 31].
Table 1.1 *Tentative Arbitrary Criteria Employed at the Mayo Clinic in the Diagnosis of Diabetes Mellitus* [32].

<table>
<thead>
<tr>
<th>Test</th>
<th>True blood glucose, mg per 100ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Fasting</td>
<td>65 to 90</td>
</tr>
<tr>
<td>Glucose tolerance*</td>
<td></td>
</tr>
<tr>
<td>1 hour</td>
<td>140 or less</td>
</tr>
<tr>
<td>2 hour</td>
<td>90 or less</td>
</tr>
</tbody>
</table>

In the interpretation of the glucose tolerance curve, both the 1 and 2-hour values for blood glucose must fulfill the designated criteria: the fasting value is not considered.

Table 1.2 *Diagnostic values for the OGTT for diabetes mellitus: WHO definitions for 1980, 1985 and 1999 compared.* [26].

<table>
<thead>
<tr>
<th>Glucose concentration mmol/litre (mg/dl)</th>
<th>Whole Blood</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic criteria for diabetes mellitus compared</td>
<td>Venous</td>
<td>Capillary</td>
</tr>
<tr>
<td>Fasting Value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980</td>
<td>≥7.0</td>
<td>≥7.0</td>
</tr>
<tr>
<td>1985</td>
<td>≥6.7 (≥120)</td>
<td>≥6.7 (≥120)</td>
</tr>
<tr>
<td>1999</td>
<td>≥6.1 (≥110)</td>
<td>≥6.1 (≥110)</td>
</tr>
<tr>
<td>OGTT: 2 hours post glucose load of 75g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980</td>
<td>≥10.0</td>
<td>≥11.0</td>
</tr>
<tr>
<td>1985</td>
<td>≥10.0 (≥180)</td>
<td>≥11.1 (≥200)</td>
</tr>
</tbody>
</table>
The SuRF report [26] includes data on the prevalence of diabetes which is presented with well-defined detection methods and diagnostic criteria. Detection methods of choice are a fasting blood glucose measure and/or an oral glucose tolerance test (using a 75 gram glucose load). The preferred diagnostic criteria are those of WHO from one of the following three time periods, 1980, 1985 and 1999 as shown in Table 1.2.

The cut-off point for fasting blood glucose concentration has been lowered, meaning that the number of people considered to be diabetic now is different than in the past, based on this screening test. For the oral glucose tolerance test (OGTT), the diagnostic blood glucose concentration has remained the same. The OGTT is the preferred measure of diabetes in the population because it also detects impaired glucose tolerance and it provides a consistent measure of the prevalence of diabetes in populations over time.

1.3.2 Physiological Modeling Techniques

The paper [46] only works on one equation: \( G = G_0 + Ae^{-\alpha t} \sin \omega t \) for glucose response. Only critical damping and underdamp cases were studied. No overdamp cases were ever studied.

In the paper [47], both the diabetic and non-diabetic clinical data sets are evaluated by the same equation. The data sets used are from a published paper [2]. Only 1 set per class for each example. Besides, 2 points were removed in figure 2 and 2 points added in figure 3, in order to get a fit. No experiments were done on reproducibility. No normalization has been performed.

The paper [46] does not derive the any overdamp system equation. The diabetic data set used in figure 3 has never been verified by the overdamp case. The single parameter \( \omega_n^2 \) gives the results of the subject under study. No insulin response to the bolus of glucose has been studied.

In the paper [33], it is an extension of the earlier paper based on a segmented set of
characteristic equations. Only non-diabetic cases are studied even though 31 subjects are involved in this research. Only glucose response was studied.

1.3.3 Why OGTT?

Elrick et al. [45] had compared the insulin response to oral and intravenous glucose administration with the results of ten metabolically normal adult humans. They had discovered that plasma insulin responses shown a significant difference: oral glucose resulted in a significant and sustained rise, whereas intravenous glucose was associated with a smaller and transient increase. The plasma insulin increase with intravenous glucose is due to the effect of hyperglycemia on insulin secretion. The greater and more sustained increase in plasma insulin with oral glucose due to an additional stimulus to insulin secretion, possibly a gastrointestinal or liver factor triggered by alimentary glucose. Similar observations were also observed by Franckson et. al [50], Hales et al. [51] and Vallance-Owen [52].

The Figure 1.5 from Elrick et al [45] shows the mean blood glucose throughout the 2-hour study period for two routes of glucose administration plotted as values above the fasting level. During the first hour, the glucose levels with the intravenous glucose averaged 14.8mg/dl higher than with oral glucose. During the second hour, the glucose concentrations averaged 7.6mg/dl higher with the oral glucose. In the combined 2-hour study period, the mean blood glucose difference between the two routes of glucose administration was 4.1 mg/dl (intravenous higher then oral).

![Figure 1.5 Blood glucose response to oral and intravenous glucose [45]. Each point is the mean value (for 10 patients) above the fasting level during and following a 60-min constant infusion of glucose.](image-url)
The Figure 1.6 is a plot of the mean plasma insulin levels at each time interval for the two routes of glucose administration plotted as values above the fasting level. During the first hour, there was a significant rise in plasma insulin with both oral and intravenous glucose. The mean increase with oral glucose was about $2/3$ greater than that with intravenous.

**Figure 1.6** Plasma insulin responses to oral and intravenous glucose [45]. Each point is the mean value (for 10 patients) above the fasting level during and following a 60-min constant infusion of glucose.

Solomon and Rosalyn [53] have investigated into the glucose and insulin responses of about 200 nondiabetic subjects and untreated nonketotic diabetic patients in various categories according to weight and degree of impairment of glucose tolerance. Both obesity and impairment of glucose tolerance are associated with higher than normal plasma insulin curves following glucose administration as shown in the Figure 1.7. The classifications are very similar what we had discussed earlier by Tables 1.1 and 1.2.
Figure 1.7 Blood glucose and plasma insulin concentrations in the fasting state and following oral administration of glucose in adult subjects [53]. Criteria employed: Non-diabetic peak <160 mg/dl and 2-hour glucose < 120 mg/dl; frank diabetes peak glucose > 180 mg/dl and 2-hour glucose > 120 mg/dl; impaired glucose tolerance – glucose curves not satisfying either of above criteria.

Because OGTT exhibits more responsive insulin responses after a bolus of glucose administered orally, we have selected OGTT modeling in our work [2, 10, 30, 31]. We will elaborate the details in the later part of this thesis.
1.3.4 OGTT Kinetic Modeling

1.3.4.1 Bolie Model

Bolie [1] has formulated a glucose-insulin feedback theory for the purpose of determining which physiological sensitivity coefficients dominate the mathematical characteristics of normal insulin and glucose tolerance curves. The mathematical model consists of coefficients for the insulin and glucose responses of liver, pancreas and peripheral tissues.

The applicability of Bolie’s model has been justified by numerous medical publications [54-59]. The model has focused on the functions of major organs such as liver, pancreas and peripheral tissues acting through a single compartmental system. The model has been simplified to omit the actions of the kidneys and does not account for intravascular-extravascular differences in concentrations of insulin and glucose. As a result, the model has been the following limitations [1]:

(a) glucose fluctuations outside the range of about 150 mg/dl;
(b) rapid phenomena requiring gradations of time finer than 5-minute intervals;
and
(c) slow phenomena requiring time spans of more than 5-hour.

\[
\begin{align*}
\dot{x} &= p(t) - \alpha x + \beta y \\
\dot{y} &= q(t) - \gamma x - \delta y
\end{align*}
\]

(1) (2)

where \(x\): blood insulin concentration (from its fasting level) in \(U/l\), \(y\): blood glucose concentration (from its fasting level) in \(g/l\), \(p\): insulin input-rate in \(U/hr/l\), \(q\): glucose input-rate in \(g/hr/l\), for unit blood-glucose compartment volume \((V)\) in \(l\), where \(\dot{x}, \dot{y}\) denote the first-derivatives of \(x\) and \(y\) with respect to time. In these equations, the Glucose-Insulin model system parameters (regulatory coefficients) are \(\alpha, \beta, \gamma, \delta\).

\(\alpha\): represents pancreatic insulin sensitivity to insulin in \((hr)^{-1}\)
\[ \beta : \text{pancreatic insulin sensitivity to elevated glucose blood concentrations in (Units)} \]
\[ (\text{hr})^{-1}(\text{gms})^{-1} \]
\[ \gamma : \text{liver glycogen storage to elevated blood-glucose concentrations in (gms)(hr)}^{-1} \]
\[ (\text{Units})^{-1} \]
\[ \delta : \text{tissue glucose utilisation to elevated blood-glucose concentrations in (hr)}^{-1} \]

The experimental data by Bolie [1] shows that these physiological coefficients approximate the critical-damping criteria of servomechanism theory.

During his time, Bolie has no access to powerful digital computer which has perform iterative numerical calculations for convergence when calculating the regulatory coefficients (\(\alpha, \beta, \gamma, \delta\)). As a result, his work is mainly focused on critical damping response. In this thesis, our work [2, 10, 30, 31] explores the underdamp and overdamp responses as well as critical damping. We have adapted Bolie’s model into our multi-compartmental model which includes gastrointestinal and blood pool responses which we will elaborate in details later.

1.3.4.2 Ackerman Model

Ackerman et al [46] have derived a simplified block diagram the response of the body to added glucose as depicted in figure 1. Emphasis has been given to two variables; the blood-glucose concentration, \(G\), and the blood-insulin concentration, \(H\), both of which will vary as functions of time.
Figure 1.8 Block-diagram representation of feedback loop involved in glucose tolerance test. Question marks indicate uncertain reactions. Diagram is vastly oversimplified in that there is a different rate of metabolic utilization of glucose for each tissue [46].

From Figure 1.8, we can observe that organs and tissues are interlocked in a feedback loop. As a result, the system can oscillate. Ackerman et al.’s contains 16 physiological parameters, a few of which are uncertain. However, this number 16 is a minimum since one should indicate, for example, a different rate of glucose utilization in each tissue and also the roles of other hormones and of the nervous system. The model is also oversimplified in that it fails to take explicit account the role of the adrenal cortical and medullary function in glucose economy and of the portable heterogeneity of pancreatic insulin.

Ackerman et al [46] have shown that the natural period measured can be used to distinguish diabetics, non-diabetic and normal-diabetic. But they only used one equation for all cases:
\[ G = G_0 + Ae^{-\alpha t} \sin \omega t \]

where \( G_0 \): Fasting blood glucose concentration
\( \alpha \): independent removal rates of glucose and insulin
\( A \): Underdamped amplitude
\( \omega \): \( \omega^2 = \omega_0^2 - \alpha^2 \); \( \omega_0 \) system natural frequency; and
\( \omega \): system damped frequency

The following Figures 1.9 to 1.11 show three types of curves that they have encountered. The curves are the best least-squares fit to the glucose concentrations in the blood. The Figure 1.9 is a physiologically normal one, and has constants that are slightly altered by deleting points at 30 and 90 minutes.

![Glucose tolerance test with fitted curve](image)

**Figure 1.9** A normal glucose-tolerance curve (example A of Table 2). Points show measured values, whereas solid curve shows computed best fit [46].

The curve in Figure 1.10 is a typical abnormal one which also be only slightly altered by adding points 30 and 90 minutes.
Figure 1.10 An abnormal glucose-tolerance curve (example C of Table 2). Note high, slow response [46].

The Figure 1.11 is a typical clinically normal subject response. It has normal $\omega_0^2$, but it differs from the earlier normal curve in that the damping factor is and the free frequency is very small. This type of curve as shown would be drastically misinterpreted by the author’s curve-fitting routine if the 30-minute point were omitted.
Figure 1.11 A normal glucose-tolerance curve (example B of Table 2). Note difference between this critically damped curve and the more usual normal curve of Figure 1.9 [46].

Table 1.3 Glucose-tolerance test. Curves fitted by formula \( G = G_0 + Ae^{-\omega t} \sin \omega t \) [78].

<table>
<thead>
<tr>
<th>Example</th>
<th>( G_0 ) mg/100 ml</th>
<th>( A ) mg/100 ml</th>
<th>( \alpha ) min(^{-1}) ( \times 10^3 )</th>
<th>( \omega ) min(^{-1}) ( \times 10^3 )</th>
<th>( \omega_0^2 ) min(^{-2}) ( \times 10^3 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>67.8</td>
<td>100</td>
<td>13.9</td>
<td>41.5</td>
<td>1.92</td>
</tr>
<tr>
<td>B</td>
<td>78.7</td>
<td>1606</td>
<td>49.0</td>
<td>5.83</td>
<td>2.44</td>
</tr>
<tr>
<td>C</td>
<td>86.4</td>
<td>205</td>
<td>4.82</td>
<td>16.7</td>
<td>0.302</td>
</tr>
</tbody>
</table>

Ackerman et al. emphasize the importance of the choice of \( \omega_0 \) rather than \( \omega \) or \( \alpha \) as the single most significant parameter in distinguishing health from disease. In order for a curve to be diagnosed as ‘abnormal’ on the criterion of low \( \omega_0 \), it is necessary that both \( \omega \) and \( \alpha \) have low values. Our work [10, 30] have also the similar observations which we will describe in details later.
The response as shown in the Figure 1.11, is referred as ‘critically damping’ by Bolie [1]. In their works [78, 79], they have concluded that more than half of the normal curves and all of their abnormal subjects are ‘underdamp’. Ackerman et al. have reinforced their results for critically damped subjects in [79]. In our work [41, 61], we have discovered that some subjects who classified as normal were in fact at-risk (critically damped) and some classified as diabetic clinically damped were at-risk; while some classified as normal were diabetic.

1.3.4.3 Glucose Clamp Model

During the 70’s, there were several new techniques had been introduced to quantify the influence of decreased peripheral insulin sensitivity on the impairment of the patient’s ability to tolerate a standard glucose load. These techniques allow for observation of the relationship between insulin and glucose utilization under conditions, in which the usual effect of glucose on the $\beta$-cells is prevented. This interaction is prevented either by suppression of insulin release by a combined infusion of glucose, epinephrine, and propranolol (“pancreatic Suppression Test” (PST)) [60-62] or by manual stabilization of the blood glucose concentration by variable “glucose-clamp” [3, 62].

The maintenance of blood sugar in man is a complex process involving feedback control of insulin on glucose and of glucose on insulin. For example, insulin administration to a person in a postabsorptive state produces hypoglycemia which is followed by counterregulatory mechanisms aimed at raising the decreased blood glucose but which may also affect the secretion of insulin itself. By use of the glucose clamp technique [74-75], the blood glucose concentration is maintained by a feedback-controlled glucose infusion after administration of physiologic amounts of insulin, thus preventing the appearance of such counterregulatory variables. The glucose infused to maintain a constant blood glucose is a measure of glucose utilization under such conditions.

Insulin is also known to inhibit endogenous glucose productions in experimental animals and in man [63-73]. This effect supplements increased peripheral glucose utilization in causing blood glucose concentration to fall.
Analysis of isotope kinetic data involving a combination of tracer and tracee (cold) glucose experiments allows the development of a formal mathematical model in which the various metabolic factors can be imbedded and studied. A number of glucose models have been described so far; include feedback control of insulin on glucose [76-81]. These models did not isolate the individual controls but rather combined the entire system into a simplified glucose-insulin feedback system. By maintaining a constant blood glucose concentration, Insel et al. [34] have disrupted the feedback loop and were able to study isolated subsystem.

**Figure 1.12** The three-compartment basal glucose model with the mean population values for masses and exchange constants (n=6). Rate constants are in units/min; mean±SD. [3]

Analyses of the control of glucose metabolism by insulin have been hampered by changes in blood glucose concentration induced by insulin administration with resultant activation of hypoglycemic counter regulatory mechanisms. To eliminate such mechanism, Insel et al. [3] have employed the glucose clamp technique which allows maintenance of fasting blood glucose concentration during and after the administration of insulin.

Glucose clamp involves $[^{14}\text{C} ]$ glucose administered during a glucose clamp experiment. The analysis permitted Insel et al. [3] to define a three-compartment glucose model to describe the control of insulin on glucose utilization, to quantify changes in endogenous glucose production induced by changes in insulin.
Pancreatic Suppression Test (PST) [60-62] and glucose-clamp techniques [3] have complicated technical problems for the estimation of insulin resistance. Thus we will not pursue further for our work.

1.3.4.4 Minimal Model by Bergman

Bergman et al. [4] has derived a set of seven mathematical models of glucose disappearance to estimate insulin sensitivity. Glucose was injected into subjects and the measured time course of insulin was regarded as “input”, and the falling glucose concentration as “output” of the physiological system storing and using glucose. The seven mathematical models of glucose uptake were compared to identify the representation most capable of simulating glucose disappearance in Table 3.

The model structure, $G$ is the measured plasma glucose concentration; $G_x$ is concentration in a compartment different from plasma; $i$ is the deviation from basal value of actual plasma insulin concentration $I$; $\dot{i}$ is the deviation of insulin concentration $\dot{I}$ in a compartment remote from plasma; $P_L$ is glucose liver production; the $k$’s represent either fractional turnover rates or control actions; $V$ is the glucose space; $V_m$, $K_m$ are Michaelis-Menten parameters.
Figure 1.13 Three proposed insulin-independent models of glucose metabolism. Left panel: proposed structure; middle panel: mathematical representation when parameters are defined as shown on the right panel. Values of $k$ represent fractional turnover rates (min$^{-1}$); $P$, hepatic glucose production; $V$, glucose space, and $V_{\text{max}}$ and $K_m$, Michaelis-Menten parameters. $G(0)$ is glucose concentration that would obtain immediately after injection assuming no dynamics of mixing in glucose space [4].
Figure 1.14 Four proposed insulin-dependent models of glucose metabolism. $I(t)$, time course of plasma insulin supplied to model; $I'$, concentration of insulin in a compartment remote from plasma. $B_0$, extrapolated hepatic glucose production at 0 glucose concentration [4].

1.3.4.4.1 Model I

It is assumed in this model that glucose production is constant, that glucose distributes in a single compartment, and that the rate of glucose utilization is a linear function of plasma glucose concentration. The parameter $k_i$ in this model (Figure 1.13) represents the classical diagnostic glucose disappearance term KG, which is obtained from a semilogarithmic plot of glucose disappearance kinetics. The success of this model is therefore related to the acceptability of KG as a measure of the
glucose disappearance rate. The equation of this model is thus

\[
\frac{dG}{dt} = p_1 G + p_2, \quad G(0) = G_{ss}
\]

where \( G(0) = G_{ss} \), \( p_1 = k_1 \) and \( p_2 = p_L \).

1.3.4.4.2 Model II

This model is identical to model I except that glucose utilization is a saturable process that obeys Michaelis-Menten kinetics and depends on the plasma glucose concentration:

\[
\frac{dG}{dt} = \frac{p_1 G}{p_2 + G} + p_3,
\]

where \( p_1 = \frac{-V_m}{V} \), \( p_2 = K_m \), and \( p_3 = p_L \).

1.3.4.4.3 Model III

The third model assumes that glucose distribution is represented by two compartments. Disappearance from either compartment is linearly dependent on glucose concentration in that compartment. Glucose production is constant. Multicompartamental glucose distribution has been widely suggested.

\[
\frac{dG}{dt} = p_1 G + p_2 X + p_3, \quad G(0) = G_{ss}
\]

\[
\frac{dX}{dt} = G + p_4 X, \quad X(0) = 0
\]

where \( X = \frac{G_2}{k_1} \), \( p_1 = -(k_1 + k_3) \), \( p_2 = k_1 k_2 \), \( p_3 = p_L \), and \( p_4 = -(k_2 + k_4) \).
1.3.4.4.4 Model IV

Glucose disappearance in this model is linearly dependent on both the plasma glucose and insulin concentrations. Glucose distributes in a single compartment, and the production is assumed constant. The relationships among insulin, glucose, and glucose disappearance used in this model were first proposed by Bolie [1] and have been assumed in a substantial fraction of those studies that have used system (model) identification to analyze glucose kinetics for clinical purposes e.g. Ackerman [38] and Segre et al. [76]. The extent of the success of model IV to account for disappearance relates to the potential applicability of the Bolie model [1] (and its descendants) for purposes of diagnosis.

\[
\frac{dG}{dt} = p_1 G + p_2 I + p_3, \quad G(0) = G_{ss}
\]

where \( p_1 = -k_1, p_2 = -k_2, \) and \( p_3 = p_L. \)

1.3.4.4.5 Model V

This model assumes that glucose uptake is directly dependent on the concentration of insulin, not in plasma but in a second compartment of insulin distribution remote from plasma. This proposition is based on the studies of Sherwin et al. [75] and is consistent with the existence of a remote receptor compartment that is intimately involved in the action of insulin, Zeleznik and Roth [82]. In this model insulin enters the remote compartment, concentration \( I' \), and it is this which increases glucose disappearance independent of insulin, and glucose production is constant.

\[
\frac{dG}{dt} = p_1 G + p_2 I + p_3, \quad G(0) = G_{ss}
\]

\[
\frac{dX}{dt} = p_4 X + i, \quad X(0) = 0
\]
In models I-V, glucose production is assumed to be constant at all times. Because it has long known that insulin inhibits glucose production, model VI and VII are introduced in which this interaction is included. Two approaches are used. In model VI, glucose production and hepatic glucose uptake are lumped together as net hepatic glucose balance. In model VII an alternative approach is used; that is hepatic and peripheral glucose utilization are lumped together, and absolute glucose production is represented explicitly.

1.3.4.4.6 Model VI

In this model the rate of change of glucose is the difference between the net hepatic glucose balance $B$ (which may take on positive (production) or negative (uptake) values), and the disappearance of glucose into peripheral tissues only ($U_p$). It has previously been shown that hepatic glucose balance varies according to a relation of the form [4].

\[
B = B_0 - \left( k_5 - k_i \dot{i} \right) G
\]

where $B$ is the net hepatic glucose balance; and $B_0$ is the value expected when plasma glucose concentration is extrapolated to zero. It is assumed that the insulin acts from a remote compartment, as in model V.

For glucose utilization we may write a similar expression

\[
U_p = \left( k_1 + k_i \dot{i} \right) G
\]

where $X = (k_4 + k_6) \dot{i}$, $p_1 = -(k_1 + k_3)$, $p_2 = -k_3$, $p_3 = k_2 (k_4 + k_6)$, and $p_4 = B_0$. 

\[
X = \frac{\dot{i}}{k_2}, \quad p_1 = -k_1, \quad p_2 = -k_2 k_4, \quad p_3 = p_4 = -k_3, \quad i = I - I_{ss}, \quad \text{and} \quad \dot{i} = I - I_{ss}.
\]
1.3.4.7 Model VII

In this model “absolute” hepatic glucose production and its inhibition by remote insulin are explicitly represented. Utilization (which, in this case, includes hepatic and peripheral) is described by a similar nonlinear function as in model VI.

\[
\frac{dG}{dt} = (p_1 + p_2X)G + \frac{p_5}{1 + p_4X^*}, \quad G(0) = G_w
\]

\[
\frac{dX}{dt} = p_3X + i, \quad X(0) = 0
\]

where \( X = \frac{i}{k_2} \), \( p_1 = -k_1 \), \( p_2 = -k_2k_4 \), \( p_3 = \frac{P_i}{k_5} \), \( p_4 = \frac{k_2}{k_5} \) and \( p_5 = -k_3 \).

Initial conditions in all models are related to basal values of glucose and insulin concentrations. The rapid glucose intravenous injection is treated as an impulsive input function [in all models a parameter \( G(0^+) \) can also be defined, that is, the glucose concentration that would obtain immediately after the injection assuming no dynamics of mixing in the glucose space]. In models IV-VII the measured time course of insulin was supplied as a model input.
Table 1.4 Summary of Minimal Model selections and behaviours.

<table>
<thead>
<tr>
<th>Model</th>
<th>Theoretical Identifiably</th>
<th>Practical Identifiably</th>
<th>Statistics Of Residual Errors</th>
<th>Goodness of Fit and Number of Parameters</th>
<th>Acceptance on the Basics of Identification Results</th>
<th>Overall Physiological Plausibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Uniquely Identifiable</td>
<td>Unacceptable</td>
<td>Acceptable</td>
<td>Unacceptable</td>
<td>No</td>
<td>Not considered</td>
</tr>
<tr>
<td>II</td>
<td>Uniquely Identifiable</td>
<td>Unacceptable</td>
<td>Unacceptable</td>
<td>Not considered</td>
<td>No</td>
<td>Not considered</td>
</tr>
<tr>
<td>III</td>
<td>Uniquely Identifiable</td>
<td>Unacceptable</td>
<td>Unacceptable</td>
<td>Not considered</td>
<td>No</td>
<td>Not considered</td>
</tr>
<tr>
<td>IV</td>
<td>Uniquely Identifiable</td>
<td>Unacceptable</td>
<td>Unacceptable</td>
<td>Not considered</td>
<td>No</td>
<td>Not considered</td>
</tr>
<tr>
<td>V</td>
<td>Uniquely Identifiable</td>
<td>Acceptable</td>
<td>Acceptable</td>
<td>Acceptable</td>
<td>Yes</td>
<td>Marginally acceptable</td>
</tr>
<tr>
<td>VI</td>
<td>Uniquely Identifiable</td>
<td>Acceptable</td>
<td>Acceptable</td>
<td>Acceptable</td>
<td>Yes</td>
<td>Acceptable</td>
</tr>
<tr>
<td>VII</td>
<td>Identifiable</td>
<td>Unacceptable</td>
<td>Unacceptable</td>
<td>Not considered</td>
<td>No</td>
<td>Not considered</td>
</tr>
</tbody>
</table>
The works and results of Bergman et al. [4] are summarized; the results are shown in Table 1.4. From the table, only models V and VI appear to be acceptable in being able to describe the experimental data set with the smallest set of identifiable and feasible parameters. They have been compared from a physiological point of view: model VI includes insulin inhibition of liver glucose production (represented as net hepatic glucose balance), whereas model V assumes constant production. Model VI was therefore selected as it is more consistent with known physiology on glucose metabolism. Implicit assumption in the chosen model are that:

(a) glucose distributes into a single well-mixed compartment, and
(b) the disappearance of glucose and the net rate of hepatic glucose appearance are nonlinear functions of plasma glucose and insulin in a compartment remote from plasma.

Bergman et al. [4] have discussed the failure of model IV, which represents the glucose portion of the model first introduced by Bolie [1] to analyze glucose tolerance tests for clinical purposes. The failure is as a result of the poor parameters identification and fitting. Prof Dhanjoo Ghista has adopted and improved the works of Bolie [1] and model VI by Bergman et al. [4] to form a new model for our continual research work [2, 10, 30]. Numerous simulations have been done to verify the new model and non-dimensional indices were derived based on the identified system parameters for glucose and insulin responses from clinical data collected by OGTT. We will discuss the details later in the chapter.

1.3.5 Reproducibility

[35] has reported that changes in glucose tolerance may occur if a glucose tolerance test is repeated more than once in 5 days. [47] suggests, however, that the occurrence of such changes is restricted to the day following a glucose tolerance test.

Loh KM et al. [2, 10, 30, 31] have tested the reproducibility of the system models by performing simulations with clinical data. The derived non-dimensional indices NDIs have shown convergence and reproductivity discussed by Loh KM and Prof Dhanjoo
Ghista [30].

Our work’s parameters were chosen for quality reflect the key medical attributes of the patient response (fitting process with very high R-Square (>95%) and low SSE (<<5%)).

1.3.6 Fitting Results

Displays detailed results for the current fit including the fit type (model, spline, or interpolant), the fitted coefficients and 95% confidence bounds for parametric fits, and these goodness of fit statistics:

SSE -- The sum of squares due to error. This statistic measures the deviation of the responses from the fitted values of the responses. A value closer to 0 indicates a better fit.

R-square -- The coefficient of multiple determinations. This statistic measures how successful the fit is in explaining the variation of the data. A value closer to 1 indicates a better fit.

1.3.7 The Oral Glucose Tolerance Testing Protocol Adopted

The test subjects need to fast for 12 hours before the test and during the 2-hour test. A blood sample of the subject is taken before the beginning of the test. After the subject drinks a 75 g of glucose solution dissolved in 250 mL to 300 mL of water, the subject’s blood glucose and insulin concentrations are measured at specified intervals of 30 minutes, 60 minutes, 90 minutes and 120 minutes.
1.3.7.1 Qualitative interpretation of the results, for preliminary categorisation of the patients:

(a) Blood glucose normal values [11, 12, 26, 42]:
   - fasting: 70 to 115 mg/dL,
   - 30 min: less than 200 mg/dL,
   - 1 hour: less than 200 mg/dL,
   - 2 hours: less than 140 mg/dL.

Normal insulin level (reference range): 1 to 30 mU/L [11, 12, 26, 42]:

(b) Impaired Glucose Regulation:
   When a person has a fasting glucose equal to or greater than 110 mg/dL and less than 126 mg/dL, it is considered as **impaired fasting glucose**. This is considered as a risk factor for diabetes and will likely trigger another test in the future, but by itself does not provide sufficient evidence for the diagnosis of diabetes.

A person is said to have **impaired glucose tolerance** when the 2-hour glucose results from the oral glucose tolerance test are greater than or equal to 140 mg/dL but less than 200 mg/dL. This is also considered a risk factor for future diabetes. A person is deemed to be diabetic when the oral glucose tolerance tests show that the blood glucose level at 2 hours is equal to or more than 200 mg/dL. This must be confirmed by a second test on another day.
1.3.7.2 Test Results [2, 10, 30-32]
In Tables 1.5 and 1.6 we have classified the subjects, based on the above stated criteria.

**Table 1.5 Subjects Classified as Normal Clinically.**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex/Age</th>
<th>Fasting</th>
<th>15 min</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
<th>120 min</th>
<th>Fasting</th>
<th>15 min</th>
<th>30 min</th>
<th>60 min</th>
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</tr>
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<tbody>
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<td>87</td>
<td>N/A</td>
<td>144</td>
<td>123</td>
<td>123</td>
<td>117</td>
<td>0.93</td>
<td>NA</td>
<td>13</td>
<td>7.84</td>
<td>9.43</td>
<td>9.31</td>
</tr>
<tr>
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<td>M/22</td>
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<td>152</td>
<td>80</td>
<td>83</td>
<td>84</td>
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<td>NA</td>
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<td>3.18</td>
</tr>
<tr>
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<td>96</td>
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<td>0.99</td>
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<td>11.9</td>
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<td>12.7</td>
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</table>
Table 1.6 Subjects Classified as Diabetic Clinically [2, 10, 30-32].

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex/Age</th>
<th>Blood Glucose Level (mg/dL)</th>
<th>Insulin (mU/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Fasting 15 min 30 min 60 min 90 min 120 min</td>
<td>Fasting 15 min 30 min 60 min 90 min 120 min</td>
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<td>D01</td>
<td>F/67</td>
<td>114 N/A 258 317 349 334</td>
<td>1.67 N/A 3.82 5.7 7.96 2.37</td>
</tr>
<tr>
<td>D02</td>
<td>M/38</td>
<td>132 N/A 224 225 213 140</td>
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</tr>
<tr>
<td>D03</td>
<td>M/51</td>
<td>110 N/A 201 189 176 107</td>
<td>0.55 N/A 5.81 7.97 14.9 5.77</td>
</tr>
<tr>
<td>D04</td>
<td>M/58</td>
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<td>1.25 N/A 1.9 1.83 2.4 1.42</td>
</tr>
<tr>
<td>D05</td>
<td>M/51</td>
<td>86 N/A 215 237 186 92</td>
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</tr>
<tr>
<td>D06</td>
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</tr>
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</tr>
<tr>
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</tr>
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<tr>
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<td>M/45</td>
<td>113 N/A 173 180 154 151</td>
<td>1.24 N/A 11.5 17 14.1 26.9</td>
</tr>
<tr>
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<td>M/55</td>
<td>122 N/A 213 238 222 189</td>
<td>0.99 N/A 7.53 9.15 12.8 9.45</td>
</tr>
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<td>1.2 N/A 8.12 11.9 5.34 14</td>
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<tr>
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<tr>
<td>D20</td>
<td>M/58</td>
<td>173</td>
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</table>
1.4 Author’s Work of Systems Engineering View of OGTT Blood Glucose & Insulin Responses

When a glucose bolus is administered to a normal person, typical blood glucose and insulin concentration-time profiles are illustrated in Figure 1.15, and can be regarded to be under-damped responses [10, 30]. However, when a glucose bolus is administered to a typical diabetic patient, the blood glucose and insulin concentration-time profiles (illustrated in Figure 1.16) appear to be over-damped.

![Figure 1.15](image)

**Figure 1.15** *When glucose bolus is administered to a normal person, a typical response of blood glucose and insulin correlation (normalised).*
Figure 1.16 When glucose bolus is administered to a diabetic patient, a typical response of blood glucose and insulin correlation (normalized).

Comparing figures 1.15 and 1.16 [1-3, 10, 30], we note that a normal person’s glucose response is such that the blood-glucose concentration (normalised with respect to the fasting or initial value) peaks at levels of up to 1.06 g/L, and is back to 0 g/L by the end of 2 hours. Likewise, the response curve for blood-insulin (normalised with respect to fasting blood-insulin concentration) can peak up to 0.2 U/l and should return to 0 U/L at the end of 2-hour. On the other hand for this typically diabetic patient, the blood-glucose concentration is peaking at 2.28 g/L, and falls to only 2.20 g/L by the end of 2 hours. The blood insulin curve peaks at 0.04 U/L at the end of 2 hours, and remains at this level.

The advantage in plotting the responses in the form of curves is that it enables us to quantify the clinical criteria in the form of the nature (and parameters) of the response curve (i.e., under-damped or over-damped). There are patients who do not fall into either clinical category. Their response curves can place them into a critically damped domain, whereby they are neither normal nor diabetic but at risk of becoming
diabetic. Even more relevantly, we can combine the parameters into a nondimensional index.

There are many works on modeling of glucose-insulin dynamic and regulation [1-3, 5-10, 30]. However, this paper is specifically oriented to modeling the glucose and insulin responses to ingested glucose bolus for OGTT. Herein, the glucose concentration-time data is simulated by an appropriate type of solution (under- or over- or critically damped) of the governing differential equations for glucose and insulin responses to glucose bolus ingestion. The diagnosis of the patient (as normal, at risk of being diabetic, as borderline diabetic, as diabetic) depends on the solution category into the clinical data fall.

This chapter uses 3 equations from the author’s work [10, 30]. Each set of equations for each system response and \( y(t) \) for glucose and \( x(t) \) for insulin responses (the derivations are shown in section 1.4.1.2):

\[
y(t) = \left(\frac{G}{\omega}\right) e^{-At} \sin \omega t \quad \text{(underdamp : non-diabetic)}
\]

\[
x(t) = \frac{-(\sin(wt)Ae^{-(-At)}) - \sin(wt)ae^{(-At)} - e^{(-at)}w + \cos(wt)e^{(-At)}w\beta G}{A^2 - 2Ax + \alpha^2 + w^2}
\]

\[
y(t) = \frac{G}{\omega} e^{-At} \sinh wt \quad \text{(overdamp : diabetic)}
\]

\[
x(t) = \frac{\left(\frac{1}{2}(\cosh(wt + At - at)A + \sinh(-wt + At - at)A - \cosh(-wt + At - at)A - 
\sinh(wt + At - at)A + \sinh(wt - At - at)w - \cosh(wt + At - at)w - 
\sinh(-wt - At - at)A + \sinh(wt - At - at)A - \cosh(wt + At - at)A - 
\cosh(wt - At - at)w + \sinh(-wt + At - at)A + \sinh(wt + At - at)w)e^{(-at)}\beta G}{(-w^2 + A^2 - 2Ax + \alpha^2)}
\]

\[
y(t) = Ge^{-At} \quad \text{(critically damp : at the rim of becoming diabetic)}
\]

\[
x(t) = \frac{-\beta G(tAe^{(-At)} - t\alpha e^{(-At)} + e^{(-at)} - e^{(-at)})}{(A - \alpha)^2}
\]
In the author’s published paper [10, 30], each set of clinical data is analyzed by the above 3 equations to determine the class of system response based on the best fit result. All the clinical data sets are collected and analyzed by a qualified clinician concurrently. The models are tested for reproducibility using about 37 sets of clinical data. The results are verified against the clinician’s diagnosis. None of the points were removed. All the data points were crucial.

All the clinical data is normalized by the respective fasting values. Normalization helps improve the accuracy of subsequent numeric computations. All the glucose & insulin parameters \((a, \beta, \gamma \& \delta)\) to determine the actual physiological performance of the system. The best fit results of individual determines the class of response.

Both the blood glucose and insulin responses are analyzed simultaneously. From our work it is very crucial to know both the glucose and insulin responses simultaneously to be certain if the patient has been diagnosed correctly. The worst scenario will be a at-risk case be wrong classified as non-diabetic \(\rightarrow\) no pre-emptive treatment can be done. The models applied in this paper can help to reduce the risk.

We do not used segmented equation as published in [33, 46-47] as a result, we do need predetermined ranges and hence we do not have discontinuities. The system is modeled continuously. We have studiess 37 subjects aged range from 19 to 67 years old, all 3 classes of responses were studied in detail. Both glucose and insulin were studies simultaneously. How the physiological system responses to the orally ingested bolus of glucose were monitored closely for 2 hours at 30 minutes intervals. In all cases, we have accurately diagnosed the heath conditions of the patients. The accuracy of diagnosis is contributed by both the glucose and insulin responses being analyzed simultaneously.
1.4.1 Differential equation model of the Glucose-Insulin System

The compartmental block diagram of the Blood Glucose & Insulin Regulatory System (BGIRS) [1-3] is illustrated in figure 1.17. The glucose input-rate into the blood-pool is represented by ‘q’ in the figure. From the blood-pool, glucose is metabolised into the tissues in two ways, as represented by the two terms δy (removal-rate of glucose from the blood-pool independent of insulin) and γx (removal-rate of glucose under the influence of insulin). In return, the glucose influences the release-rate of insulin into the blood-pool by the pancreas, as represented by the term βy. The insulin is also removed independently of glucose, as per the term αx.

1.4.1.1 Modeling of Glucose-Insulin Regulation of Oral Glucose Tolerance Test (OGTT)

We will adopt the linearised bio-mathematical model of Bolie [1], as the basis of our modelling, because it is simple but still compatible with the known physiological mechanisms. This model characterizes the Glucose - Insulin system by means of the differential equations (given below as equations 1& 2) with four parameters: α, β, γ and δ, representing pancreatic insulin sensitivity to insulin and glucose blood concentrations, tissue glycogen storage and tissue glucose utilization to elevated blood-glucose concentrations.
Figure 1.17 Blood Glucose-Insulin Control System (BGIRS). Block diagram of (i) insulin level & rate-of-change of insulin $x(t)$ governs blood-glucose concentration $y(t)$, and (ii) rate-of-change of glucose $y(t)$ is influenced by insulin concentration $x(t)$ & ingested glucose input rate $q(t)$.

The above block diagram [1, 3] of how (i) Insulin level and rate of change of insulin governs blood-glucose concentration $y(t)$, and (ii) rate-of-change of glucose is influenced by insulin concentration $x(t)$ and injected glucose input rate $q(t)$.

$\alpha$: represents pancreatic insulin sensitivity to insulin in (hr)$^{-1}$
\[\beta: \text{pancreatic insulin sensitivity to elevated glucose blood concentrations in (Units)} \]
\[(\text{hr})^{-1}(	ext{gms})^{-1}\]
\[\gamma: \text{liver glycogen storage to elevated blood-glucose concentrations in (gms)(hr)}^{-1}\]
\[(\text{Units})^{-1}\]
\[\delta: \text{tissue glucose utilisation to elevated blood-glucose concentrations in (hr)}^{-1}\]

1.4.1.2 The Governing Differential equations for Glucose and Insulin Systems

By considering the conservation-rates of glucose and insulin in their respective compartments, we obtain the basic equations, governing BGIRS. With reference to the Blood Glucose-Insulin Control System (depicted in figure 1.17), the corresponding first-order differential - equations of the insulin and glucose regulatory sub-systems are given by [32, 34, 35]:

\[\dot{x} = p(t) - \alpha x + \beta y \quad (1)\]
\[\dot{y} = q(t) - \gamma x - \delta y \quad (2)\]

where \(x\): blood insulin concentration (from its fasting level), \(y\): blood glucose concentration (from its fasting level), \(p\): insulin input-rate, \(q\): glucose input-rate, for unit blood-glucose compartment volume(\(V\)), where \(x', y'\) denote the first-derivatives of \(x\) and \(y\) with respect to time. In these equations, the Glucose-Insulin model system parameters (regulatory coefficients) are \(\alpha, \beta, \gamma, \delta\).

From equations (1) & (2), we obtain the differential-equation model (for glucose-concentration \((y)\) and insulin-concentration \((x)\), for insulin infusion rate \(p=0\) and glucose inflow rate \((q)\). For glucose response, we obtain:

Differentiating equation (2) on either side with respect to ‘\(t\)’, we get:
\[ y = q - \gamma x - \delta y \]

\[ = q - \gamma (-\alpha x + \beta y) - \delta y, \text{ upon substituting for } x \text{ from equation (1)} \]

\[ = q + \alpha (\gamma x) - \beta y - \delta y \]

\[ = q + \alpha (q - \delta y - y') - \beta y - \delta y, \text{ upon substituting for } (\gamma x)\text{ from equation (2)} \]

\[ = q + \alpha q - y(\alpha + \delta) - y(\alpha \delta + \beta \gamma) \]

Rearranging we get the Differential equation:

\[ ^\cdot y + y(\alpha + \delta) + y(\alpha \delta + \beta \gamma) = q + \alpha q \quad (3) \]

wherein \(^\cdot y\) & \( ^\cdot\cdot y\) denote first & second time derivatives of \( y \).

Differentiating equation (1) on both sides with respect to ‘t’, we get

\[ x = -\alpha x + \beta y, \text{ assuming } p = 0 \]

\[ = -\alpha x + \beta (q - \gamma x - \delta y), \text{ upon substituting for } y \text{ from equation (2)} \]

\[ = -\alpha x + \beta q - \beta \gamma x - \delta(\beta y) \]

\[ = -\alpha x + \beta q - \beta \gamma x - \delta(x + \alpha x), \text{ upon substituting for } \beta y \text{ from equation (1)} \]

\[ ^\cdot x + x(\alpha + \delta) + x(\alpha \delta + \beta \gamma) = \beta q \quad (4) \]

wherein \(^\cdot x\) & \( ^\cdot\cdot x\) denote first & second time derivatives of \( x \).

1.4.1.3 Laplace Transform Representation of the Governing Equations (3 & 4)

The Transfer-function (TF) corresponding to equation (3) is obtained by taking Laplace transforms on both sides (assuming the initial conditions to be zero):
\[ s^2Y(s) + sY(s) (\alpha+\delta) + Y(s) (\alpha\delta + \beta\gamma) = Q(s) (s + \alpha) \]

Thereby, we obtain (for glucose response):

\[
G(s) = Y(s)/Q(s) = \frac{(s + \alpha)}{s^2 + s(\alpha + \delta) + (\alpha\delta + \beta\gamma)} = G(s)
\] (5)

This transfer function, \( G(s) \) can be expressed in the form

\[
G(s) = Y(s)/Q(s) = \frac{(s + \alpha)}{(s + p_1)(s + p_2)}
\] (6)

and if \( p_1 + p_2 = \alpha + \delta \), and \( p_1p_2 = \alpha\delta + \beta\gamma \), and \( p_1 \) & \( p_2 \) are the roots of the quadratic equation:

\[
p^2 - (\alpha + \delta)p + (\alpha\delta + \beta\gamma) = 0
\] (7-a)

and are given by

\[
p_1 \text{ & } p_2 = \frac{(\alpha + \delta) \pm \left( (\alpha + \delta)^2 - 4(\alpha\delta + \beta\gamma) \right)^{1/2}}{2}
\] (7-b)

Let us put

\[
\alpha + \delta = 2A, \text{ & } \alpha\delta + \beta\gamma = \omega_u^2
\]
Then
\[ p_1, p_2 \]
\[ = A \pm \left( A^2 - \omega_n^2 \right)^{\frac{1}{2}} \]
\[ = A \pm \omega, \text{ if } A > \omega_n \]
\[ = A \pm i\omega, \text{ if } A < \omega_n \]  \hspace{1cm} (7-c)

and for \( A > W_n \):

\[ p_1 p_2 = A^2 - \omega^2 = \omega_n , \]

\[ p_1 + p_2 = 2A , \quad p_1 - p_2 = 2\omega , \quad \frac{A}{\omega} = \frac{p_1 + p_2}{p_1 - p_2} , \]

While \( (\alpha - \delta) = \alpha + \alpha - 2A = 2(\alpha - A) \)  \hspace{1cm} (7-d)

Then the response of the system, \( y(t) \) i.e., the solution of the differential equation (3), is obtained by taking the inverse transform of

\[ Y(s) = \frac{Q(s)(s + \alpha)}{s^2 + s(\alpha + \delta) + (\alpha\delta + \beta\gamma)} = \frac{Q(s)(s + \alpha)}{(s + p_1)(s + p_2)} \]  \hspace{1cm} (7-e)

A. Similarly from eq (4), we get for insulin response

\[ X(s)/Q(s) = \frac{\beta}{s^2 + s(\alpha + \delta) + (\alpha\delta + \beta\gamma)} \]  \hspace{1cm} (8)

In OGTT test, the glucose is administered in a single dose orally (instead of being injected into blood). In this test, a fasting person is given an oral glucose dose of 1 gm/kg, for diabetes diagnostic purpose. If the subject is normal and free from diabetes, the blood glucose level rises from the fasting value of, say, 80mg/dl to 120-140mg/dl, and then falls back to below normal in about 2 hours.
The physiology of the GI tract suggests that the intestinal glucose absorption rate is constant for a limited time duration. Hence, the glucose rectangular-pulse input \( q(t) \) into the blood pool is representative of this phenomena. This in fact is made physiologically possible by means of the combined effect of two mechanisms: (i) due to the pyloric sphincter valve-resistance which controls the transfer of glucose from the stomach to the intestines in inverse proportion to the stomach distension, and (ii) due to the active transport of glucose from the intestines into the blood (across the intestinal wall) at its maximum rate, according to Michaelis - Menten equation, graphically depicted in Figure 1.18.

![Figure 1.18](image)

**Figure 1.18** Effect of substrate and enzyme concentrations on the rate of enzyme-catalyzed reaction. The general form of Michaelis-Menten equation for active transport is:

\[
\text{Rate of Reaction} = k_1 (\text{Enzyme conc.}) (\text{substrate conc.})/(k_2 + \text{substrate conc.})
\]

When there is no glucose in blood, during hypoglycaemia (i.e., when 'y' is much below the fasting level), the active transport is carried out at its maximum rate. Thus the passive and active transports work together to maximize the intestinal glucose transport, so as to tide over the crisis of hypoglycaemia in diabetics.
The Transfer-function (TF) corresponding to equation (3) is obtained, by taking Laplace transforms on both sides (assuming the initial conditions to be zero), as:

\[ s^2 Y(s) + s Y(s)(\alpha + \delta) + Y(s)(\alpha \delta + \beta \gamma) = Q(s)(s + \alpha) \]

Thereby, we obtain (for glucose response):

\[ G(s) = \frac{Y(s)}{Q(s)} = \frac{(s + \alpha)}{s^2 + s(\alpha + \delta) + (\alpha \delta + \beta \gamma)} \]

or, \[ Y(s) = \frac{(s + \alpha)Q(s)}{s^2 + s(\alpha + \delta) + (\alpha \delta + \beta \gamma)} \] (5)

Similarly from equation (4), we get for insulin response

\[ X(s) / Q(s) = \frac{\beta}{s^2 + s(\alpha + \delta) + (\alpha \delta + \beta \gamma)} \]

or, \[ X(s) = \frac{\beta Q(s)}{s^2 + s(\alpha + \delta) + (\alpha \delta + \beta \gamma)} \] (6)

Now for OGTT simulation, we note that (i) the GI has the transfer function \(1/(s + \alpha)\), [2, 7] which is tantamount to a decay in glucose concentration (at the rate of \(\alpha\)) during its transmission through the GI tract, while \(Q(s) = G\) (amount of glucose per litre of blood-pool volume per hour) constitutes the glucose input into the blood-pool, as shown in Figure 1.19.
Hence, from equation (5), we have:

\[ Y(s) = \frac{(s + \alpha)}{s^2 + s(\alpha + \delta) + (\alpha \delta + \gamma \beta)} \times \frac{1}{(s + \alpha)} \times G \]

\[ = \frac{G}{s^2 + s(\alpha + \delta) + (\alpha \delta + \gamma \beta)} = \frac{G}{s^2 + \lambda T_d s + \lambda} \]

where \( \lambda = (\alpha \delta + \gamma \beta) \) and \( \lambda T_d = (\alpha + \delta) \)

This equation (7) can be adopted to represent the response of the blood-glucose (proportional + derivative) feedback control-system model for simulating glucose metabolism during OGTT, as illustrated by Figure 3.

Equation (7) can also be written as:

\[ Y(s) = \frac{G \text{(in gms litre}^{-1}\text{hr}^{-1})}{s^2 + 2As + \omega_n^2} \]  

(8)

where \( \omega_n = \sqrt{\lambda} \) is the natural frequency of the system; \( A \) (the attenuation or damping constant of the system) \( \lambda = 2A/T_d = \omega_n^2 \), and \( \omega = \sqrt{(\omega_n^2 - \lambda^2)} \) is the angular frequency of dampened oscillation of the system.

**1.4.1.4 Solutions to the Governing Differential Equation, for Glucose Response (\( y \)) to Glucose Bolus Ingestion [2, 10]**

Based on equation (8), the governing differential equation is
\[ y'' + 2Ay' + \omega_n^2 y = G \delta(t) \quad (9) \]

wherein \( y_0 = 0 \), \( y_0 = G \), and the damped oscillation-frequency \( \omega = (\omega_n^2 - A^2)^{1/2} \)

**Solution For Under-damped Case:**

For \( A^2 < \omega_n^2 \) or \( A^2 - \omega_n^2 < 0 \), i.e., for \( \omega_n^2 - A^2 (=\omega^2) > 0 \), we have the solution to equation (9) as:

\[ y(t) = \left( \frac{G}{\omega} \right) e^{-At} \sin \omega t \quad (10) \]

**Solution For Over-damped Case:**

For \( A^2 > \omega_n^2 \), or \( A^2 - \omega_n^2 > 0 \), we have:

\[ y(t) = \frac{G}{\omega} e^{-At} \sinh \omega t \quad (11) \]

**Solution for Critically Damped Case:**

For \( \omega = 0 \), we have:

\[ y(t) = Ge^{-At} \quad (12) \]

From the above equations, we can determine \( G, \omega, A \) for each clinical case, by making the corresponding solution (for under-damped or over-damped or critically damped) response match the clinical data, by MatLab-based parameter identification procedure.
1.4.2 Solutions to the Governing Differential Equations and for Insulin Response to Glucose Bolus Ingestion

Having developed the analysis for evaluating the model parameters \((G, w, A)\), we will now proceed to solve for the remaining parameters \(\beta, \gamma\) and \(\delta\). Then from the knowledge of \((w, A)\) and \((\beta, \gamma, \delta)\), we can also evaluate the \(\alpha\) parameter.

For underdamped response of normal subjects, we obtain from equations (1) and (10):

\[
x = -\alpha x + \beta y = -\alpha x + \beta \frac{G}{\omega} e^{-\omega t} \sin \omega t
\]

(13)

Solving equation (13), we get the corresponding insulin response as:

\[
x(t) = \frac{-(\sin(\omega t)A e^{\omega t}) - \sin(\omega t) e^{\omega t} - \cos(\omega t)\beta \frac{G}{\omega}}{A^2 - 2A\alpha + \alpha^2 + \omega^2}
\]

(14)

For over-damped response of a diabetic subject, we obtain from equations (32) and (41):

\[
x' = -\alpha x + \beta y = -\alpha x + \beta \frac{G}{w} e^{-\omega t} \sinh \omega t
\]

(15)

Solving equation (15), we get the insulin response as follows:

\[
x(t) = \frac{\left(\frac{1}{2}(\cosh(\omega t + A - \alpha t)A + \sinh(-\omega t + A - \alpha t)A - \cosh(-\omega t + A - \alpha t)A - \sinh(\omega t + A - \alpha t)A + \sinh(\omega t - A - \alpha t)\omega - \cosh(\omega t - A - \alpha t)\omega - \sinh(-\omega t - A - \alpha t)\alpha + \sinh(\omega t + A - \alpha t)\alpha - \cosh(\omega t + A - \alpha t)\alpha - \cosh(\omega t - A - \alpha t)\omega + \cosh(-\omega t + A - \alpha t)\alpha + 2\omega + \sinh(-\omega t + A - \alpha t)\omega e^{\omega t} \beta \frac{G}{\omega})\right)}{\left(-\omega^2 + A^2 - 2A\alpha + \alpha^2\right)}
\]

(16)

For a critically-damped response (of a borderline subject), we obtain the insulin
response from equations (1) and (12):

\[ x' = -\alpha x + \beta yx = -\alpha x + \beta Ge^{-\lambda t} \]  

(17)

The solution of equation (17) is given by:

\[ x(t) = \frac{-\beta G(t\lambda e^{-\lambda t}) - t\alpha e^{-\lambda t} + e^{\lambda t} - e^{(-\lambda t)}}{(A - \alpha)^2} \]  

(18)

1.4.2.1 Obtaining Solutions for All the Model Parameters

By simulating the glucose response with our \( y(t) \) solutions (of equations 10 or 11 or 12), we can evaluate the parameters \( G, A \) and \( \omega \). We will now proceed to solve for the parameters: \( \beta, \gamma \) and \( \delta \).

From equations (7) & (8), we have the following relationships:

\[ \omega^2 = \lambda = (\gamma \beta + \alpha \delta) \]  

(19)

\[ \lambda T_d = 2A = (\gamma + \alpha) \]  

(20)

Then, after evaluating the parameter \( A \) (by matching the \( y(t) \) solution to the glucose response data), we can obtain the value of \( \alpha + \gamma \) from equation (20), as:

\[ \alpha + \gamma = 2A \]  

(21)

Now, by matching the \( x(t) \) solution to the insulin response data, we can evaluate the parameters \( a & \beta \). Hence, from equation (21), by substituting this evaluated value of \( a \), we can obtain the value of \( \gamma \). Now, we have solved for \( a, \beta \) & \( \gamma \). But we still need to determine the parameter \( \delta \).

For instance, in the case of under-damped response (of normal subjects)

\[ \omega_n^2 = \omega^2 - A^2 \]  

(22)

Upon substituting equation (22) into equation (19), we obtain:
\[
\omega_n^2 = \lambda = (\gamma \beta + \alpha \delta)
\]
and hence, \(\omega^2 - A^2 = \lambda = \gamma \beta + \alpha \delta\) \hspace{1cm} (23)

Now, in this equation, since only \(\delta\) is unknown, we can evaluate it. Hence, we can determine all the four model parameters \(\alpha, \beta, \gamma\) and \(\delta\) for normal subjects.

In the case of over-damped response (of diabetic subjects),
\[
\omega^2 = A^2 - \omega_n^2
\]
(24)

Upon substituting (24) into (19):
\[
\omega_n^2 = \lambda = (\gamma \beta + \alpha \delta), \text{or}
\omega^2 - A^2 = \lambda = (\gamma \beta + \alpha \delta)
\]
(25)

Hence, again in this above equation, since only \(\delta\) is as yet unknown, we can determine \(\delta\). Hence all the model parameters \((\alpha, \beta, \gamma \& \delta)\) can be determined.
1.5 Clinical Application of Model

We will now study typically normal patients (so classified as per clinical criteria delineated in section 1). We have decided that for a patient to be classified in any one of the three (under-damped, over-damped and critically damped) categories, the model solution equation should fit the data with a very high degree of correlation coefficients: R-square $\geq 0.90$ and SSE $\leq 0.1$. In case a patient data fits all the 3 (under-damped, over-damped and critically damped) response categories, we will designate the patient to the category for which the R-Square value is the highest.

1.5.1 Under-damped Category for Patients Clinically Designated to be Normal

Based on the high degree of fit, patients as shown in Table 1.7 fit best the under-damped category, and hence are also designated as normal by our systems-engineering basis. Their Glucose and Insulin responses are shown in Appendix A respectively.

Table 1.7 Subjects that were well fitted by underdamped characteristic model equation.

<table>
<thead>
<tr>
<th>Best Fitted (R-Square &gt; 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N02</td>
</tr>
<tr>
<td>N05</td>
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<tr>
<td>N11</td>
</tr>
<tr>
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</tr>
<tr>
<td>D03</td>
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<td>Parameters</td>
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<tr>
<td>------------</td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>G</td>
</tr>
<tr>
<td>ω</td>
</tr>
<tr>
<td>α</td>
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<td>β</td>
</tr>
<tr>
<td>γ</td>
</tr>
<tr>
<td>δ</td>
</tr>
</tbody>
</table>

**Figure 1.20** The Glucose-Insulin response of N02 is a good example of a normal response e.g. no-diabetic. This result correlates very well with clinically diagnosis.
**Table 1.21** The Glucose-Insulin response of D02 is a good example of a wrong clinical diagnosis. The subject may be subjected to unnecessary medication and procedures which are physiologically and morally depressing.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
<th>Fitting</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.2845</td>
<td>Glucose</td>
<td>SSE</td>
</tr>
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<td>G</td>
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<tr>
<td>α</td>
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<td>SSE</td>
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</table>

**Figure 1.21** The Glucose-Insulin response of D02 is a good example of a wrong clinical diagnosis. The subject may be subjected to unnecessary medication and procedures which are physiologically and morally depressing.
1.5.2 Over-damped Category of Patients Clinically Designated as Diabetic

Now, we display patients who were well fitted by overdamp characteristic model equation. Because they fit best our over-damped model category, we also designate them to be diabetic by our systems-engineering methodology. Their Glucose and Insulin responses are shown in Appendix B.

Table 1.8 Subjects that were well fitted by overdamped characteristic model equation.

<table>
<thead>
<tr>
<th>Best Fitted (R-Square &gt; 95%)</th>
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</thead>
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<td>$\delta$</td>
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Figure 1.22 The Glucose-Insulin response of N01 is another good example of a wrong clinical diagnosis. The subject may not be given the required medical attention and the consequences can be very depressing.
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
<th>Fitting</th>
<th>Remarks</th>
</tr>
</thead>
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Figure 1.23 The Glucose-Insulin response of D01 is a good example of a overdamp response e.g. diabetic. This result correlates very well with clinically diagnosis. D01 will undergo immediate medical attention.
1.5.2.1 Critically-damped Category of Patients

There are some patients (as shown in Table 1.9) who were clinically diagnosed to be normal, for whom the critically damped solution gives a better fit of their glucose and insulin response data (and a higher value of R-Square) than the under-damped solution. One such patient is N04, whose response curves for under-damped and critically (refer to Appendix A for figures). This patient is clinically diagnosed to be normal, but are at risk of becoming diabetic. This is because their data is best represented by the critically-damped solution. Likewise, patient D05 who has been identified as diabetic, but he is only at-risk of getting diabetic. Their response curves are illustrated in Appendix C.

Table 1.9 Subjects that were well fitted by critically damped characteristic model equation.

<table>
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<th>Best Fitted (R-Square &gt; 95%)</th>
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**Figure 1.24** The Glucose-Insulin response of N03 is a good example of a missed clinical diagnosis or a good example of pre-emptive treatment beneficial. Even though the subject is diagnosed as normal clinically e.g. non-diabetic, the subject in fact is at-risk e.g. preventive medical attention is required to prevent the current health conditions to deteriorate. N03 requires prevent medical measures immediately.
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
<th>Fitting</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A$</td>
<td>1.3530</td>
<td>Glucose</td>
<td>SSE</td>
</tr>
<tr>
<td>$G$</td>
<td>5.0750</td>
<td>Fit</td>
<td></td>
</tr>
<tr>
<td>$\omega$</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\alpha$</td>
<td>2.24</td>
<td>Insulin</td>
<td>R-Square</td>
</tr>
<tr>
<td>$\beta$</td>
<td>0.1862</td>
<td>Fit</td>
<td></td>
</tr>
<tr>
<td>$\gamma$</td>
<td>4.2254</td>
<td></td>
<td>R-Square</td>
</tr>
<tr>
<td>$\delta$</td>
<td>0.4660</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1.25** The Glucose-Insulin response of D05 is a good example of a wrong clinical diagnosis. The subject may be subjected to unnecessary medication and procedures which are physiologically and morally depressing. D05 only requires only preventive medical attention to prevent the current health conditions to deteriorate and not diabetic medical procedures which can be health hazardous.
1.6 Non-Dimensional Physiological Index (NDPI)

Classification based on NDPI. Comparing the NDIs from 3 classes, we can determine which class the patients belong to:

System Parameters Identification

The resulting OGTT glucose and insulin data of individual will be used for system parameter identification process [30-31]. The non-dimensionless for blood glucose response \( G_{\text{NDI}} \) is given by:

\[
G_{\text{NDI}} = \frac{y_{\text{max}} \times y_2}{G^2} \times \frac{T_d}{A} \times \frac{T_{\text{max}}}{T_2} \times 10^6
\]  

(26)

where: \( y_{\text{max}} \): maximum blood glucose value in gram/liter; \( y_2 \): blood glucose value at 2h; \( G \): glucose administered to the system in gram/liter hour; \( T_d \): derivative-time in hour derivative time; \( A \): attenuation constant in hour\(^{-1} \); \( T_{\text{max}} \): time at which \( y_{\text{max}} \) occurs; \( T_2 \): 2h.

The non-dimensionless for insulin response is given by:

\[
I_{\text{NDI}} = \frac{\beta \gamma \delta}{\alpha}
\]  

(27)

where: \( \alpha \): represents pancreatic insulin sensitivity to insulin in (hr\(^{-1} \)); \( \beta \): pancreatic insulin sensitivity to elevated glucose blood concentrations in (Units)(hr\(^{-1} \)(gms\(^{-1} \)); \( \gamma \): liver glycogen storage to elevated blood-glucose concentrations in (gms)(hr\(^{-1} \)(Units\(^{-1} \)); \( \delta \): tissue glucose utilisation to elevated blood-glucose concentrations in (hr\(^{-1} \)).

The final non-dimensionless index is given by:

\[
NDI = G_{\text{NDI}} \times I_{\text{NDI}}
\]

\[
= \frac{y_{\text{max}} \times y_2}{G^2} \times \frac{T_d}{A} \times \frac{T_{\text{max}}}{T_2} \times 10^6 \times \frac{\beta \gamma \delta}{\alpha}
\]  

(28)

\( \alpha \): increases means insulin removed
\( \beta \): increases means insulin responsive to glucose concentration
\( \gamma \) : decreases means blood glucose increases and not enough glucose absorbed by tissues.

\( \delta \) : decreases means blood glucose increases and inadequate tissue glucose utilization.
Table 1.10 Results of the patients who were classified as normal (non-diabetic) and having underdamp response from the OGTT.

<table>
<thead>
<tr>
<th>Subject</th>
<th>A</th>
<th>G</th>
<th>ω</th>
<th>T_d</th>
<th>(G_{-NDI} = \frac{y_{\text{max}} \times y'<em>1}{G^2} \times \frac{T_d}{A} \times \frac{T</em>{\text{max}}}{T'_d} \times 10^4)</th>
<th>α</th>
<th>β</th>
<th>γ</th>
<th>δ</th>
<th>(I_{-NDI} = \frac{\beta_1 \gamma_2}{\alpha})</th>
<th>(G_{-NDI} / I_{-NDI})</th>
</tr>
</thead>
<tbody>
<tr>
<td>N02</td>
<td>2.86</td>
<td>9.90</td>
<td>3.56</td>
<td>1.28</td>
<td>-1.51</td>
<td>0.93</td>
<td>0.05</td>
<td>0.05</td>
<td>4.80</td>
<td>0.01</td>
<td>-126.84</td>
</tr>
<tr>
<td>N05</td>
<td>0.72</td>
<td>1.33</td>
<td>2.37</td>
<td>0.28</td>
<td>-87.67</td>
<td>0.03</td>
<td>0.02</td>
<td>283.56</td>
<td>1.42</td>
<td>232.86</td>
<td>-0.38</td>
</tr>
<tr>
<td>N11</td>
<td>1.01</td>
<td>1.46</td>
<td>3.64</td>
<td>0.17</td>
<td>4.63</td>
<td>0.04</td>
<td>0.07</td>
<td>176.47</td>
<td>1.97</td>
<td>532.51</td>
<td>0.01</td>
</tr>
<tr>
<td>N14</td>
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<td>2.80</td>
<td>1.88</td>
<td>10.51</td>
<td>0.00</td>
<td>4.00</td>
<td>0.11</td>
<td>3.08</td>
<td>0.01</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>N16</td>
<td>1.66</td>
<td>3.44</td>
<td>3.61</td>
<td>0.32</td>
<td>6.71</td>
<td>0.42</td>
<td>0.08</td>
<td>118.17</td>
<td>2.89</td>
<td>62.73</td>
<td>0.11</td>
</tr>
<tr>
<td>N19</td>
<td>0.70</td>
<td>1.91</td>
<td>2.18</td>
<td>0.33</td>
<td>-321.57</td>
<td>1.40</td>
<td>0.06</td>
<td>68.36</td>
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<td>-27790.00</td>
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<tr>
<td>D03</td>
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<td>2.34</td>
<td>1.59</td>
<td>0.23</td>
<td>-139.53</td>
<td>0.55</td>
<td>0.02</td>
<td>145.11</td>
<td>0.02</td>
<td>0.08</td>
<td>-1659.73</td>
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</table>
Table 1.11 Results of the patients who were classified as at-risk and having critical damp response from the OGTT.

<table>
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<tr>
<th>Subject</th>
<th>A</th>
<th>G</th>
<th>ω</th>
<th>T_d</th>
<th>$G_{-NDI} = \frac{y_{max} \times y_2}{G^2} \times \frac{T_d \times T_{max}^2 \times T_{B}^2}{A}$</th>
<th>α</th>
<th>β</th>
<th>γ</th>
<th>δ</th>
<th>$I_{-NDI} = \frac{B - \delta}{\alpha}$</th>
<th>$G_{-NDI}$</th>
<th>$I_{-NDI}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>N03</td>
<td>1.97</td>
<td>3.67</td>
<td>0.00</td>
<td>1.02</td>
<td>63.09</td>
<td>3.00</td>
<td>0.12</td>
<td>8.97</td>
<td>0.93</td>
<td>0.33</td>
<td>189.98</td>
<td></td>
</tr>
<tr>
<td>N04</td>
<td>2.31</td>
<td>3.05</td>
<td>0.00</td>
<td>0.87</td>
<td>19.46</td>
<td>3.90</td>
<td>2.37</td>
<td>1.07</td>
<td>0.72</td>
<td>0.47</td>
<td>41.73</td>
<td></td>
</tr>
<tr>
<td>N08</td>
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<td>1.33</td>
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<td>0.55</td>
<td>0.00</td>
<td>0.86</td>
<td>1.37</td>
<td>5.71</td>
<td>6.46</td>
<td>58.75</td>
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</tr>
<tr>
<td>N10</td>
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<td>2.37</td>
<td>0.00</td>
<td>0.84</td>
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<td>4.70</td>
<td>1.82</td>
<td>2.95</td>
<td>0.06</td>
<td>0.07</td>
<td>484.80</td>
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<tr>
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<td>5.53</td>
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<td>0.51</td>
<td>0.18</td>
<td>1.11</td>
<td>2.47</td>
<td>3.19</td>
<td>6.73</td>
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</tr>
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<td>0.99</td>
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<td>0.03</td>
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<td>1.13</td>
<td>152.38</td>
<td>1.01</td>
<td>0.21</td>
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<td>1.50</td>
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<td>0.74</td>
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<td>5.40</td>
<td>3.20</td>
<td>2.25</td>
<td>0.04</td>
<td>0.06</td>
<td>63.80</td>
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</tr>
<tr>
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<td>1.35</td>
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<td>0.00</td>
<td>1.48</td>
<td>81.21</td>
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<td>2.04</td>
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<td>1.64</td>
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<td>0.32</td>
<td>0.08</td>
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<tr>
<td>D12</td>
<td>1.32</td>
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<td>0.00</td>
<td>1.52</td>
<td>1324.10</td>
<td>0.27</td>
<td>0.29</td>
<td>3.79</td>
<td>2.37</td>
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</tr>
<tr>
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<td>0.32</td>
<td>1.11</td>
<td>0.00</td>
<td>6.31</td>
<td>1401586.72</td>
<td>0.60</td>
<td>0.78</td>
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<tr>
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<td>0.00</td>
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<td>0.00</td>
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<td>0.01</td>
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<td></td>
</tr>
</tbody>
</table>
Table 1.12 Results of the patients who were classified as diabetic and having overdamp response from the OGTT.

<table>
<thead>
<tr>
<th>Subject</th>
<th>$A$</th>
<th>$G$</th>
<th>$\omega$</th>
<th>$T_d$</th>
<th>$G_{-NDI} = \frac{v_{max} \times y_1}{G^2} \times \frac{T_d}{A} \times \frac{T_{max}}{T_1^2} \times 10^4$</th>
<th>$\alpha$</th>
<th>$\beta$</th>
<th>$\gamma$</th>
<th>$\delta$</th>
<th>$I_{-NDI} = \frac{B_0\sigma}{\alpha}$</th>
<th>$G_{-NDI} \frac{I_{-NDI}}{I_{-NDI}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>N01</td>
<td>17.06</td>
<td>23.81</td>
<td>16.60</td>
<td>2.20</td>
<td>0.19</td>
<td>0.46</td>
<td>0.05</td>
<td>1.25</td>
<td>33.66</td>
<td>4.88</td>
<td>0.04</td>
</tr>
<tr>
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<td>26.79</td>
<td>19.38</td>
<td>9.12</td>
<td>1.16</td>
<td>0.11</td>
<td>0.05</td>
<td>0.80</td>
<td>38.87</td>
<td>13.82</td>
<td>0.08</td>
</tr>
<tr>
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<td>2.64</td>
<td>0.00</td>
<td>1.89</td>
<td>183.04</td>
<td>1.17</td>
<td>0.04</td>
<td>0.27</td>
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<td>0.01</td>
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<td>0.31</td>
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<td>3.30</td>
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<td>0.00</td>
<td>1.88</td>
<td>3654.79</td>
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<td>0.81</td>
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</table>
Figure 1.26 Non-dimensional plot of Tables 1.10-12 Non-dimensional plot of

\[
\frac{G_{\text{NDI}}}{I_{\text{NDI}}} = \left( \frac{y_{\text{max}}^2 \times y_2}{G^2} \times \frac{T_d}{A} \times \frac{T_{\text{mm}}}{32} \times 10^6 \right) \left( \frac{\beta \gamma \delta}{\alpha} \right).
\]
The above figure shows the final plot of the non-dimensional indexes. The above figure confirms that the chosen index provides the best discrimination e.g. separating non-diabetic from diabetic at the extreme ends of the plot while those at-risk diabetic patients are at the centre of the plot.

The other plots which are used to determine goodness of discrimination were shown in the Appendix D.
1.7 CONCLUSIONS

We have shown that we can obtain more accurate assessment of diabetic patients by means of our under-damped, over-damped and critically-damped simulation model solutions. Some patients were diagnosed clinically as normal but were in-fact diabetic. The consequences can be very depressing to the patients. They may be given the immediate essential medical attention which could lead them to acute complications such as diabetic ketoacidosis, hyperosmolar non ketotic coma, kidney failures, etc [12, 19-20]. While some of those are diagnosed as normal but were in fact at-risk. They require immediate preventive medical attention to prevent their current health conditions from deteriorating any further. While some of patient who are at-risk but were diagnosed as diabetic clinically. The unnecessary medial attention and procedures can be a health hazardous.

As we continue this work, we will develop a clinically-implementable software for model parameters identification and designation of the subjects as normal or at-risk of becoming diabetic or border-line diabetic or distinctly diabetic.

In conclusion, the NDPI can assist clinicians in determining the patients’ diabetic state and concentrate precious scarce medical resources for appropriate treatment accordingly, especially for those in the borderline case where early preventative measures can be exercised immediately before the endocrine system failed.
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Chapter 2 Automated Insulin Infusion Regulation System for Lowering Blood Glucose After a Meal

In the previous chapter, we have discussed the classification of normal, at-risk and diabetic patients, and how we have derived the required relevant models for the respective group of patients for glucose-insulin kinematics. In this chapter, we will discuss the development of an artificial pancreas for type II diabetic patients. The system we are proposing are non-invasive in nature and based on our findings from the previous chapter.

2.1 Motivation behind the Project

Long-term clinical studies show that the onset of complications can be significantly reduced through proper control of blood glucose levels [6]. A vital element of diabetes management is the self-monitoring of blood glucose levels by diabetics in the home environment. A significant disadvantage of current monitoring techniques is that they discourage regular use due to the inconvenient and painful nature of drawing blood through the skin prior to analysis. Therefore, new methods for self-monitoring of blood glucose levels are required to improve the prospects for more rigorous control of blood glucose in diabetic patients.

The artificial pancreas are developed from 1980’s, this device senses continuous blood glucose concentration level and controls injection quantity of insulin. The control methodologies for the artificial pancreas are to provide quantitative bounds on the required performance of sensors/actuators to be used in an artificial pancreas system. The four most important areas of concern in the design of the artificial pancreas are [1]:

(a) The subject dynamic systems (a patient’s glucose/insulin kinematics) are inherently nonlinear and poorly modeled relative to required performance levels.
(b) The subject dynamic systems are subject to external disturbances that are not under the authority of the control system (physical activity or food consumption by diabetic patient).
(c) The subject dynamic systems have limited actuator authority (insulin delivery rates are bounded and non-negative) and may suffer from unreliable actuation (patient compliance).

(d) Safe operation of the subject dynamic systems requires that system state variables be kept within a prescribed operating range.

(e) The glucose & insulin regulations must consider the controllable inputs such as meals, insulin injection and exercise. In other words, the artificial pancreas must mimic the actual healthy pancreas functions and only limited by our current technologies.

2.2 Functions of the Pancreas

The key hormones involved in glucose counter regulation are insulin, glucagon, and in cases of glucagon deficiency, adrenaline [3]. Insulin, secreted from the $\beta$ cells in the pancreas, is the only hormone involved in lowering glucose levels.

Glucagon is secreted from the $\alpha$ cells of the pancreas during periods of low glucose concentrations and is suppressed by high insulin levels [2]. Somastatin, secreted from the $\delta$ cells of the pancreas, inhibits glucagon and insulin secretion [3].

The normal fasting concentration of glucagon in circulating blood is $\approx 100-150$ pg/ml and has a half-life of $\approx 5-10$ minutes. Insulin secretion is stimulated by glucagon [2], a rise in glucose levels, a rise in blood ketones and by glucagon from the $\alpha$ cell. In contrast, insulin is inhibited by the secretion of somastatin, adrenaline and by decreasing blood glucose levels [3]. The normal basal rate of insulin release from the $\beta$ cell is 1 iu/hour ($1\mu\text{U}=0.04\text{ng}$ [2]). Insulin degrades in the liver by 50% each time it passes through, but this fraction varies among individuals and in an individual under different instances [2]. The typical fasting concentrations of insulin in circulating blood is $10-50\ \mu\text{iu/ml}$, and have a half-life of 5-10 minutes [3].

Glucagon is secreted from the $\alpha$ cells of the pancreas during periods of low glucose concentrations and is suppressed by high insulin levels [2]. Somastatin is of insulin in circulating blood are $10-50\ \mu\text{iu/ml}$, and have a half-life of 5-10 minutes [3].

2.2.1 Glucose production

In the basal state glucose production is approximately 2 mg/kg body weight per minute. In this state, gluconeogenesis, the formation of glucose or glycogen from
non-carbohydrate sources, contributes 30% of glucose production in the liver, and this percentage increases as fasting continues [2]. The remaining hepatic production relies on glycogenolysis, the conversion of glycogen to glucose. During fasting the liver depletes glycogen stores at a rate of 11% per hour. As fasting continues, glycogen stores are depleted thus increasing the role of gluconeogenesis. Glycogen stores consist of 60 grams in a 1.5kg liver, and 250 grams in 28 kg muscle tissue [2].

Increases in glucose production are controlled by several hormones including glucagon, adrenaline, cortisol, and growth hormone [3]. Glucagon and adrenaline have an immediate effect on raising blood glucose levels via glycogenolysis, and in prolonged hypoglycemia, via gluconeogenesis. Cortisol and glucagon, in the presence of prolonged hypoglycemia, promote gluconeogenesis. During acute insulin induced hypoglycemia, glucagon levels increase by a factor of four [3], in attempts to return glucose levels within the normal range. Growth hormone and cortisol act to increase glucose concentrations by suppressing glucose uptake as well as increasing hepatic glucose production [2]. Cortisol, growth hormone and thyroxin have slower onsets and more prolonged effects to increasing the glucose level [3].

Glucose production is inhibited by an increase in insulin concentration. In the liver, a 5-7 µU/ml increase of plasma insulin concentration will result in a half-maximum suppression of hepatic glucose production [2], and an increment of 100 µU/ml will decrease hepatic glucose production to less than 10-15% of basal production [4]. The inhibition of hepatic glucose production is three times as sensitive to insulin than peripheral glucose uptake [2]. Glycogenolysis and gluconeogenesis are decreased by insulin [2], which in part is due to the reduction of circulating glucagon.

### 2.2.2 Glucose Uptake

Insulin acts to lower blood glucose levels by increasing cellular glucose uptake [3]. Insulin increases cell membrane permeability to glucose, amino acids and potassium and it meanwhile decreases intracellular cyclic adenosine monophosphate (cAMP), the basic regulator of cell metabolism. Classic insulin sensitive tissues are adipocyte and brown fat, skeletal, heart and smooth muscle [2], this constitutes only a fraction of the tissues involving glucose uptake. The brain, liver, kidneys, and intestines undergo insulin independent glucose uptake. The brain requires \( \approx 1 \text{mg/kg} \) of glucose per minute, and glucose oxidation provides
almost 90% of the energy required for the brain and nervous system to operate properly. Basal glucose uptake is \( \approx 2 \text{ mg/kg per minute} \) of which 50% is required by the brain, 25% by the splanchnic (liver and gut) tissues, and the other 25% by insulin dependent tissues. Under normal circumstances the rate limiting step for glucose uptake is the phosphorylation within the cell by hexokinase [2]. Glucose uptake is inhibited other hormones. Half-maximal glucose utilization is produced when insulin concentration increase by a factor of 3.

2.3 Literature Review

2.3.1 Glucose Measurement

Currently there are numerous approaches for measuring blood glucose levels, ranging from invasive methods such as microdialysis [7] to noninvasive technologies that rely on spectroscopy [8], ion sensitive field effect transistor (ISFET) [9] and millimeter waves [10]. Each method has associated advantages and disadvantages, but only a few have received approval from certifying agencies. To date, no noninvasive techniques for the self-monitoring of blood glucose have been certified.

One method, near-infrared spectroscopy involves the illumination of a spot on the body with near-infrared electromagnetic radiation (light in the wavelength range 750-2500 nm). The light is partially absorbed and scattered, according to its interaction with the constituents of the tissue prior to being reflected back to a detector. The detected light contains quantitative information that is based on the known interaction of the incident light with components of the body tissue including water, fat, protein and glucose.

2.3.1.1 Noninvasive Glucose Measurement

Previously reported methods for the noninvasive measurement of glucose through near-infrared spectroscopy rely on the detection of the magnitude of light attenuation caused by the absorption signature of blood glucose as represented in the targeted tissue volume. The tissue volume is the portion of irradiated tissue from which light is reflected or transmitted to the spectrometer detection system. The signal due to the absorption of glucose is extracted from the spectral measurement through various methods of signal processing and one or more mathematical models. The models are developed through the process of calibration on the basis of an exemplary set of
spectral measurements and associated reference blood glucose values (the calibration set) based on an analysis of capillary (fingertip) or venous blood.

Near-infrared spectroscopy has been demonstrated in specific studies to represent a feasible and promising approach to the noninvasive prediction of blood glucose levels. M. Robinson and et. al. [8] have reported three different instrument configurations for measuring diffuse transmittance through the finger in the 600-1300 nm range. Meal tolerance tests were used to perturb the glucose levels of three subjects and calibration models were constructed specific to each subject on single days and tested through cross-validation. Absolute average prediction errors ranged from 19.8 to 37.8 mg/dl. The papers [11-14] present results through a diffuse reflectance measurement of the oral mucosa in the 1111-1835 nm range with an optimized diffuse reflectance accessory. In vivo experiments were conducted on single diabetics using glucose tolerance tests and on a population of 133 different subjects. The best standard error of prediction reported was 43 mg/dl and was obtained from a two-day single person oral glucose tolerance test that was evaluated through cross-validation.

The papers [15-18] recorded spectra in diffuse reflectance over the 800-1350 nm range on the middle finger of the right hand with a fiber-optic probe. Each experiment involved a diabetic subject and was conducted over a single day with perturbation of blood glucose levels through carbohydrate loading. Results, using both partial least squares regression and radial basis function neural networks were evaluated on single subjects over single days through cross-validation. Danzer et al. [17] reports an average root mean square prediction error of 36 mg/dl through cross-validation over 31 glucose profiles.

J. Burmeister et al. [19] collected absorbance spectra through a transmission measurement of the tongue in the 1429-2000 nm range. A study of five diabetic subjects was conducted over a 39-day period with five samples taken per day. Every fifth sample was used for an independent test set and the standard error of prediction for all subjects was greater than 54 mg/dl.

In T. Blank et al. [20], reported studies demonstrate noninvasive measurement of blood glucose during modified oral glucose tolerance tests over a short time period. The calibration was customized for the individual and tested over a relatively short time period.
In all of these studies, limitations were cited that would affect the acceptance of such a method as a commercial product. These limitations included sensitivity, sampling problems, time lag, calibration bias, long-term reproducibility and instrument noise. Fundamentally, however, accurate noninvasive estimation of blood glucose is presently limited by the available near-infrared technology, the trace concentration of glucose relative to other constituents and the dynamic nature of the skin and living tissue of the patient [21]. As reported by S. Malin, T et al. [22], the entirety of which is hereby incorporated by reference, chemical, structural and physiological variations occur that produce dramatic and nonlinear changes in the optical properties of the tissue sample [23-30].

The measurement is further complicated by the heterogeneity of the sample, the multi-layered structure of the skin and the rapid variation related to hydration levels, changes in the volume fraction of blood in the tissue, hormonal stimulation, temperature fluctuations and blood analyte levels. This can be further considered through a discussion of the scattering properties of skin.

2.3.1.2 Skin Structure

The structure and composition of skin varies widely among individuals as well as between different sites and over time on the same individual. Skin consists of a superficial layer known as the stratum corneum, a stratified cellular epidermis, and an underlying dermis of connective tissue. Below the dermis is the subcutaneous fatty layer or adipose tissue. The epidermis, with a thickness of 10-150 um, together with the stratum corneum provides a barrier to infection and loss of moisture, while the dermis is the thick inner layer that provides mechanical strength and elasticity [31]. In humans, the thickness of the dermis ranges from 0.5 mm over the eyelid to 4 mm on the back and averages approximately 1.2 mm over most of the body [32].
Figure 2.1 Components of the integumentary system. The skin consists of a thin, superficial epidermis and a deep, thicker dermis. Deep to the skin is the subcutaneous layer, which attaches the dermis to underlying organs and tissues [10].

In the dermis, water accounts for approximately 70% percent of the volume. The next most abundant constituent is collagen, a fibrous protein comprising 70-75% of the dry weight of the dermis. Elastin fibers, also a protein, are plentiful though they constitute only a small proportion of the bulk. In addition, the dermis contains a wide variety of structures (e.g., sweat glands, hair follicles and blood vessels) and other cellular constituents [31]. Conversely, the subcutaneous layer (adipose tissue) is by volume approximately 10% water and consists primarily of cells rich in triglycerides (fat). The concentration of glucose varies in each layer according to the water content, the relative sizes of the fluid compartments, the distribution of capillaries and the perfusion of blood. Due to the high concentration of fat, the average concentration of glucose in subcutaneous tissue is significantly lower than that of the dermis.
2.3.1.3 Optical Properties of Skin

When near-infrared (NIR) light is delivered to the skin, a percentage of it is reflected, while the remainder penetrates into the skin. The proportion of reflected light, or specular reflectance is typically between 4-7% of the delivered light over the entire spectrum from 250-3000 nm (for a perpendicular angle of incidence) [33]. The 93-96% of the incident light that enters the skin is attenuated due to absorption and scattering within the many layers of the skin. These two processes, combined with orientation of the sensors of the spectrometer instrument, determine the tissue volume irradiated by the source and "sampled" through the collection of diffusely reflected light.

Diffuse reflectance or remittance is defined as that fraction of incident optical radiation that is returned from a turbid sample. Alternately, diffuse transmittance is the fraction of incident optical radiation that is transmitted through a turbid sample. Absorption by the various skin constituents mentioned above accounts for the spectral extinction of the light within each layer. Scattering is the only process by which the beam may be returned to contribute to the diffuse reflectance of the skin. Scattering also has a strong influence on the light that is diffusely transmitted through a portion of the skin.

The scattering in tissues is due to discontinuities in the refractive index on the microscopic level, such as the aqueous-lipid membrane interfaces between each tissue compartment or the collagen fibrils within the extracellular matrix [34]. The spatial distribution and intensity of scattered light depends upon the size and shape of the particles relative to the wavelength, and upon the difference in refractive index between the medium and the constituent particles. The scattering of the dermis is dominated by the scattering from collagen fiber bundles in the 2.8 μm diameter range occupying 21% of the dermal volume, and the refractive index mismatch is 1.38/1.35 [33]. The spectral characteristics of diffuse remittance from tissue result from a complex interplay of the intrinsic absorption and scattering properties of the tissue, the distribution of the heterogeneous scattering components and the geometry of the point(s) of irradiation relative to the point(s) of light detection.
Figure 2.2 Shows a typical absorbance spectrum measurement from the forearm of a human subject [33].

The absorption of light in tissue is primarily due to three fundamental constituents: water, protein and fat. As the main constituent, water dominates the near-infrared absorbance above 1100 nm and is observed through pronounced absorbance bands (for example, see Figure 2.2). Protein in its various forms, and in particular collagen, is a strong absorber of light that irradiates the dermis. Near-infrared light that penetrates to subcutaneous tissue is absorbed primarily by fat. In the absence of scattering, the absorbance of near-infrared light due to a particular analyte, A, can be approximated by Beers Law at each wavelength by

\[ A = \varepsilon cl \]  

where \( \varepsilon \) is the analyte specific absorption coefficient, \( c \) is the concentration and \( l \) is the pathlength. The overall absorbance at a particular wavelength is the sum of the individual absorbances of each particular analyte given by Beer's Law. The
concentration of a particular analyte, such as glucose, can be determined through a multivariate analysis of the absorbance over a multiplicity of wavelengths because $E$ is unique for each analyte. However, in tissue compartments expected to contain glucose, the concentration of glucose is at least three orders of magnitude less than that of water. Consequently, the signal targeted for detection by reported approaches to near-infrared measurement of glucose (the absorbance due to glucose in the tissue) is expected to be at most three orders of magnitude less than other interfering tissue constituents. Therefore, the near-infrared measurement of glucose requires a high level of sensitivity over a broad wavelength range, and the application of methods of multivariate analysis.

However, the diverse scattering characteristics of the skin (e.g., multiple layers and heterogeneity) cause the light returning from an irradiated sample to vary in a highly nonlinear manner with respect to tissue analytes, in particular, glucose. Simple linear models, such as the Beer's Law have been reported to be invalid for the dermis [R. Anderson, J. Parrish, The optics of human skin, Journal of Investigative Dermatology, 77:1, pp. 13-19 (1981)]. Such nonlinear variation is a recognized problem and several reports have disclosed unique methods for compensating for the nonlinearity of the measurement while providing the necessary sensitivity [22, 36].

2.3.1.4 Dynamic Properties of the Skin

While knowledge of and utilization of the optical properties of the skin, high instrument sensitivity and compensation for inherent nonlinearities are all vital for the application of near-infrared spectroscopy to noninvasive blood analyte measurement, an understanding of biological and chemical mechanisms that lead to time dependent changes in the optical properties of skin tissue is equally important and, yet, largely ignored. At a given measurement site, skin tissue is often assumed to be static except for changes in the target analyte and other absorbing species. However, variations in the physiological state of tissue profoundly affect the optical properties of tissue layers and compartments over a relatively short period of time. Such variations are often dominated by fluid compartment equalization through water shifts and are related to hydration levels and changes in blood analyze levels.

Total body water accounts for over 60% of the weight of the average person and is distributed between two major compartments: the extracellular fluid (one-third of total body water) and the intracellular fluid (two-thirds of total body water) [37]. The extracellular fluid in turn is divided into the interstitial fluid (extravascular) and the
blood plasma (intravascular). Water permeable lipid membranes separate the compartments and water is transferred rapidly between them through the process of diffusion, in order to equalize the concentrations of water and other analytes across the membrane. The net water flux from one compartment to another constitutes the process of osmosis and the amount of pressure required to prevent osmosis is termed the osmotic pressure. Under static physiological conditions the fluid compartments are at equilibrium. However, during a net fluid gain or loss as a result of water intake or loss, all compartments gain or lose water proportionally and maintain a constant relative volume.

The primary mechanism for distributing substances contained in blood serum that are needed by the tissues, such as water and glucose, is through the process of diffusion. The invention recognizes that Fick's law of diffusion drives the short-term intra-/extravascular fluid compartment balance. The movement of water and other analytes from intravascular to extravascular compartments occurs rapidly as tremendous numbers of molecules of water and other constituents, in constant thermal motion, diffuse back and forth through the capillary wall. On average, the rate at which water molecules diffuse through the capillary membrane is about eighty times greater than the rate at which the plasma itself flows linearly along the capillary. In the Fick's Law expression, the actual diffusion flux, $I_{OA}$, is proportional to the concentration gradient, $dC/dx$ between the two compartments and the diffusivity of the molecule, $D_A$ according to the equation:

$$I_{OA} = -D_A \frac{dC}{dx}$$  \hspace{1cm} (2)

Short-term increases (or decreases) in blood glucose concentrations lead to an increase (or decrease) in blood osmolality (number of molecules per unit mass of water). Fluid is rapidly re-distributed accordingly and results in a change in the water concentration of each body compartment. For example, the osmotic effect of hyperglycemia is a movement of extravascular water to the intravascular space. Conversely, a decrease in blood glucose concentration leads to a movement of water to extravascular space from the intravascular compartment.

Because the cell membrane is relatively impermeable to most solutes but highly permeable to water, whenever there is a higher concentration of a solute on one side of the cell membrane, water diffuses across the membrane toward the region of higher solute concentration. Large osmotic pressures can develop across the cell membrane with relatively small changes in the concentration of solutes in the extracellular fluid.
As a result, relatively small changes in concentration of impermeable solutes in the extracellular fluid, such as glucose, can cause tremendous changes in cell volume.

Long-term fluid compartment balances are influenced by fluid intake, exercise, diet, drug therapy and other physiological factors. The ancillary calibration of glucose to fluid compartment shifts is possible over short-term periods. The calibration of glucose to fluid shifts over longer periods of time requires a bias correction of the analytical signal and the associated blood glucose to compensate for the sources of long-term fluid compartment shifts. It is noted that Fick's Law equation (2) relates the flux in water concentration to the change in glucose concentration. Thus, this measurement based on first principles only permits the determination of the relative movement of glucose. Bias correction of both the spectroscopic water signal and the associated glucose concentration are required because the initial water concentration is not strictly a function of the associated glucose concentration. Accordingly, without more, it is only feasible to predict relative movement of glucose. Generating an absolute glucose value would require using a paired glucose/ water measurement to adjust the time dependent bias in the ancillary fluid shift signal.

**2.3.1.5 Issues Regarding NIR Spectrometry**

Re-distribution of water between various tissue compartments alters the optical properties of the tissue through changes in the water concentration, the concentration of other analytes, the refractive indices of various layers, the thickness of tissue layers and the size and distribution of scattering centers. Therefore, the optical properties of the tissue sample are modified in a highly nonlinear and profound manner. In addition, the actual tissue volume sampled (and the effective or average pathlength of light) is varied. Consequently, the spectral measurement varies in a complex manner that is incompatible with current modes of near-infrared detection of glucose. For example, changes in blood glucose concentration will result in water compartment shifts to compensate for the increase or decrease in intravascular osmolality. A change in the distribution of water will lead to a rapid change in the optical properties of the tissue that is correlated to a change in the absorption of glucose.

Several methods are reported to compensate in some part for the dynamic variation of the tissue. For example, several reported methods of noninvasive glucose measurement develop calibration models that are specific to an individual over a short period of time [8, 19-20]. This approach avoids modeling the differences between patients and therefore cannot be generalized to more individuals. However, the
calibration models have not been tested over long time periods and no means of compensating for variation related to the dynamic water shifts of fluid compartments is reported.

Malin et al. [22] and Ruchti et al [20] report a method for compensating for variation related to the structure and state of the tissue through an intelligent pattern recognition system capable of determining calibration models that are most appropriate for the patient at the time of measurement. The calibration models are developed from the spectral absorbance of a representative population of patients that have been segregated into groups. The groups or classes are defined on the basis of structural and state similarity such that the variation within a class is small compared to the variation between classes. Classification occurs through extracted features of the tissue absorbance spectrum related to the current patient state and structure. However, the described invention does not use features for directly compensating for physiological changes in the tissue. Further, the direct use of features representing the physiological state of the subject (or subject's measurement site) for noninvasive measurement of glucose was not described.

E. Thomas et al. [38] identifies a method for reducing intra-subject variation through the process of mean-centering both the direct and indirect measurements. However, this does not address the key problem related to short-term physiological and chemical changes related to the dynamic nature of the tissue.

No reported method provides a method and apparatus for detecting features that reflect changes in the optical properties of tissue related to physiological properties of the tissue such as the shifting of water between fluid compartments. Second, no reported method utilizes features that reflect the dynamic nature of the tissue to detect conditions unsuitable for near-infrared measurement of blood glucose. Third, no method exists to use these features to compensate glucose measurements for bias caused by physiological changes. Finally, no reported method utilizes fluid compartment shifts as reflected in spectral features related to the optical properties of tissue to indirectly measure glucose. As a result, noninvasive measurement of glucose is limited by the dynamic nature of tissue related to the tissue's physiological response to various conditions and the re-distribution of water among tissue fluid compartments.

In view of the problems left unsolved by the prior art, there exists a need for a method and apparatus to first detect changes in the optical properties of the tissue due to the changing physiology of the subject, specifically changes related to water shifts
between tissue compartments. Second, use of these features to determine conditions unsuitable for glucose measurement through near-infrared spectroscopy would be a useful advancement. Finally, it would be a significant advancement to determine a means for either using the features to compensate for the changing optical properties of the tissue or alternately, utilizing the features to measure glucose.

Throughout their studies, Salzsieder, Fischer, and their coauthors have examined closed-loop control of diabetic patient glucose in dogs and humans [26-29]. For humans, the control algorithms were employed as decision support systems or in simulation studies using individualized patient models. Linear algorithms were employed for insulin delivery based on a glucose measurement using proportional-derivative control [26], pole-placement techniques [28], adaptive methods [27], and modifications of the Biostator algorithm [29]. Fischer and coauthors [27] demonstrated that blood glucose controllers showed markedly improved performance when the controller either adapted on-line or was customized to the specific patient. Of potential concern for these control algorithms is the sampling rate (typically one minute intervals), which is faster than the speed of response of implantable in vivo biosensors [11].

Sorensen [30], using the internal model control framework, developed a detailed compartmental model and a linear model-based controller. To simplify controller synthesis, the 19th-order nonlinear model was approximated by a first-order-plus-time-delay (FOTD) transfer function. The controller resulting from this simplified structure was then implemented in the time domain. Performance was adequate, although improvement through use of a more detailed model in controller design is virtually guaranteed. Also, the controller demonstrated significant performance loss (in terms of ability to reject meal disturbances) when patient parameters differed from those of the model.

An analysis paper by Doyle, et al. [31], examined modeling and experimental techniques for controlling blood glucose. A key observation in their work was that low-order models may not adequately describe the real process and therefore could contain both unacceptable levels of modeling error and significant process-model mismatch. A nonlinear feedforward-feedback controller synthesized using feedback linearization, a nonlinear differential-geometric technique, was the control scheme proposed for glucose regulation. Also proposed was a polymer (gel) device able to act as sensor, controller, and actuator all-in-one. This device would sense glucose as pH changes, and release insulin into the bloodstream according to the pH variation. The
control characteristics, such as dynamic behavior and magnitude of release, are designed into the gel through material selection and preparation.

State-dependent Riccati equations were used by Parrish and Ridgely [32] to control blood glucose concentration in diabetic patients. Their controller was designed from a partial linearization of the model developed by Naylor, et al. [33]. This nonlinear full-state feedback control method is limited by an inability to measure several states in the diabetic patient model, such as total stores of glucose and insulin. Cancellation of the nonglucose feedback gains resulted in successful rejection of low-magnitude disturbances, although overaggressive control and increased insulin usage were both observed. The authors used manipulated variable weighting to reduce insulin delivery rates, while maintaining adequate glucose control. Due to the formulation of their controller, the tracking problem demonstrated steady-state offset.

Robust control using the H_ control methodology was the topic of a paper by Kienitz and Yoneyama [34]. Glucose and insulin dynamics were governed by a low-order model containing patient-dependent parameters. The controller was designed based on a nominal patient model, and a set of frequency-dependent weighting functions was tuned to capture the entire expected patient population (based on parameter variations). Patients who are within the design set will, by definition, satisfy the performance criterion because H_ controllers bound worst-case performance. Meal disturbance simulations were promising for the nominal patient. The controller was robust to small amounts of patient uncertainty, but inferences to larger patient variability sets would require retuning of certain controller parameters.
2.4 Overview of Current Treatment and Monitoring Methods

The current treatment methods for insulin-dependent diabetes include subcutaneous insulin injection or continuous infusion of insulin. Subcutaneous insulin treatment may require four to five daily injections, which usually correspond with mealtimes. The amount of insulin injected is typically based on consideration of a glucose measurement (finger prick), an approximation of the glucose content of the upcoming meal, and the estimated insulin release kinetics from the subcutaneous depot. Lente or ultra-lente (slower release) insulin preparations allow for an overnight release of insulin to prevent highly elevated glucose concentrations in the early morning hours. The continuous infusion insulin pump allows for more predictable delivery due to its constant infusion rate into an intraperitoneal or subcutaneous delivery site. An additional feature of some pumps is their ability to be “primed” so that a bolus of insulin can be released to compensate for anticipated glucose intake.

Either of the above two diabetes treatment methods can result in significant, and sometimes frequent, glucose concentration variations because of the predominantly open-loop nature of the insulin delivery. Intravenous delivery of insulin has significant advantages: (i) rapid delivery with negligible dead-time; (ii) a higher percentage of drug reaches the bloodstream, as compared with subcutaneous or intraperitoneal delivery sites; (iii) faster response to insulin over-delivery; and (iv) potential for improved closed-loop controller performance. However, there are shortcomings to this approach as well: (i) indwelling venous catheters may irritate the blood vessel; (ii) the catheter may dislodge from the vein; and (iii) the catheter may occlude (although this problem is present in all catheter delivery devices). Given the significant benefits of utilizing intravenous insulin delivery versus subcutaneous or intraperitoneal approaches, this review will concentrate on intravenous delivery methods for glucose control.

The development of a closed-loop device capable of maintaining normoglycemia over extended periods of time could dramatically improve the quality of life for insulin-dependent diabetic patients (Fig. 1). A device of this type would contain three primary components: (i) a mechanical pump; (ii) an in vivo glucose sensor; and (iii) a mathematical algorithm to regulate the pump given a sensor measurement. Extracorporeal and implantable insulin pumps have been in service for over 15 years.
Recent advances have made available programmable and variable-rate infusion pumps [42].

Current blood glucose monitoring is accomplished through invasive methods, such as a finger prick, but the use of a noninvasive monitor would increase patient comfort and therefore compliance to the insulin therapy. An implantable glucose concentration sensor would measure diabetic patient blood glucose levels on-line and thus eliminate the patient from the feedback loop. A number of research groups are working on implantable glucose sensors (see, for example, [43–45]), and the duration of in vivo sensor reliability continues to increase. This review will focus on the various control algorithms proposed by researchers working on this problem, as well as some new results by the authors on uncertainty characterization and model-based controller synthesis in the presence of uncertainty.

### 2.4.1 Intravenous Insulin Delivery Algorithms Biostator™ and Nonlinear PID

Early diabetes regulation work dates to the glucose controlled insulin infusion system (GCIIS) [46] and later to the “Biostator” algorithm and device of Clemens [47]. This feedback controller utilized a low-volume continuous-flow blood glucose sampling mechanism with a dual infusion system (insulin and dextrose) to maintain blood glucose concentration at a user-defined value. The control algorithm was a nonlinear proportional-plus-derivative type structure, using a five-point moving average of glucose measurements to minimize noise effects. While adequate for bedside implementation, implantation would be more difficult due to the additional size associated with the dual-reservoir system necessary for a device of this type. Patient specificity was also an issue, as the algorithm would require individualization prior to its use.

Albisser, et al. [48], studied blood glucose control, also using a two-channel system. Dextrose infusion was regulated by a nonlinear function of glucose concentration,
while the infusion of insulin was governed by a projected glucose concentration. This prediction used the current measured value of blood glucose plus an exponential difference factor computed from the four-minute average rate of change of glucose concentration. This factor was designed to emphasize increasing glucose trends over decreasing concentrations. Several patient-dependent or operator-selected parameters were required in this control algorithm.

A comparison of similar methods for artificial (3-cell control, based on a glucose measurement and its rate of change, was presented by Broekhuysse, et al. [49]. These algorithms included a modified version of the algorithm in Albisser, et al. [48] by Botz [50] and by Marliss, et al. [51]; a modification of this controller introduced by Kraegen, et al. [52]; two variants of the Biostator algorithm [47, 53, 54]; and a linear glucose control algorithm developed by Fischer, et al. [55]. No single controller was found to be uniformly superior, and it was concluded that significant further work in controller development was required to normalize diabetic patient blood glucose concentration.

Bellomo, et al. [56], examined the use of the Biostator control algorithm on diabetic patients but extended its application through the use of a patient model update mechanism. This update occurred over a period defined by the particular parameters being estimated. Rising and falling gains (related to the derivative term in the proportional-plus-derivative type algorithm), as well as the endogenous insulin release and glucose effectiveness, are calculated to minimize the sum-squared error (SSE) between the predicted and actual glucose concentrations over the duration of the current trend in blood glucose (rising or falling). This discrimination, based on the direction of glucose change, is used because of the different controller dynamics desired for the two cases. Other patient-specific coefficients in the controller minimize a quadratic objective function, with terms representing insulin expense and glucose deviation from the basal state. This controller represents a clear advantage over the static Biostator algorithms but still displays significant hyperglycemic peaks during controller operation.

An extended version of the Bergman “minimal model” [70], including insulin antibody binding, was studied by Furler, et al. [57]. The control algorithm was governed by a saturation function that calculated insulin delivery rate as a function of the current glucose measurement. Linear interpolation between the two limits was used to set the rate of insulin infusion. Measurements were taken at intervals of one to four hours, and performance was shown to be superior to a similar control algorithm used in clinical studies [58]. The controller based on the modified saturation function [57] performed well in returning initially hyperglycemic patients to steady state, although no analysis
of meal disturbances was performed. It should be noted, however, that this algorithm was not intended for meal disturbance rejection but for basal-level glucose control in a controlled environment such as a hospital.

### 2.4.2 Advanced Control Algorithms

Throughout their studies, Salzsieder, Fischer, and their coauthors have examined closed-loop control of diabetic patient glucose in dogs and humans [59-62]. For humans, the control algorithms were employed as decision support systems or in simulation studies using individualized patient models. Linear algorithms were employed for insulin delivery based on a glucose measurement using proportional-derivative control [59], pole-placement techniques [61], adaptive methods [60], and modifications of the Biostator algorithm [62]. Fischer and coauthors [60] demonstrated that blood glucose controllers showed markedly improved performance when the controller either adapted on-line or was customized to the specific patient. Of potential concern for these control algorithms is the sampling rate (typically one minute intervals), which is faster than the speed of response of implantable in vivo biosensors [45].

Sorensen [72], using the internal model control framework, developed a detailed compartmental model and a linear model-based controller. To simplify controller synthesis, the 19th-order nonlinear model was approximated by a first-order-plus-time-delay (FOTD) transfer function. The controller resulting from this simplified structure was then implemented in the time domain. Performance was adequate, although improvement through use of a more detailed model in controller design is virtually guaranteed. Also, the controller demonstrated significant performance loss (in terms of ability to reject meal disturbances) when patient parameters differed from those of the model.

An analysis paper by Doyle, et al. [63], examined modeling and experimental techniques for controlling blood glucose. A key observation in their work was that low-order models may not adequately describe the real process and therefore could contain both unacceptable levels of modeling error and significant process-model mismatch. A nonlinear feedforward-feedback controller synthesized using feedback linearization, a nonlinear differential-geometric technique, was the control scheme proposed for glucose regulation. Also proposed was a polymer (gel) device able to act as sensor, controller, and actuator all-in-one. This device would sense glucose as pH changes, and release insulin into the bloodstream according to the pH variation. The
control characteristics, such as dynamic behavior and magnitude of release, are designed into the gel through material selection and preparation.

State-dependent Riccati equations were used by Parrish and Ridgely [64] to control blood glucose concentration in diabetic patients. Their controller was designed from a partial linearization of the model developed by Naylor, et al. [65]. This nonlinear full-state feedback control method is limited by an inability to measure several states in the diabetic patient model, such as total stores of glucose and insulin. Cancellation of the nonglucose feedback gains resulted in successful rejection of low-magnitude disturbances, although overaggressive control and increased insulin usage were both observed. The authors used manipulated variable weighting to reduce insulin delivery rates, while maintaining adequate glucose control. Due to the formulation of their controller, the tracking problem demonstrated steady-state offset.

Robust control using the $H_\infty$ control methodology was the topic of a paper by Kienitz and Yoneyama [66]. Glucose and insulin dynamics were governed by a low-order model containing patient-dependent parameters. The controller was designed based on a nominal patient model, and a set of frequency-dependent weighting functions was tuned to capture the entire expected patient population (based on parameter variations). Patients who are within the design set will, by definition, satisfy the performance criterion because $H_\infty$ controllers bound worst-case performance. Meal disturbance simulations were promising for the nominal patient. The controller was robust to small amounts of patient uncertainty, but inferences to larger patient variability sets would require retuning of certain controller parameters.

### 2.4.3 Optimal Control Theory

Using a linear diabetic patient model and a quadratic performance criterion, Swan [63] solved the glucose control problem for the optimal insulin infusion rate. This approach uses optimal control theory and solution of a nonlinear algebraic Riccati equation, and it refines the results of Kikuchi [64, 65], who solved the problem using an approximate solution to the Riccati equation. The insulin delivery rate is a function of both the current insulin and glucose concentrations, although under certain assumptions (no glucose-dependent endogenous insulin release) the insulin state can be removed to yield a solution only in terms of the glucose concentration. The article focused on the initially hyperglycemic diabetic patient, so meal disturbance attenuation was not treated.
Normalization of patient blood glucose in response to both meal consumption and initial hyperglycemia was studied by Fisher and Teo [38]. Various infusion protocols were tested, with Fisher and Teo [38]. Various infusion protocols were tested, with the objective being the minimization of sum-squared glucose tracking error. Impulse control (a single injection at time = 0 min) was found to provide superior control in both cases, with perfect reference tracking achievable if a good estimate of the meal was available (under certain assumptions regarding the shape of the meal disturbance and insulin effects). Lim and Teo [66] studied impulse control for the same situations, but in the presence of fuzzy model parameters (patient uncertainty). For the chosen uncertainty set, and again under assumptions about the dynamic behavior of meals and insulin injection, the impulse control method was found to be robust and numerically stable.

Application of optimal control theory to the “minimal model” of Bergman, et al. [70], was undertaken in two studies. One, by Ollerton [67], utilized an integral-squared error (ISE) cost function based on deviation from the desired glucose value. Sampling times of 10 min and 180 min were studied. The longer sampling time was less sensitive to noise about the basal state, but it had a longer rise time and could also miss significant disturbances that occurred within the inter-sample window. Due to the calculation times experienced, Ollerton discretized the “minimal model” for use in the 10 min sampling time studies. This controller was sensitive to oscillation of the glucose profile about the basal state, and it resulted in physiologically unrealistic insulin profiles characterized by high amplitude sustained oscillations (ringing). An insensitive model was introduced, most likely based on a type of dead-band control, but no method for its development was discussed.

Fisher [68] performed another study of the “minimal model,” also using an ISE-based objective function. His cost criterion minimized deviations in glucose concentration from a reference value. As a secondary objective, the amount of insulin to perform the corrective action was minimized. The study examined three insulin infusion profiles, determining that an initial injection plus optimal hourly infusion minimized the cost function for an initially hyperglycemic patient. Similar to the control design of Ollerton [40], this algorithm was not robust to patient uncertainty, and it also suffered from the long sampling time (180 min) problem of missing fast or inter-sample disturbances.
Parker, et al. [69], and Parker [71] examined the use of a model predictive controller (MPC), both with and without state estimation, for regulating blood glucose. Controller synthesis was accomplished by linearizing a modified version of the nonlinear patient model from Sorensen [72]. This controller solved an optimization problem with a quadratic objective function at each time step. Terms were included for setpoint tracking over a future prediction time horizon as well as a penalty for insulin delivery. Constraints on insulin delivery rate and rate of change were included in the control algorithm, and the linear controller was evaluated in simulation studies treating the full nonlinear model as the patient. Disturbance rejection and hyperglycemic initial condition simulations showed the efficacy of the controller, which maintained glucose above the hypoglycemic bound of 60 mg/dL as well as regulated blood glucose within 20 mg/dL of the 80 mg/dL setpoint when challenged with unmeasured 50 g meal disturbances. It was also demonstrated that a nonlinear control algorithm (nonlinear quadratic dynamic matrix control with state estimation [67]) did not radically improve blood glucose control.

2.4.4 Model-Based Predictive Control Under Patient Uncertainty

Model predictive control has characteristics that make it an attractive choice for blood glucose concentration regulation. These include (i) the ability to regulate nonlinear systems using a linear algorithm; (ii) inherent input constraint handling; (iii) the explicit prediction of future behavior based on past manipulated variable moves; and (iv) straightforward incorporation of parameter updating. The unconstrained controller guarantees optimal drug delivery through solution of an optimization problem at each time step [73]. Although significant computational power can be required, an analytic solution is available in the unconstrained case [73]. A key benefit of using predictive control in place of a classical control algorithm is the estimation of future glucose behavior based on the past insulin inputs using an explicit model of patient dynamics. As a result, the MPC controller can adjust insulin delivery in response to a predicted hypo- or hyperglycemic excursion well before the event occurs. A feedback-only controller would respond only after the effect of the disturbance manifests itself in the measured output. The patient glucose concentration measurement is used as a feedback signal to correct the predictions for deviations between the internal model and the actual patient dynamics. The human glucose-insulin control problem has inherent input rate and magnitude constraints, as well as an output magnitude constraint, which are all incorporated into the MPC algorithm [73, 74] in a straightforward manner. In the controller development, an implantable glucose sensor is considered with measurements representative of the well-mixed blood being delivered to the organs (an “arterial” glucose measurement). Insulin delivery is assumed to be directly into
the venous bloodstream, such that the controller could be utilized in both an implantable device as well as a bedside or portable unit for hospitalized patients. Although research has demonstrated that portal vein insulin delivery is necessary to return the diabetic glucose distribution to that of a healthy patient [75], the choice of delivery location does not have a dramatic impact on the ability to regulate glucose concentration.

Although many of the above control methodologies demonstrated adequate performance, the inherent uncertainty in the model (or patient) typically has not been explicitly addressed. This omission can lead to significant performance degradation should the model parameters not represent the actual dynamics of patient glucose and insulin dynamics. Significant variability among patients, and within a given patient over the course of a day or week, has been documented in the literature [76-79]. To avoid complete retuning of the controller for each patient, while recognizing that some minor patient-to-patient adjustments will be required, the control algorithms utilized in an insulin delivery device must be able to compensate for the uncertainty that exists between the internal model and the actual patient. An adaptation mechanism that updates the controller internal model based on the variability between the predicted glucose concentration and the measured patient glucose concentration is incorporated into the MPC with state estimation (MPCSE) algorithm developed in [69]. The resulting MPC with state and parameter estimation (MPCSPE) algorithm updates selected model parameters through a Kalman filter at each time step [80].

2.4.5 Uncertainty Characterization

Uncertainty due to differences between an actual patient and the diabetic patient model may be related to variations in model parameters. A sensitivity analysis, using the modified Sorensen model [71, 72], identified the metabolic terms as most responsible for changes in blood glucose and insulin dynamics, and glucose metabolism is described by the following threshold function:

$$\Gamma_e = E \left\{ A_f + B_f \tanh\left[ C_f \left( x_i + D_f \right) \right] \right\} \quad (1)$$

Here the subscript $i$ is the state vector element involved in the metabolic effect and the $e$ subscript denotes specific effects within the model, such as the effect of glucose on hepatic glucose production (EGHGP), the effect of glucose on hepatic glucose uptake (EGHGU), or the effect of insulin on peripheral glucose uptake.
(EIPGU). Inter- or intra-patient uncertainty could be classified physiologically as either a receptor (parameter) or post-receptor (EΓ parameter) defect. This uncertainty formulation implies a structured effect of variability on the model, such that the tissues most important to parametric uncertainty are the liver and the peripheral (muscle/fat) tissues.

Parametric sensitivity was determined individually and pair-wise for the glucose metabolic parameters in the diabetic patient model. Mathematically, it was assumed that 50% parametric variability represented a broad range of potential patients. Parameter sets were contrasted using sensitivity in the large [81], where the time-domain SSE between the nominal and parametrically perturbed patient models was the sensitivity criterion. The up-to-four possible parameter pairings were combined with a series of five insulin step changes from the nominal delivery rate in the analysis. A “total sensitivity” was used for comparison, where the total represented the summation of squared errors for: (i) a specified parameter or parameter pair perturbation set, and (ii) the series of insulin step changes.

The most sensitive parameter pairing that resulted from this procedure was EGHGP-EΓ with EIPGU-DΓ, which had 17% more total error than the next highest pairing. A concise graphical analysis is shown in Fig. 2. Variations in the EGHGP- EΓ parameter had dramatic effects on the process dynamic response, with the ±50% changes shown by the dashed lines. The range of possible process behaviors displayed by the perturbed models was further increased by adding the EIPGU- DΓ parameter variations to those of EGHGP- EΓ. Note that increases in EGHGP- EΓ and decreases in EIPGU- DΓ produced the worst-case variations shown in Fig. 2. Also, observe that greater variability in process dynamics and steady-state behavior was demonstrated by insulin-sensitive patients (lower dashed and dash-dot lines in the figure), while insulin-resistant patients were dynamically similar, with only moderate steady-state variation.
2.4.6 Derivative Control

J. Geoffrey Chase, et al. [80-83] have applied a modified PD control algorithm in their insulin infusion system. In their work, they have used a PD controller with heavy emphasis on the derivative term. They found that the derivative term outperforms the typically used proportional-weighted controllers in glucose tolerance and multi-meal tests. The form of the PD controller is:

\[
    u(t) = u_0 \left(1 + k_p G + k_d \dot{G}\right)
\]

This controller incorporates proportional and derivative control with independent weightings and the basal infusion \(u_0\). Heavy emphasis implies that the derivative gain, \(k_d\), is significantly larger than the proportional gain, \(k_p\). As a result, this controller focuses almost exclusively on controlling the slope of the blood glucose curve rather than its absolute magnitude. This approach is a far different one than normally taken and made possible by the emerging capability to measure blood sugar far more regularly via semi- or non-invasive means.
The optimal control discussed in the earlier section has also been explored by J. Geoffrey Chase, et al. [80, 81]. The equation applied is:

\[
u(t) = \frac{V}{p_b G_b} \left[ \dddot{P}(t) + \dot{P}(0) + (n + p_2) \left( \dot{P}(t) + P(0) \right) + np_2 P(t) \right] + u_0
\]

The optimal solution includes first and second derivatives of the exogenous glucose \( P(t) \). However, it is unrealistic to implement since \( P(t) \) is not known a priori, and because it is not practical to remove insulin (or add glucose) as is suggested if some terms become negative. This equation is also an explicit function of the time constants and other model parameters subjecting it to potential modeling error. This solution does act as a benchmark for the performance of the other controllers.

J. Geoffrey Chase, et al. [80, 81] have also explored the Relative Proportional Control (RPC) [84].

\[
u(t) = u_b \left( 1 + \frac{G}{G_b} \right), \quad u_0 = nV I_b
\]

This controller is based on a relative proportional control \((G/G_b)\) with a constant term. Note that \( G = G_b \), the blood sugar is at the desired level and the insulin infusion rate \( u_0 \), the basal infusion rate necessary to maintain blood glucose at a constant level.

J. Geoffrey Chase, et al. [80, 81] have modeled the OGTT by equation:

\[
P(t) = P_m \exp \left( -a \left( \ln (bt) - c \right)^2 \right)
\]

where \( P_m \) is the peak value and \( a, b \) and \( c \) are constants, which determine the slopes and curvatures.
Figure 2.5 Glucose input model of OGTT curve used in the simulations by Geoffrey Chase, et al. [80-81].

The Figure 2.6 shows the glucose response for an OGTT using the PD controller with sensor measures every 1 and 20 min, and for the RPC system measuring every 20 min. The nearly flat optimal control result is shown as well. There is also a graph of no controller, labeled ‘Accumulation of glucose input’, which shows glucose input profile.

Figure 2.6 Glucose response for an OGTT [81].
The Figure 2.7 shows the insulin infusion rate for the RPC and PD controllers, where the step shape is due to the 20 min between sensor measurements and changes to the insulin infusion (control) input. Note that the insulin infusion rate is smoother and more like an injection for the PD controller in both cases and particularly when sensor measurements are made every minute.

In judging controller performance the critical factors are the magnitude of the excursion for a given input and the time required to return to basal blood sugar levels. The PD controller limits the excursion and returns to the basal level much faster, in each case, due to the higher infusion rates generated by large initial slopes of the glucose curve.

As seen in Figure 4, the optimal controller has an almost flat response. The insulin infusion rate for the optimal solution is not shown, however, it is effectively an injection of approximately 3U of insulin followed by a small glucose infusion over 25 min. Although the optimal solution cannot be practically implemented, it does show that the optimal solution approaches current injection practice in a way that achieves neat perfect glucose response given the controllers knowledge of the input $P(t)$. 

Figure 2.7 Insulin infusion rate for an OGTT [80-81].
2.4.7 Multi-Meal Tests

J. Geoffrey Chase, et al. [81] have designed multi-meals tests to give the system a more strenuous physiological test such as two meals within 6 h. The inputs vary in magnitude from 50 to 400 kcal and are given in two groups, at \( t = 0, 10, 30 \) min and for the second meal at \( t = 210 \) and \( 300 \) min. At the end of 6 h, the total intake of glucose into the body is over 1000 kcal with 1000 kcal input over the first 4 h. Fig. 6 shows the glucose input profile for these meals and the results are shown in Figures 2.9 – 2.11.

![Figure 2.8 Multi-meal glucose input profile [81].](image)

The Figure 2.9 shows that the PD controller works slightly better than a normal person, in terms of peak reduction as well as settling time with a sensor bandwidth of 1 min. This result illustrates the potential of this controller to replace physiological dysfunction. Figure 2.9 also includes a plot of the response for a normal subject under the same conditions.
Figure 2.9 Glucose level of a normal human and controlled diabetic individual with 1-min sampling period for each controller type.

Figure 2.10 compares results at different sensor bandwidths and Figure 2.11 shows the insulin infusion profiles. These figures show similar trends to the OGTT results, where the more the insulin infusion profile tends towards injections, the better the control of blood sugar. For the optimal controller, inset in Figure 2.10 with a scaled glucose input profile, the insulin input is essentially two injections closely following the onset of each meal. The optimal controller glucose curve in Figure 2.10 is nearly flat and as the sensor sampling period approaches zero this solution should not vary at all to glucose inputs.
Figure 2.10 Multi-meal glucose level for controllers at different sampling periods.

It is worth noting that the RPC performance is relatively resistant to changes in sampling period from 1 to 20 min. The PD controller result almost doubles in magnitude and requires slightly more time to return to basal level. The PD controller with a sample period of 20 min also has a slightly hypoglycemic response where the graph dips just below the basal value.

Figure 2.11 Infusion rate for controllers at different sampling periods for the multi-meal test.
The primary results from this testing are that the algorithm is robust to significant multiple inputs with the same gains as designed for OGTT inputs and that as sampling period decreases the insulin input profile for the PD controller approaches that of injections at the beginning of a meal input. This latter result tends to match current accepted clinical practice for the management of Type I diabetes in New Zealand and elsewhere. In particular, the PD controller with derivative weighting provides a basal input, $u_0$, in the absence of elevated blood sugar and leads to injection-like insulin infusion profiles when glucose inputs are applied. In clinical practice low, basal insulin infusion is required to prevent diabetic ketoacidosis (DKA) in the absence of insulin in the system, while injections of rapid-acting insulin are used to handle meals and other post-prandial glucose spikes. Basal levels are typically maintained, clinically, via long-acting insulin injections. As a result, the behaviour of the derivative-weighted PD controller mimics current clinical practice that has evolved over several years with a basal infusion level augmented in injection-like insulin infusion profiles for hyperglycemic events due to exogenous glucose input. Hence, there exists a great similarity between the insulin infusion profile for the PD and optimal controllers, and typical clinical recommendations using current practice. The primary difference is that these controllers are able to effectively take advantage of a greater amount of blood glucose data using a model-based controller.
2.5 Non-Invasive Insulin Deliver System

Since the introduction of the first through the skin (TTS) therapeutic in 1980, a total of 34 TTS products have been marketed and numerous drugs have been tested by more than 50 commercial organisations for their suitability for TTS delivery [122]. Most of the agents which have been tested have had low molecular weights, due to the impermeability of the skin barrier. This barrier resides in the outermost skin layer, the stratum corneum. It is mechanical, anatomical, as well as chemical in nature; laterally overlapping cell multi-layers are sealed by tightly packed, intercellular, lipid multi-lamellae. Chemical skin permeation enhancers increase the transport across the barrier by partly solubilising or extracting the skin lipids and by creating hydrophobic pores. This is often irritating and not always well-tolerated. The TTS approach allows drugs (< 400 kDa in size) to permeate through the resulting pores in the skin, with a short lag-time and subsequent steady-state period. Drug bioavailability for TTS delivery is typically below 50%, avoiding the first pass effect. Wider, hydrophilic channels can be generated by skin poration, with the aid of a small electrical current (> 0.4 mA/cm2) across the skin (iontophoresis) or therapeutic ultrasound (few W/cm2; sonoporation). High-voltage (> 150 V, electroporation) widens the pores even more and often irreversibly. These standard poration methods require experience and equipment and are therefore, not practical; at best, charged/small molecules (< or = 4000 kDa in size) can be delivered efficiently across the skin. In spite of the potential harm of gadget-driven skin poration, this method is used to deliver molecules which conventional TTS patches are unable to deliver, especially polypeptides. Lipid-based drug carriers (liposomes, niosomes, nanoparticle microemulsions, etc.) were proposed as alternative, low-risk delivery vehicles. Such suspensions provide an improved drug reservoir on the skin, but the aggregates remain confined to the surface. Conventional carrier suspensions increase skin hydration and/or behave as skin permeation enhancers. The recently developed carriers; Transferomes [112], comprise pharmaceutically-acceptable, established compounds and are thought to penetrate the skin barrier along the naturally occurring transcutaneous moisture gradient. Transfersomes are believed to penetrate the hydrophilic (virtual) channels in the skin and widen the former after non-occlusive administration. Both small and large hydrophobic and hydrophilic molecules are deliverable across the stratum after conjugation with Transfersomes. Drug distribution after transdermal delivery probably proceeds via the lymph. This results in quasi-zero order kinetics with significant systemic drug levels reached after a lag-time of up to a few hours. The relative efficiency of TTS drug delivery with Transfersomes is typically above 50%; with the added possibility of regional drug targeting.
Using Transfersomes [113], ensures reproducible and efficient transcutaneous carrier and drug transport. Insulin-loaded Transfersomes, for example, can deliver the drug through the non-compromised skin barrier with a reproducible drug effect that resembles closely that of an ultralente insulin injected under the skin; the pharmacokinetic and pharmacodynamic properties of the injected and transdermal insulin are also comparable. The efficacy of transcutaneously delivered insulin in Transfersomes is not affected by the previous therapy, similar results having been measured in patients normally receiving intensified insulin therapy or a continuous subcutaneous infusion of insulin solution.

**2.5.1 Insulin Delivery by Ultrasound**

Seungjun Lee, et al. [5, 115] have demonstrated the feasibility of using short ultrasound exposure times to noninvasively deliver insulin with a lightweight (<22 g), low-profile (37 x 37 x 7 mm$^3$) cymbal array (f = 20kHz).

![Figure 2.12](image)

**Figure 2.12** The cymbal transducer made of piezoelectric material PZT-4 operated at a frequency of 20kHz. The cymbal disk was placed between two titanium caps with air cavities beneath the caps that give rise to radial oscillations of the disk [5, 115].
The lightweight, low-profile array was constructed using 4 cymbal transducers connected in parallel and encased in URALITE polymer. The dimensions of the array were 37x37x7 mm$^3$ and it weighed less than 22g [5].

The device has been demonstrated successfully on diabetic rats to delivery insulin transdermally in a short period of time. But the intensity of the ultrasound energy must be kept low (100-125mW/cm$^2$) without damaging the skin.
Figure 2.14 Over a period of 90 minutes, the blood glucose level of the rats decreased from the insulin with ultrasound (US) exposure ($I_{sep} = 100\text{mW/cm}^2$) using the cymbal array. Both control experiments (insulin-no US or saline-US) varied no greater than 40 mg/dl over the 90 minutes from the baseline. With 10 minutes of ultrasound exposure, the glucose level decreased -224.7 mg/dl, and the 5 minutes of ultrasound exposure decreased the glucose level -233.3 mg/dl [5].

2.5.2 Insulin Delivery by Pulsation

Zakzeswski C, el at. [85] have applied electrically-enhanced iontophoretic transdermal delivery of insulin. The iontophoretic drug electrode was filled with insulin.
Figure 2.15 Profile of the pulsed current simulation used to enhance transdermal penetration of insulin [85].

They found that when iontophoretic drug electrode was applied on the shaved skin surface, regular insulin (100 IU/ml) did move across the skin and reduce blood glucose levels in the chronic diabetic rat model.

Sershen SR, et al. [116] have applied composites of thermally-sensitive hydrogels and optically-active nanoparticles for transdermal photothermally modulated drug delivery. Copolymers of N-isopropylacrylamide (NIPAAm) and acrylamide (AAm) exhibit a lower critical solution temperature (LCST) that is slightly above body temperature. Gold-gold sulfide nanoshells have been incorporated into poly(NIPAAm-co-AAm) hydrogels to initiate a temperature change with light. The nanoshells heat upon irradiation at their peak absorption wavelight, causing the collapse of the polymer and the subsequent release of any drug contained within the polymer matrix. For this to occur, the light must pass through the skin and retain enough power to cause sufficient heating in the nanoshells. Light between 800 and 1200 nm has been shown to have relatively low levels of attenuation in tissue. Composite polymers of the nanoshells and NIPAAm-co-AAm can deliver controlled pulsatile doses of insulin in response to near-IR (NIR) irradiation. The activity of the released insulin was determined by measuring glucose uptake by adipocytes that had been exposed to photothermally released insulin.

The Figure 2.16 shows the multiple “bursts” of release of insulin from nanoshell-composite hydrogels via periodic irradiation. The release rate of insulin peaks during the periods in which the laser was active, and returns to a baseline level once the laser is turned off.
Figure 2.16 Release rate of insulin from nanoshell-composite hydrogels in response to cyclic irradiation of 821 nm (1.7 W/cm²). The data are mean ± SEM. The lower graph shows the irradiation response [116].

2.5.3 Glucose Responsive Insulin Release System and Techniques

Since 1980s, a new type microcapsules, environmental stimuli-sensitive microcapsules have been investigated widely. These microcapsules can control permeation of their contents responding to environmental stimuli. They are considered to have potential usefulness as a controlled release system especially a drug delivery system, because the target of a controlled drug delivery system is for an improved drug treatment (outcome) through rate- and time-programmed and site-specific drug delivery [88]. By encapsulated inside these microcapsules, chemicals or drugs can be released at a desired rate only when and/or where the release is needed. Up to date, environmental stimuli-sensitive microcapsules have been reported to act in response to changes in environmental temperature [89–95], pH [96–102], light [103], external electric field [104], redox [105], ions [106], and other stimuli, and these “smart” microcapsules are gathering increasing attention. In order to promote the applications of environmental stimuli-responsive microcapsules, development of new signal-sensitive microcapsules remains essential.
Chu LY, et al. [87] have developed a glucose-sensitive microcapsule with a porous membrane and glucose-responsive functional gates is prepared by using plasma-graft pore-filling polymerization method. The concept of the proposed microcapsule is schematically illustrated in Figure 2.17. The proposed microcapsule is composed of a porous membrane and linear grafted polyacrylic acid (PAAC) chains in the membrane pores and covalently bound glucose oxidase (GOD) enzymes. The linear grafted PAAC chains in the membrane pores act as the pH-responsive gates, and the immobilized GOD enzymes act as glucose sensors and catalyster. At neutral pH in the absence of glucose, the pores in the microcapsule membrane are closed because the repulsion between negative charges make the PAAC chains extended; On the other hand, when environmental glucose concentration increases, GOD catalyzes the oxidation of glucose into gluconic acid, as a result the grafted PAAC chains shrink because of the reduced electrostatic repulsion and then the pores open. This is the first time that glucose-sensitive hollow microcapsule particulate drug carriers with a porous membrane and functional gates have been fabricated.
Figure 2.17 Schematic [87] representation of the glucose-sensitive release principle of microcapsules with a porous membrane and functional gates. The microcapsule is composed of a core-shell porous membrane and grafted PAAC chains and covalently bound glucose GOD enzymes in the pores. The substance to be released is dissolved in a solution inside the microcapsule interior. At neutral pH in the absence of glucose, the membrane pores are closed because the repulsion between negative charges make the PAAC chains extended; when environmental glucose concentration increases, the grafted PAAC chains shrink because of the reduced electrostatic repulsion and then the pores open.

The developed glucose-sensitive microcapsule with a porous membrane and with linear-grafted polyacrylic acid (PAAC) chains and covalently bound glucose oxidase (GOD) enzymes in the membrane pores acting as functional gates was successfully prepared. Polyamide microcapsules with a porous membrane were prepared by interfacial polymerization, PAAC chains were grafted into the pores of the microcapsule membrane by plasma-graft pore-filling polymerization, and GOD enzymes were immobilized onto the PAAC-grafted microcapsules by a carbodiimide method. The release rates of model drug solutes from the fabricated microcapsules were significantly sensitive to the existence of glucose in the environmental solution. In solution, the release rate of either sodium chloride or VB_{12} molecules from the
microcapsules was low but increased dramatically in the presence of 0.2 mol/L glucose. The prepared PAAC-grafted and GOD-immobilized microcapsules showed a reversible glucose-sensitive release characteristic. The proposed microcapsules provide a new mode for injection-type self-regulated drug delivery systems having the capability of adapting the release rate of drugs such as insulin in response to changes in glucose concentration, which is highly attractive for diabetes therapy.

Liang YC, et al. [86] have developed a glucose-responsive gating membranes with grafted poly(acrylic acid) (PAAC) gates and covalently bound glucose oxidase (GOD) were prepared by grafting PAAC onto porous polyvinylidene fluoride (PVDF) membrane substrates with a plasmagraft pore-filling polymerization method [107–110], and immobilizing GOD onto the grafted membranes with a carbodiimide method [111]. The preparation process route and the principle of glucose-responsive control of the permeation through the gatingembrane are schematically illustrated in Figure 4. Investigations were carried out on the morphological examination of the grafting, on the control of pH-responsive pore size of the membrane and pH- and glucose-responsive permeability through the membrane by the PAAC grafting yield, and on the glucose-responsive insulin diffusion coefficient.

Liang YC, et al. [86] have developed membrane with a pore size and permeability control of a glucose-responsive gating membrane with plasma-grafted poly(acrylic acid) (PAAC) gates and covalently bound glucose oxidase (GOD) enzymes were investigated systematically. The PAAC-grafted porous polyvinylidene fluoride (PVDF) membranes with a wide range of grafting yields were prepared using a plasma-graft pore-filling polymerization method, and the immobilization of GOD was carried out by a carbodiimide method. The linear grafted PAAC chains in the membrane pores acted as the pH-responsive gates or actuators. The immobilized GOD acted as the glucose sensor and catalyzer; it was sensitive to glucose and catalyzed the glucose conversion to gluconic acid. The experimental results showed that the glucose responsivity of the solute diffusional permeability through the proposed membranes was heavily dependent on the PAAC grafting yield, because the pH-responsive change of pore size governed the glucose-responsive diffusional permeability. It is very important to design a proper grafting yield for obtaining an ideal gating response. For the proposed gating membrane with a PAAC grafting yield of 1.55%, the insulin permeation coefficient after the glucose addition (0.2 mol/l) was about 9.37 times that in the absence of glucose, presenting an exciting result on glucose-sensitive self-regulated insulin permeation.
Figure 2.18 Schematic [86] illustration of the preparation process route and the principle of glucose-responsive control of the permeation through the gating membrane: (a) porous membrane substrate; (b) pH-responsive gating membrane with poly(acrylic acid) (PAAC) gates prepared using a plasma-graft pore-filling polymerization to graft linear PAAC chains into the pores of the membrane substrate; (c) glucose-responsive gating membrane prepared by immobilizing glucose oxidase (GOD) onto the PAAC-grafted membrane. At neutral pH in the absence of glucose, the carboxyl groups of the grafted PAAC chains are dissociated and negatively charged, therefore the membrane gates ‘‘closed’’ because the repulsion between negative charges make the PAAC chains extended; and (d) when glucose concentration increased, GOD catalyzes the oxidation of glucose into gluconic acid, thereby lowering the local pH in the microenvironment, protonating the carboxylate groups of the grafted PAAC chains, therefore the gates ‘‘open’’ because of the reduced electrostatic repulsion between the grafted PAAC chains in the pores.

The membrane developed by Liang YC, et al. [86] shows that the glucose-responsive diffusional permeability of insulin through the proposed gating membrane with PAAC grafting yield of 1.55% caused by glucose addition. In the absence of glucose, the diffusional permeation coefficient of insulin molecules across the membrane was as
low as $0.79 \times 10^{-7}$ cm$^2$/s, and the amount of insulin permeated increased linearly with time. When the environmental glucose concentration was changed from 0 to 0.2 mol/l by adding glucose, the insulin permeation coefficient increased to $7.40 \times 10^{-7}$ cm$^2$/s dramatically. The permeation coefficient after the glucose addition was about 9.37 times that before the addition of glucose. The results presented an exciting glucose-sensitive self-regulated permeation of insulin molecules.

![Figure 2.19 Glucose-responsive diffusional permeation of insulin through the proposed gating membrane with PAAC grafting yield of 1.55% [86].](image)

### 2.5.4 Inhale Insulin

Subcutaneous injection has been the only route of insulin administration for patients with type 1 or type 2 diabetes for the past 80 years. Although research and development in this time has improved the insulin treatments themselves, it is only now that alternative routes of insulin administration are becoming viable. Many avenues of insulin administration have been explored, including oral, buccal, and pulmonary routes. However, these methods of noninvasive insulin delivery are not free from difficulties and only preliminary data are available for oral insulin pills and buccal insulin sprays. The most promising alternative route of delivery appears to be inhaled insulin and two devices are already in phase III testing [114].
2.6 System Block Diagram

The figure below shows the control block of the artificial pancreas without Insulin Sensor. The glucose sensor monitors the blood glucose concentration continuously. Each sample will refine the controller response.

![Block diagram of an insulin infusion system without insulin sensor.](image)

**Figure 2.20** Block diagram of an insulin infusion system without insulin sensor.

![Responses of controllers based on patient D18 data.](image)

**Figure 2.21** Responses of controllers based on patient D18 data.
The figure below shows the control block of the artificial pancreas with Insulin Sensor.

![Diagram of the Insulin Release System]

**Figure 2.22** Overview of the Insulin Release System. In this system, there are two sensors; namely non-invasive glucose and insulin sensors. The sensors provide the instant glucose and insulin concentrations to the respective computation sub-systems. In turn, the Glucose-Insulin Kinetics System Response Parameters Computer will derive the required amount of insulin the human biological system required after a meal.

### 2.6.1 Non-Invasive Blood Glucose Sensor

Numerous methods and techniques have been explored for measuring blood glucose levels, ranging from invasive methods such as microdialysis to noninvasive technologies such as spectroscopy and millimeter waves.

### 2.6.2 Non-Invasive Insulin Sensor

#### 2.6.2.1 Blood Glucose Response Computer

This controller is constructed based on the formulation as described in the previous chapter. It will calculate the values of $A$, $G$ and $\omega$ for underdamp, critical and overdamp scenarios based on the glucose concentration response, $y(t)$. 

127
2.6.2.2 Insulin Response Computer

This controller is constructed based on the formulation as described in the previous chapter. It will calculate the values of $\beta$, $x'$ for underdamp, critical and overdamp scenarios based on the insulin concentration $x(t)$ response caused by the glucose input impulse, $y(t)$ and the preceding controller’s $A$, $G$ and $\omega$ outputs.

2.6.2.3 Glucose-Insulin Kinetics System Response Parameters Computer $(\alpha, \gamma, \delta)$

This controller is constructed based on the formulation as described in the previous chapter. It will calculate the values of $\alpha$, $\gamma$, $\delta$ for underdamp, critical and overdamp scenarios based on the insulin concentration $x(t)$ response caused by the glucose input impulse, $y(t)$ and the preceding controller’s $A$, $G$, $\beta$ and $x'$ outputs.

It will calculate the physiological indexes and determine if the patient is normal, at-risk and diabetic. It will determine the insulin amount requires at that moment and send a signal which represents the amount of insulin requires in the blood-pool. This amount is modulated by the current amount of insulin present in the blood pool. The resulting amount will be sent to the next module for insulin release.

2.7 Control System

We will discuss the design of the insulin infusion controller in this chapter. The basics in control theory can be found in the standard reference book by Ogata [79]. The key function of the controller in our system is to bring the blood glucose concentration down as soon as possible but prevent hypoglycemia within a sample period of two hours.

We will discuss the three common control techniques and recommend the most suitable controller type for the insulin infusion system.

2.7.1 Time-Domain Interpretation of Proportional-Derivative (PD) Control

The effect of the PD control on the transient response of a control system can be investigated by referring to the time responses shown in the following figure.
Assuming that a unit-step response of a stable system with only proportional control is as shown in (a), which has a relatively high maximum overshoot and is rather oscillatory. The corresponding error signal, which is the difference between the unit-step input and the output $y(t)$, and its time derivative $de(t)/dt$ are shown in (b) and (c) respectively. The overshoot and oscillation characteristics are also reflected in $e(t)$ and $de(t)/dt$.

Figure 2.23 Waveforms of $y(t)$, $e(t)$, and $de(t)/dt$, showing the effect of derivative control. (a) Unit-step response, (b) Error signal and (c) Time rate of change of the error signal [78].

For the sake of illustration we assume that the system contains a motor of some kind with its torque proportional to $e(t)$. The performance of the system with proportional control is analyzed as follows:

(a) During the time interval, $0 < t < t_1$. The error signal $e(t)$ is positive. The motor torque is positive. The large overshoot and subsequent oscillations in the output $y(t)$ are due to the excessive amount of torque developed by the motor and the lack of damping during this time interval.
(b) During the time interval, \( t_1 < t < t_3 \). The error signal \( e(t) \) is negative, and the corresponding motor torque is negative. This negative torques tends to slow down the output acceleration and eventually causes the direction of the output \( y(t) \) to reverse and undershoot.

(c) During the time interval, \( t_3 < t < t_5 \). The motor torque is again positive, thus tending to reduce the undershoot in the response caused by the negative torque in the previous time interval. Since the system is assumed to be stable, the error amplitude is reduced with each oscillation, and the output eventually settles to its final value.

Considering the analysis above of the system time response, we can say that the contributing factors to the high overshoot are:

(a) The positive correcting torque in the interval \( 0 < t < t_1 \) is too large.
(b) The retarding torque in the time interval \( t_1 < t < t_2 \) is inadequate.

Therefore, to reduce the overshoot in the step response, without significantly increasing rise time, a logical approach would be to:

(a) Decrease the positive correcting torque in the interval \( 0 < t < t_1 \).
(b) Increase the retarding torque during \( t_1 < t < t_2 \).

Similarly, during the time interval, \( t_2 < t < t_4 \), the negative corrective torque in \( t_2 < t < t_3 \), should be reduced, and the retarding torque during \( t_3 < t < t_4 \), which is now in the positive direction, should be increased to improve the undershoot of \( y(t) \).

The PD series controller can be described with the transfer function:

\[
G_c(s) = k_p + k_ds
\]

where \( k_p \) and \( k_d \) are the proportional and derivative constants, respectively.

The PD control described by the above equation gives precisely the compensation effect required.

(a) For \( 0 < t < t_1 \), \( de(t)/dt \) is negative; this will reduce the original torque developed due to \( e(t) \) alone.
(b) For $t_1 < t < t_2$, both $e(t)$ and $de(t)/dt$ are negative, which means that the negative retarding torque developed will be greater than that with only proportional control.

(c) For $t_2 < t < t_3$, $e(t)$ and $de(t)/dt$ have opposite signs. Thus the negative torque that originally contributes to the undershoot is reduced.

Therefore, all these effects will result in smaller overshoots and undershoots in $y(t)$.

Since $de(t)/dt$ represents the slope of $e(t)$, the PD control is essentially an anticipatory control. That is, by knowing the slope, the controller can anticipate direction of the error and use it to better control the process. Normally, in linear systems, if the slope of $e(t)$ or $y(t)$ due to a step input is large, a high overshoot will subsequently occur. The derivative control measures the instantaneous slope of $e(t)$, predicts the large overshoot ahead of time and makes a proper corrective effort before the excessive overshoot actually occurs [78, 79].

Derivative control affects the steady-state error of a system only if the steady-state error varies with time. If the steady-state error of a system is constant with respect to time, the time of this error is zero, and the derivative portion if the controller provides no input to the process. But the steady-state error increases with time, a torque is developed in portion to $de(t)/dt$, which reduces the magnitude of the error.

2.7.1.1 Frequency-Domain Interpretation of Proportional-Derivative (PD) Control

For frequency-domain design, the transfer function of the PD controller is given by:

$$G_c(s) = k_p + k_ds = k_p\left(1 + \frac{k_d}{k_p}s\right)$$

So that it is more easily interpreted on the Bode plot. The Bode plot of the above equation is shown in the following figure with $k_p=1$. In general, the proportional-control gain $k_p$ can be combined with a series gain of the system, so that the zero-frequency gain of the PD controller can be regarded as unity. The high-pass filter characteristics of the PD controller are clearly shown by the Bode plot as follows. The phase-lead property may be utilized to improve the phase margin of a control system. Unfortunately, the magnitude of the PD controller pushes the gain-crossover
frequency to a higher value. Thus the design principle of the PD controller involves the placing of the corner frequency of the controller, \( \omega = k_p/k_D \), such that an effective improvement of the phase margin is realized at the new gain-crossover frequency. For a given system, there is a range of values of \( k_p/k_D \) that is optimal for improving the damping of the system. Another practical consideration in selecting the values of \( k_p \) and \( k_D \) is in the physical implementation of the PD controller. Other apparent effects of the PD control in the frequency domain is that due to its high-pass characteristics, in most cases it will increase the BW of the system and reduces the rise time of the step response. The practical disadvantage of the PD controller is that the differentiator portion is a high-pass filter, which usually accentuates any high-frequency noise that enters at the input.

Figure 2.24 Bode diagram of \( 1 + k_D/k_p \cdot k_p=1 \) [78].
2.7.1.2 Effects of PD Control

A properly designed PD controller will affect the performance of a control system in the following ways:

(a) Improves damping and reduces maximum overshoot.
(b) Reduces rise time and settling time.
(c) Increases bandwidth (BW).
(d) Improves gain margin (GM), phase margin (PM) and maximum resonant amplitude (Mr).
(e) May accentuates noise at higher frequencies.
(f) Not effective for lightly damped or initially unstable systems.

Figure 2.25 Unit-step responses of the attitude control system with and without PD control [78].
Figure 2.26 The plot of $k_P$ versus $k_D$ parameter plane for a PD control system with 
\[ \xi = \frac{0.2 + 451.46k_D}{\sqrt{k_P}} \] [78].
2.7.2 Proportional-Integral (PI) Control

In the previous section, we can observe that PD controller can improve the damping and rise time of a control system at the expense of higher bandwidth and resonant frequency, and the steady-state error is not affected unless it varies with time, which is typically not the case for step-function inputs.

The integral part of the PID controller produces a signal that is proportional to the time integral of the input of the controller. The transfer function of the PI controller is:

\[ G_c = k_p + \frac{k_i}{s} \]

The immediate effect of the PI controller are:

(a) Add a zero at \( s = -\frac{k_i}{k_p} \) to the forward-path transfer function.

(b) Adds a pole at \( s = 0 \) to the forward-path transfer function. This means that the system is increased by one to a type-2 system. Thus the steady-state error of the original system is improved by one order; that is, if the steady-state error to a given input is constant, the PI control reduces it to a zero (provided that the compensated system remains stable).

2.7.2.1 Time-Domain Interpretation of Proportional-Integral (PI) Control

The pole-zero configuration of the PI controller as shown by the equation above is shown in the following figure. At the first glance it may seem that the PI control will improve the steady-state error at the expense of stability. However, if the location of the zero of \( G_c(s) \) is properly selected, both the damping and steady-state error can be improved.
Since the PI controller is essentially a low-pass filter, the compensated system usually will have a slower rise time and longer settling time. A feasible method of designing the PI control is to select the zero at \( s = -\frac{k_i}{k_p} \) so that it is relatively close to the origin and away from the most significant poles of the process, and the values of \( k_p \) and \( k_i \) should both be relatively small.

### 2.7.2.2 Frequency-Domain Interpretation of Proportional-Integral (PI) Control

For the frequency-domain design the transfer function of the PI controller is written:

\[
G_c = k_p + \frac{k_i}{s} = \frac{k_i (1 + k_p/k_i) s}{s}
\]

The Bode plot of \( G_c(j\omega) \) is shown in the figure below. Notice that the magnitude of \( G_c(j\omega) \) at \( \omega = \infty \) is \( 20\lg k_p \) dB, which represents an attenuation if the value of \( k_p \) is less than 1. This attenuation may be utilized to improve the stability of the system. The phase of \( G_c(j\omega) \) is always negative, which is detrimental to stability. Thus we should place the corner frequency of the controller, \( \omega = k_i/k_p \), as far to the left as the bandwidth requirement allows, so that the phase-lag properties of \( G_c(j\omega) \) do not degrade the achieve phase margin of the system.
Figure 2.28 Bode plot of the PI controller $G_c = k_p + \frac{k_i}{s}$ [78].

### 2.7.2.3 Effects of PI Control

A properly designed PI controller will affect the performance of a control system in the following ways:

(a) Improved the damping and reduces maximum overshoot.
(b) Increases rise time.
(c) Decreases BW.
(d) Improves gain margin (GM), phase margin (PM) and maximum resonant amplitude ($M_r$).
(e) Filters out high frequencies noise.
(f) Not effective for lightly damped or initially unstable systems.

Figure 2.29 Unit responses of systems with PI and PD controllers [78].

2.7.3 Proportional-Integral-Derivative (PID) Control

From the preceding discussions we observe that the PD controller could add damping to a system, but the steady-state response is not affected. The PI controller could improve the relative stability and improve the steady-state error at the same time, but the rise time is increased. This leads to the motivation of using a PID controller so that the best features of each of the PI and PD controllers are utilized.
From the above figure, we can observe that as low as $k_I > k_P$, the rise time is slower and settling time than when $k_I < k_P$. 

**Figure 2.30** Unit-step responses of system with PI and PD controllers [78].
Figure 2.31 Step responses of a system with PD, PI and PID controllers [78].
Figure 2.32 Bode plots of a system with PD and PID controllers [78].
2.8 Author’s work Type Controller selection

We have investigated, PD, PI and PID controllers.

2.8.1 Comparison of PD, PI and PID controllers

In the following figures (2.33-2.37), we can observe that the PD controller e outperforms the PI and PID controllers. The amount of undershoots (under the reference blood glucose level) by PD controller is not frequent as the other two controllers.
\[ kp_1 = 10; \quad kp_2 = 10; \quad kp_3 = 10; \]
\[ kd_1 = 0.1; \quad kd_2 = 0.1; \quad kd_3 = 0.1; \]

\[ kp_1 = 10; \quad kp_2 = 10; \quad kp_3 = 10; \]
\[ kd_1 = 0; \quad kd_2 = 0; \quad kd_3 = 0; \]
\[ ki_1 = 1; \quad ki_2 = 1; \quad ki_3 = 1; \]

\[ kp_1 = 10; \quad kp_2 = 10; \quad kp_3 = 10; \]
\[ kd_1 = 0.1; \quad kd_2 = 0.1; \quad kd_3 = 0.1; \]
\[ ki_1 = 1; \quad ki_2 = 1; \quad ki_3 = 1; \]

**Figure 2.33** PD, PI and PID controller responses for subject D01.
Figure 2.34 PD, PI and PID controller responses for subject D04
Figure 2.35 PD, PI and PID controller responses for subject D09.
kp1 = 100; kp2 = 100; kp3 = 100;  
kd1 = 0.1; kd2 = 0.1; kd3 = 0.1;  
ki1 = 1; ki2 = 1; ki3 = 1;  

kp1 = 100; kp2 = 100; kp3 = 100;  
kd1 = 0; kd2 = 0; kd3 = 0;  
ki1 = 1; ki2 = 1; ki3 = 1;  

kp1 = 100; kp2 = 100; kp3 = 100;  
kd1 = 0.1; kd2 = 0.1; kd3 = 0.1;  
ki1 = 1; ki2 = 1; ki3 = 1;  

Figure 2.36 PD, PI and PID controller responses for subject N01.
Figure 2.37 PD, PI and PID controller responses for subject N17.
2.8.2 The Choice Controller: PD

As our insulin infusion system is targeted diabetic patients (overdamp system response, as describe in the previous chapter) and based on the information discussed in this chapter, we proposed that PD controller be used in our insulin infusion system:

(a) The patient’s glucose-insulin kinetic physiological system is already very stable (overdamp).

(b) We need to infuse insulin as soon as possible.

(c) The system must settle with the 2-hour period cycle.

The PD control technique must be adapted for our use:

(a) A unit is appended into the basic PD control system to improve the system responsiveness.

(b) Taking the initial and subsequent effects of the insulin impulse released into the blood stream.

As a result of the above reasons, the transfer function of the insulin infusion system is:

\[ G_c = k_p + k_i s \]

The following sections will investigate the results of this controller.
2.9 Derivation of Insulin Response In Blood Pool

In our work [117], we have to determine to concentration of blood glucose after the initial release of insulin pulse. As a result, we will adapt our earlier works in Chapter 1 and remodel the glucose-insulin dynamic system for our here.

2.9.1 Insulin Impulse

\[ x' = p(t) - \alpha x + \beta y \]  
\[ y' = q(t) - \gamma x - \delta y \]  

Where:
\( x \): blood insulin concentration (from its fasting level),
\( y \): blood glucose concentration (from its fasting level),
\( p \): insulin input-rate,
\( q \): glucose input-rate, for unit blood-glucose compartment volume\((V)\), where \( x', y' \) denote the first-derivatives of \( x \) and \( y \) with respect to time. In these equations, the Glucose-Insulin model system parameters (regulatory coefficients) are \( \alpha, \beta, \gamma, \delta \).

From equations (1) & (2), we obtain the differential-equation model (for glucose-concentration \((y)\) and insulin-concentration \((x)\), for insulin infusion rate \((p)\) and glucose inflow rate \((q=0)\).

For insulin response, we obtain:
\[ sX(s) = P(s) - \alpha X(s) + \beta Y(s) \]
\[ X(s)(s + \alpha) = P(s) + \beta Y(s) \]  
(3)
\[ sY(s) = -\gamma X(s) - \delta Y(s) \]
\[ Y(s)(s + \delta) = -\gamma X(s) \]
\[ Y(s) = \frac{-\gamma X(s)}{(s + \delta)} \]  
(4)
Substitute (4) into (3):

\[ X(s)(s + \alpha) = P(s) + \frac{-\beta \gamma X(s)}{(s + \delta)} \]

\[ X(s)(s + \alpha)(s + \delta) = P(s)(s + \delta) - \beta \gamma X(s) \]

\[ X(s)(s + \alpha)(s + \delta) + \beta \gamma X(s) = P(s)(s + \delta) \]

\[ X(s) \left[ s^2 + s(\alpha + \delta) + (\alpha \delta + \beta \gamma) \right] = P(s)(s + \delta) \]

\[ X(s) = \frac{P(s)(s + \delta)}{s^2 + s(\alpha + \delta) + (\alpha \delta + \beta \gamma)} \]  

(5)

Substitute (5) into (4):

\[ Y(s) = \frac{-\gamma P(s)(s + \delta)}{(s + \delta)(s^2 + s(\alpha + \delta) + (\alpha \delta + \beta \gamma))} \]

\[ = \frac{-\gamma P(s)}{s^2 + s(\alpha + \delta) + (\alpha \delta + \beta \gamma)} \]  

(6)

We will apply the impulse of insulin \( p(t) = I \delta(t) \) where \( I \) is the amplitude of insulin impulse and \( \delta(t) \) is the finite delta function. The Laplace transform of \( p(t) \):

\[ P(s) = I \]  

(7)

Substituting equation (7) into (5) and (6):

\[ X(s) = \frac{I(s + \delta)}{s^2 + s(\alpha + \delta) + (\alpha \delta + \beta \gamma)} \]  

(8)

\[ Y(s)=\frac{-\gamma I}{s^2 + s(\alpha + \delta) + (\alpha \delta + \beta \gamma)} \]  

(9)

Using the results from the previous chapter, we can deduce the solutions for equations (8) and (9).

Solution for equation (9):

\[ y(t) = \frac{-\gamma I}{\omega} e^{-\delta t} \sin \omega t \]  

(10)

From (8):

\[ X(s) = I \left[ \frac{s}{s^2 + s(\alpha + \delta) + (\alpha \delta + \beta \gamma)} + \frac{\delta}{s^2 + s(\alpha + \delta) + (\alpha \delta + \beta \gamma)} \right] \]

Using the standard inverse Laplace table and solution from the previous chapter:
\[ x(t) = I \left[ \frac{be^{-bt} + ae^{-at}}{\omega} e^{-at} \sin \omega t + \frac{\delta}{\omega} e^{-at} \sin \omega t \right] \]

\[ \frac{I}{\omega} e^{-at} \sin \omega t \left[ \frac{be^{-bt} + ae^{-at}}{\omega} + \delta \right] \]

where \( b = \frac{1}{2} \left[ (\alpha + \delta) - \sqrt{(\alpha + \delta)^2 - 4(\alpha \delta + \beta \gamma)} \right] \)

\( a = \frac{1}{2} \left[ (\alpha + \delta) + \sqrt{(\alpha + \delta)^2 - 4(\alpha \delta + \beta \gamma)} \right] \)

### 2.9.2 Blood glucose Responses after Release of Insulin Pulse

We are expecting the system to respond as:

![Graph showing blood glucose responses](image)

**Figure 2.38** Response of blood glucose concentration after the insulin impulse infused into the GI.

Please note that the above figure is a very ideal response as it only requires a single insulin. In our simulation, we will require a few pulses to bring the blood glucose concentration down to an acceptable reference level safely without causing hypoglycemia.
Figure 2.39 Flow chart of the workings of the insulin infusion system.
Figure 2.40 The final block diagram of the insulin infusion system. The only sensor used is the non-invasive blood glucose sensor.
2.10 Simulated Results

In this section, we have make use of the clinical data from diabetic volunteers in Chapter 1 as our source. Then we perform simulations under the MatLab and Simulink environments to perform system simulations to verify the accuracies of our models.

The clinical OGTT data is only 2 hours. We have extended the simulation cycle to 4 hours to verify the system stability per data set and no insulin should be infused once the blood glucose concentration level is at reference level or under. If the concentration of the blood glucose is at the reference level or under, the controller should not take any action.

Please refer to Appendix F for details.

2.11 Conclusion

We have demonstrated that we can bring down the blood glucose concentration within 2 hours for those volunteers who were determined as diabetic in Chapter 1 based on system simulation under MatLab Simulink environment. The 4-hour simulations were also performed to show the system stability.
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Chapter 3
Lung-gas composition and transfer analysis: O₂ and CO₂ diffusion coefficients and metabolic rates ........................................... 77
D.N. Ghista, K.M. Loh & D. Ng
1 Introduction ........................................................................... 77
2 Lung-air composition analysis (and O₂ consumption and CO₂ production rates) ........................................................... 78
   2.1 Calculation of O₂ consumption rate and CO₂ production rate ...... 78
   2.2 Dead-space air composition .................................................. 79
   2.3 Alveolar air composition and partial pressures ...................... 80
3 Lung gas-exchange model and parametric analysis .................... 81
   3.1 Expressions for $D_O$ and $D_CO$ ........................................... 81
   3.2 Alveolar O₂ and CO₂ partial-pressure expressions .................. 85
   3.3 Arterial and venous O₂ and CO₂ partial-pressure expressions ..... 86
   3.4 Sequential procedure to compute $D_O$ and $D_CO$ .................. 88
   3.5 Determining $D_O$ and $D_CO$ .............................................. 89
4 Case studies ........................................................................... 90

Chapter 4
Lung ventilation modeling and assessment .................................. 95
D.N. Ghista, K.M. Loh & M. Damodaran
1 Introduction ........................................................................... 95
   1.1 Role of lung ventilation ....................................................... 95
2 Lung ventilation performance using a linear first-order model ...... 96
3 Ventilatory Index ................................................................... 101
   3.1 Noninvasively determinable ventilatory index .............. 101
4 Variations in R and C during a respiratory cycle (towards nonlinear) ............................................................. 103
   4.1 Nonlinear compliance ........................................................ 104
5 Work of breathing (WOB) ...................................................... 106
6 Second-order model for single-compartment lung model .......... 108
7 Two-compartmental linear model ........................................... 110
   7.1 Two compartmental model using first order
       ventilatory model .................................................................. 112
       7.1.1 Stiff right lung (with compliance problems) ............... 115
       7.1.2 Right lung with $R$ problems ....................................... 115

Chapter 5
Modeling of two-phase flow in the human respiratory system .......... 117
V.V. Kulish, B. Wijayanto & C.S. Lim
1 Introduction ........................................................................... 117
2 Methodology ......................................................................... 118
   2.1 Geometry of the human respiratory duct ......................... 118
CHAPTER 3

Lung-gas composition and transfer analysis: O₂ and CO₂ diffusion coefficients and metabolic rates

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Abstract

The primary function of the lung is to (i) oxygenate the blood and thereby provide oxygen to the cells for metabolism purposes, and (ii) to remove the collected CO₂ from the pulmonary blood. Herein, we will analyze the compositions of the inspired and expired air per breath, and from there compute the O₂ consumption and CO₂ production rates. Next, we derive expressions for diffusion coefficients \(D_{O₂}\) and \(D_{CO₂}\) in terms of the evaluated cardiac output, \(O₂\) and \(CO₂\) concentrations in arterial and venous blood, alveolar and blood \(O₂\) and \(CO₂\) partial pressures. We then take up a typical case study, and demonstrate the computation of \(D_{O₂}\) and \(D_{CO₂}\), to represent the lung-performance capability to oxygenate the blood.

1 Introduction

The lung-functional performance is characterized by (i) its ventilatory capacity, to bring air (and hence \(O₂\)) into the alveoli, and (ii) its capacity to transfer \(O₂\) and \(CO₂\) into and from the pulmonary capillary bed. Hence, the \(O₂\) and \(CO₂\) diffusion coefficients as well as the \(O₂\) consumption rate and the \(CO₂\) production rate represent the lung-performance indices.
2 Lung-air composition analysis (and $O_2$ consumption and $CO_2$ production rates)

We carry out a mass-balance analysis, involving:

(i) compositions of air breathed in and out
(ii) consumption or losses of $O_2$, $CO_2$ and $H_2O$.

Table 1 provides clinical data on partial pressures and volumes of $N_2$, $O_2$, $CO_2$ and $H_2O$ of atmospheric air breathed in and expired out, one breath cycle. The monitored breathing rate (BR) = 12 breaths/min, and we assume $P_{H_2O}$ at $37^\circ C$ = 47 mmHg.

It can be noted that the expired air volume exceeds the inspired air volume for this particular breath cycle. The $H_2O$ loss of 30.1 ml (=32.6–2.5 ml) contributes the major portion of this difference.

2.1 Calculation of $O_2$ consumption rate and $CO_2$ production rate

We now determine the $O_2$ consumption rate and $CO_2$ production rates from the inspired and expired gases.

Assuming the patient breathes at 12 times per minute we have

$$O_2 \text{ Consumption Rate} = (\text{Inspired } O_2 - \text{Expired } O_2) \times 12$$

$$= (104.2 - 80.6) \times 12$$

$$= 283.2 \text{ ml/min}$$

<table>
<thead>
<tr>
<th>Respiratory gases</th>
<th>Atmospheric air</th>
<th>Expired air</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmHg</td>
<td>ml/%</td>
</tr>
<tr>
<td>$N_2$</td>
<td>597</td>
<td>393.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>78.55%</td>
</tr>
<tr>
<td>$O_2$</td>
<td>159</td>
<td>104.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20.84%</td>
</tr>
<tr>
<td>$CO_2$</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.04%</td>
</tr>
<tr>
<td>$H_2O$</td>
<td>3.7</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.49%</td>
</tr>
<tr>
<td>Total</td>
<td>760</td>
<td>500</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 1: Inspired air composition and partial pressures.
Figure 1: Dead-space volume

CO₂ Production Rate = (Expired CO₂ - Inspired CO₂) × 12

= (19.1 - 0.2) × 12

= 226.8 ml/min

The amount of water vapor in the humidified expired air amounts to 6.2% of the expired air (compared to 0.49% of the dry inspired air) corresponding to the partial-pressure ratio of water vapor in the expired air (¼7/760). The volume of the dry expired air = (525.3 - 32.6) ml = 492.7 ml.

Now, assume that out of 500 ml of inspired air, the dead-space air volume (not taking part in the gas-transfer process) is 150 ml and the alveolar air volume is 350 ml. We next compute the dead-space air volume composition.

2.2 Dead-space air composition

The clinical data of expired air composition is:

N₂ = 393.1 ml
O₂ = 83.36 ml
CO₂ = 16.87 ml
H₂O = 34.15 ml
Total = 527.49 ml

Now, the dead-space air will be made up of (i) a dry air portion from the inspired air (assumed to be = 141 ml), plus (ii) the water vapor taken up by the dry air
(estimated to be 9 ml) since the expired air portion of 141 ml will not have undergone O₂ and CO₂ transfer, its composition is the same as that of the inspired air:

\[
\begin{align*}
N₂ &= 111 \text{ ml (78.55\%)}, \quad O₂ = 29.40 \text{ ml (20.84\%)}, \quad CO₂ = 0.06 \text{ ml (0.04\%)}, \\
H₂O &= 0.69 \text{ ml (0.49\%)}. \\
\end{align*}
\]

When this inspired air (in the dead space) of 141 ml is fully humidified, it will take up a further \( X \) ml of H₂O vapor, in the ratio of the partial-pressures, as:

\[
\frac{X}{141} = \frac{47}{713} = 0.0659
\]

\[
\therefore X = 0.0659 \times 141 = 9.29 \text{ ml of H₂O vapor (which is close to our estimate)}. \\
\]

So, by adding 9.29 ml of H₂O vapor to 0.69 ml of water vapor in the inspired air volume of 141 ml, the total water vapor in the dead-space air is 9.98 ml. The humidified dead-space air composition will be:

\[
\begin{align*}
N₂ &= 111.00 \text{ ml (73.78\%)}, \\
O₂ &= 29.40 \text{ ml (19.55\%)}, \\
CO₂ &= 0.06 \text{ ml (0.04\%)}, \\
H₂O &= 9.98 \text{ ml (6.63\%)}, \\
\text{Total} &= 150.44 \text{ ml} \\
\end{align*}
\]

2.3 Alveolar-air composition and partial pressures

We can now compute the alveolar air composition, by subtracting the dead-space air from the expired air. These values are tabulated in column 4 of the table below.

Finally, we compute the partial pressure of O₂ and CO₂ (as well as of N₂ and H₂O), so that we can determine next the diffusion coefficients of O₂ and CO₂ based on the monitoring of arterial and venous blood concentrations. These values are tabulated in column 5 of the below table.

<table>
<thead>
<tr>
<th></th>
<th>Expired air (ml)</th>
<th>Dead-space air (ml)</th>
<th>Alveolar air (ml)</th>
<th>Alveolar-air partial pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N₂</td>
<td>393.1</td>
<td>111.00</td>
<td>282.1</td>
<td>569.41</td>
</tr>
<tr>
<td>O₂</td>
<td>80.53</td>
<td>29.40</td>
<td>51.13</td>
<td>103.21</td>
</tr>
<tr>
<td>CO₂</td>
<td>19.12</td>
<td>0.06</td>
<td>19.06</td>
<td>38.47</td>
</tr>
<tr>
<td>H₂O</td>
<td>34.21</td>
<td>9.98</td>
<td>24.23</td>
<td>48.91</td>
</tr>
<tr>
<td>Total</td>
<td>526.96</td>
<td>150.44</td>
<td>376.52</td>
<td>760</td>
</tr>
</tbody>
</table>
3 Lung gas-exchange model and parametric analysis

3.1 Expressions for $D_{O_2}$ and $D_{CO_2}$

The gas exchange between the alveolar air and pulmonary capillary blood is represented by the following $O_2$ and CO$_2$ conservation equations (Fig. 2):

$$Q^{VE}C_{O_2}^{VE} = Q^{AE}C_{O_2}^{AE} + \dot{V}_{O_2} \quad \text{(from the alveolar air to capillary blood)}$$

$$= Q^{AE}C_{O_2}^{AE} + (\Delta P_{O_2}^{AV})D_{O_2} \quad \Rightarrow \quad P_{O_2}^{cap} = P_{O_2}^{AE},$$

(1)

in which $P_{O_2}^{cap} = P_{O_2}^{PRB}$ (O$_2$ concentration of the preoxygenated blood)

$$Q^{VE}C_{CO_2}^{VE} = Q^{AE}C_{CO_2}^{AE} - \dot{V}_{CO_2}$$

$$= Q^{AE}C_{CO_2}^{AE} - (\Delta P_{CO_2}^{AV})D_{CO_2} \quad \Rightarrow \quad P_{CO_2}^{cap} = P_{CO_2}^{VE},$$

(2)

in which $P_{CO_2}^{cap} = P_{CO_2}^{PRB}$ (CO$_2$ concentration of the preoxygenated blood).

wherein

(i) $Q^{AB}$ and $Q^{VB}$ are arterial and venous blood flow-rates;
(ii) $Q^{AB} = Q^{VE}$ (at venous end), $Q^{VB} = Q^{AE}$ (at arterial end)
(iii) $P_{O_2}^{AL}$ and $P_{O_2}^{CAP}$ are the alveolar and capillary O$_2$ partial pressures
(iv) $D_{O_2}$ and $D_{CO_2}$ are the O$_2$ and CO$_2$ diffusion coefficients
(v) $\Delta P_{O_2}^{AV}$ = average of $(P_{O_2}^{AL} - P_{O_2}^{CAP})$ over the capillary length;
$v_{CO_2}$ = average of $(P_{CO_2}^{AL} - P_{CO_2}^{CAP})$ over the capillary length.

Now we can equate the arterial and venous blood flow rates, as

$$Q^{AB} - Q^{VB} - Q = (SV)/(EP) \approx CO/60,$$

SV, EP and CO being the stroke volume, ejection period and cardiac output, respectively. Hence the above equations can be rewritten as:

(vi) $\dot{V}_{O_2}$ is the O$_2$ transfer rate from alveolar air to capillary blood ($= O_2$ consumption rate), $\dot{V}_{CO_2}$ is the CO$_2$ transfer rate from capillary blood to alveolar air.

---

Figure 2: Schematic of blood-gas concentration in the pulmonary capillary.
From eqn. (1):
\[ Q^{\text{VE}} C_{O_2}^{\text{VE}} = Q^{\text{AB}} C_{O_2}^{\text{AB}} + (\Delta P_{O_2}^{\text{aV}}) D_{O_2}; \quad P_{O_2}^{\text{cap}} = P_{O_2}^{\text{AE}} = P_{O_2} \]
\[ Q^{\text{VE}} C_{O_2}^{\text{VB}} = Q^{\text{AE}} C_{O_2}^{\text{AE}} + (\Delta P_{O_2}^{\text{aV}}) D_{O_2} \]
\[ D_{O_2} = \frac{Q(C_{O_2}^{\text{VE}} - C_{O_2}^{\text{AE}})}{(\Delta P_{O_2}^{\text{aV}})} = \frac{Q(C_{O_2}^{\text{AE}} - C_{O_2}^{\text{VB}})}{(\Delta P_{O_2}^{\text{aV}})} \]  \hspace{1cm} (3)

From eqn. (2):
\[ Q^{\text{VE}} C_{CO_2}^{\text{VE}} = Q^{\text{AE}} C_{CO_2}^{\text{AE}} - (\Delta P_{CO_2}^{\text{aV}}) D_{CO_2}; \quad P_{CO_2}^{\text{cap}} = P_{CO_2}^{\text{AE}} = P_{CO_2}^{\text{VB}} \]
\[ Q^{\text{VE}} C_{CO_2}^{\text{VB}} = Q^{\text{AE}} C_{CO_2}^{\text{AE}} - (\Delta P_{CO_2}^{\text{aV}}) D_{CO_2} \]
\[ D_{CO_2} = \frac{Q(C_{CO_2}^{\text{VE}} - C_{CO_2}^{\text{AE}})}{(\Delta P_{CO_2}^{\text{aV}})} \]  \hspace{1cm} (4)

wherin

(i) \( Q, C_{O_2}^{\text{VE}}, \text{ and } C_{CO_2}^{\text{VE}}, \text{ and } C_{CO_2}^{\text{AE}} \) can be monitored because \( C_{O_2}^{\text{VE}} \text{ and } C_{CO_2}^{\text{VE}} = C_{O_2}^{\text{AB}} \text{ and } C_{CO_2}^{\text{AB}} = C_{O_2}^{\text{AE}} \text{ and } C_{CO_2}^{\text{AE}} = C_{O_2}^{\text{VB}} \text{ and } C_{CO_2}^{\text{VB}} \)

(ii) \( D_{O_2} \text{ and } D_{CO_2} \text{ (eqns. (3) \text{ and } (4)) represent the lung gas-exchange parameters.} \)

Now from eqns. (3) \text{ and } (4), if we want to evaluate the diffusion coefficients \( D_{O_2} \text{ and } D_{CO_2} \), we need to also express \( P_{O_2}^{\text{al}}, P_{CO_2}^{\text{al}} \text{ and } P_{CO_2}^{\text{al}} \text{ in terms of monitorable quantities. In this regard,} \)

(i) Alveolar \( P_{O_2}^{\text{al}} \text{ can be expressed in terms of } \hat{V} \text{ (the ventilation rate) and } \hat{V}_{O_2} \text{ (the } O_2 \text{ consumption rate) as Fig. 3:} \)
\[ P_{O_2}^{\text{al}} = k_1 \left[ 1 - e^{-k_2 \left( \frac{\hat{V} / \hat{V}_m}{\hat{V}_{O_2}} \right)} \right] \]

where \( \hat{V}_m \text{ is the maximum ventilation rate and } \hat{V}_{O_2} \text{ (the } O_2 \text{ consumption rate or absorption rate from the alveoli) } = Q(C_{O_2}^{\text{AB}} - C_{O_2}^{\text{VB}}). \text{ Equation (5) implies that as } (\hat{V} / \hat{V}_m) \text{ increases, the exponential term decreases, and } P_{O_2}^{\text{al}} \text{ increases (as in Fig. 3), and as } \hat{V}_{O_2} \text{ increases } P_{O_2}^{\text{al}} \text{ decreases (as in Fig. 3).} \)

(ii) Alveolar \( P_{CO_2}^{\text{al}} \text{ can be expressed in terms of } \hat{V} \text{ and } \hat{V}_{CO_2} \text{ as in Fig. 4:} \)
\[ P_{CO_2}^{\text{al}} = k_3 e^{-k_4 \left( \frac{\hat{V} / \hat{V}_m}{\hat{V}_{CO_2}} \right)} \]

where \( \hat{V}_{CO_2} \text{ (the } CO_2 \text{ production rate or excretion rate from the blood) } = Q(C_{CO_2}^{\text{VB}} - C_{CO_2}^{\text{AB}}). \text{ This equation implies that as } \hat{V} / \hat{V}_m \text{ increases, } P_{CO_2}^{\text{al}} \text{ decreases; also, as } \hat{V}_{CO_2} \text{ increases (the exponential term decreases, and hence) } P_{CO_2}^{\text{al}} \text{ increases.} \)
Figure 3: Effect on alveolar $P_{O_2}$ of (i) alveolar ventilation, and (ii) rate of oxygen absorption from alveolar $P_{O_2}$ or $O_2$ consumption rate [from Guyton (1971), p. 476].

Figure 4: Effect on alveolar $P_{CO_2}$ of alveolar ventilation and rate of carbon dioxide excretion from the blood or $CO_2$ production rate [from Guyton (1971), p. 476].

(iii) Blood $P_{O_2}$ can be obtained in terms of blood $CO_2$, from the $O_2$ disassociation curve (providing concentrations in arterial and venous blood), is represented in Fig. 5 as:

$$ C_{O_2} = C_{O_2}^m \left( 1 - e^{-k_{O_2} P_{O_2}} \right), \quad \text{or} \quad C_{O_2}^b = 1 - e^{-k_{O_2} P_{O_2}}, \quad (7) $$
Figure 5: O₂ dissociation curves, showing the total oxygen in each 100 ml of normal blood, the portion dissolved in the water of the blood [from Guyton [2], p. 485].

Figure 6: The carbon dioxide dissociation curve [from Guyton [2], p. 491].

where

- \( C_{O_2}^m \) and \( P_{O_2}^m \) are the maximum values of blood O₂ partial pressure
- \( CO_2^* = CO_2/CO_2^m \)
- \( F_{O_2} = P_{O_2}/P_{O_2}^m \)

(iv) Blood \( P_{CO_2} \) can be obtained in terms of \( C_{CO_2} \), from the CO₂ disassociation curve or CO₂ concentration in arterial and venous blood can be represented
as per Fig. 6 as:

\[
C_{CO_2} = C_{O_2}^n \left(1 - e^{-k_6 \left(P_{CO_2}/P_{CO_2}^n\right)}\right)
\]

or, \[C_{CO_2}^* = 1 - e^{-k_6 \left(P_{CO_2}/P_{CO_2}^n\right)} = 1 - e^{-k_6 P_{CO_2}}. \quad (8)
\]

3.2 Alveolar O₂ and CO₂ partial-pressure expressions

Now, let us refer eqn. (4) for the \(P_{O_2}^{al}\) partial pressure curve (Fig. 3), represented by the equation:

\[
P_{O_2}^{al} = k_1 \left[1 - e^{-k_2 \left(\frac{\dot{V}}{V_m} - \dot{V}_{O_2}\right)}\right]
\]

\[
= k_1 \left[1 - e^{-k_2 \left(\frac{\dot{V}}{V_m} \cdot \frac{\dot{V}_{O_2}}{V_{O_2}}\right)}\right], \quad \text{where} \quad \frac{\dot{V}}{V_m} = \frac{\dot{V}}{V_m} \quad (9)
\]

where \(\dot{V}\) is the alveolar ventilation rate (in liters/min), \(\dot{V}_{m}\) is the maximum ventilation rate (= 50 l/min) and \(\dot{V}_{O_2}\) is the O₂ consumption rate (in liters/min). Herein, the coefficients \(k_1\) and \(k_2\) can be determined by having this equation match the Fig. 3 data. Note, in this equation, when \(\dot{V} = 0\), \(P_{O_2}^{al} = 0\) from the equation, which satisfies the data.

Now for \(\dot{V}_{O_2} = 0.25 \text{ l/min, when } \frac{\dot{V}}{V_m} = 0.5, P_{O_2}^{al} = 140 \text{ mmHg. Hence,}
\]

\[
140 = k_1 \left[1 - e^{-k_2 \left(\frac{0.5}{0.25}\right)}\right] = k_1 (1 - e^{-2k_2}). \quad (10)
\]

Also, when \(\dot{V}_{O_2} = 11/\text{min, } \dot{V}_{O_2} = 0.31/\text{min, } P_{O_2}^{al} = 100 \text{ mmHg. Hence}
\]

\[
100 = k_1 \left[1 - e^{-k_2 \left(\frac{0.3}{1}\right)}\right] = k_1 (1 - e^{-0.3k_2}). \quad (11)
\]

From eqns. (10) and (11), we get:

\[
\frac{140}{100} = \frac{k_1 (1 - e^{-2k_2})}{k_1 (1 - e^{-0.3k_2})} = \frac{1 - e^{-2k_2}}{1 - e^{-0.3k_2}}
\]

\[
\therefore 140 - 140e^{-0.3k_2} = 100 - 100e^{-2k_2}
\]

\[
or, 40 = 100e^{-2k_2} + 140e^{-0.3k_2}, \text{ so that } k_2 = 4.18 \text{ min/l.} \quad (12)
\]

Upon substituting \(k_2 = 4.18 \text{ min/l into eqn. (10)}\) we obtain:

\[
140 = k_1 (1 - e^{-(2\times4.18)}), \text{ so that } k_1 \approx 140 \text{ mmHg.} \quad (13)
\]
Hence, the $P_{O_2}^{al}$ curve can be represented by:

$$P_{O_2}^{al} = 140 \left[ 1 - e^{-4.18 \left( \frac{\hat{V}^*}{\hat{V}} \right)} \right],$$  (14)

where $\hat{V}_{O_2} = Q(C_{O_2}^{AB} - C_{O_2}^{VB})$ and $\hat{V}^* = \hat{V}/501/\text{min}$.

Now, let us look at the $P_{CO_2}^{al}$ expression:

$$P_{CO_2}^{al} = k_3 e^{-k_4 \left( \frac{\hat{V} / \hat{V}_m}{\hat{V}} \right)} = k_3 e^{-k_4 \left( \frac{\hat{V}^*}{\hat{V}_{CO_2}} \right)}.$$  

We note from Fig. 4 that for $\hat{V}_{CO_2} = 0.2 \text{ l/min}$ and $\hat{V}_m = 0.2$, $P_{CO_2}^{al} = 12$. Hence, from the above equation, we get:

$$12 = k_3 e^{-k_4}$$  (15)

Also, for $\hat{V}_{O_2} = 0.8 \text{ l/min}$ and $\hat{V}_m = 0.2$, $P_{CO_2}^{al} = 62 \text{ mmHg}$. Hence

$$62 = k_3 e^{-k_4 \left( \frac{0.8}{0.2} \right)} = k_3 e^{-\frac{k_4}{4}}.$$  (16)

From eqns. (15) and (16), we get:

$$\frac{12}{62} = \frac{e^{-k_4}}{e^{-\frac{k_4}{4}}} = e^{-\frac{1}{4}k_4} = \ln \left( \frac{12}{62} \right) = -\frac{2}{3}k_4, \text{ so that } k_4 = 2.46.$$  (17)

Substituting $k_4 = 2.46$ into eqn. (16), we obtain:

$$62 = k_3 e^{-2.46 \cdot \frac{1}{4}}, \text{ . . . } k_3 = 114.68.$$  (18)

Hence, the $P_{CO_2}^{al}$ curve can be represented as

$$P_{CO_2}^{al} = 114.68e^{-2.46 \left( \frac{\hat{V} / \hat{V}_m}{\hat{V}_{CO_2}} \right)},$$  (19)

where $\hat{V}^* = \hat{V}/501/\text{min}$ and $\hat{V}_{CO_2} = Q(C_{CO_2}^{VB} - C_{CO_2}^{AB}).$

3.3 Arterial and venous $O_2$ and $CO_2$ partial-pressure expressions

We now need to express $P_{O_2}^{AB}$ and $P_{CO_2}^{VB}$ in terms of $C_{O_2}^{AB}$ and $C_{CO_2}^{VB}$. 
So that let us look at the $O_2$ disassociation curve, as shown in Fig. 5.

\[ C_{O_2} = C_{O_2, \max} \left[ 1 - e^{-k_S P_{O_2}/P_{O_2, \max}} \right], \]

or,

\[ C_{O_2}^* = 1 - e^{-k_S P_{O_2}^*}, \]

where \( C_{O_2}^* = \frac{C_{O_2}}{C_{O_2, \max}} \), \( P_{O_2}^* = \frac{P_{O_2}}{P_{O_2, \max}} \).

From Fig. 5, at \( P_{O_2}^* = \frac{40 \text{ mmHg}}{140 \text{ mmHg}} = 0.29 \) (for normal venous blood), and

\[ C_{O_2}^* = \frac{15}{20} = 0.75. \]

Hence from eqn. (20):

\[ 0.75 = 1 - e^{-0.29k_S} \]

\[ \therefore k_S = 4.78. \]  

Also, \( P_{O_2}^* = \frac{95 \text{ mmHg}}{140 \text{ mmHg}} = 0.68 \) (for normal arterial blood), and

\[ C_{O_2}^* = \frac{19}{20} = 0.95. \]

Hence from eqn. (20):

\[ 0.95 = 1 - e^{-0.68k_S}, \text{ or } k_S = 4.4. \]  

So, we take the average value of \( k_S \):

\[ \therefore k_S = \frac{(4.78 + 4.4)}{2} = 4.59. \]

Then the $O_2$ disassociation curve is given by:

\[ C_{O_2} = C_{O_2}^B = 0.2 \left[ 1 - e^{-4.59 \left( \frac{P_{O_2}}{P_{O_2, \max}} \right)} \right], \]  

and

\[ P_{O_2} = \frac{140}{4.59} \ln \left[ \frac{0.2}{0.2 - C_{O_2}^B} \right] = 30.5 \ln \left[ \frac{0.2}{0.2 - C_{O_2}^B} \right]. \]

Finally, we look at the $CO_2$ disassociation curve

\[ C_{CO_2} = C_{CO_2, \max} \left( 1 - e^{-k_F P_{CO_2}/P_{CO_2, \max}} \right), \]

or,

\[ C_{CO_2}^* = 1 - e^{-k_F P_{CO_2}^*} \]

\[ = 1 - e^{-k_F P_{CO_2}^*}. \]
Based on Fig. 6, when $P_{CO_2}^* = \frac{20 \text{ mmHg}}{140 \text{ mmHg}} = 0.14$, $C_{CO_2}^* = \frac{38}{80} = 0.475$, so that

$$0.475 = 1 - e^{-0.14k_6}; \quad k_6 = 4.60,$$

(27)

when $P_{CO_2}^* = \frac{70 \text{ mmHg}}{140 \text{ mmHg}} = 0.5$, $C_{CO_2}^* = \frac{60}{80} = 0.75$, so that

$$0.75 = 1 - e^{-0.5k_6}; \quad k_6 = 2.77.$$

(28)

So, we take the average value of $k_6$:

$$k_6 = \frac{(4.60 + 2.77)}{2} = 3.69.$$

(29)

Then the CO$_2$ concentration is given (from eqns. (26–29)) by:

$$C_{CO_2} = C_{CO_2}^B = 0.8 \left[ 1 - e^{-4.71 \left( \frac{P_{CO_2}}{140} \right)} \right].$$

(30)

and

$$P_{CO_2} = 29.72 \ln \left( \frac{0.8}{0.8 - C_{CO_2}} \right).$$

(31)

3.4 Sequential procedure to compute $D_O_2$ and $D_{CO_2}$

1. We first monitor: $V(t)$, $\dot{V}(t)$, SV (stroke volume), EP (cardiac ejection period), $C_{O_2}^{VB}$, $C_{O_2}^{AB}$, $C_{O_2}^{VB}$, and $C_{CO_2}$ (O$_2$ and CO$_2$ concentrations in pre oxygenated and post oxygenated blood).

2. We substitute the values of $C_{O_2}^{AB}$ ($=C_{O_2}^{VB}$) and $C_{O_2}^{VB}$ ($=C_{O_2}^{AB}$) into eqn. (3), and the values of $C_{CO_2}^{AB}$ ($=C_{CO_2}^{VB}$) and $C_{CO_2}^{VB}$ ($=C_{CO_2}^{AB}$) into eqn. (4).

3. We next determine:

$$Q = \text{SV/ejection period},$$

(32)

$$\dot{V}_{O_2}(t) = Q(C_{O_2}^{AB} - C_{O_2}^{VB}).$$

(33)

$$\dot{V}_{CO_2}(t) = Q(C_{CO_2}^{AB} - C_{CO_2}^{VB}).$$

(34)

4. We then substitute the expressions for $\dot{V}_{O_2}(t)$ and $\dot{V}_{CO_2}(t)$ into the equations for $P_{O_2}^{AE}$ (eqn. (14) and $P_{CO_2}^{AE}$ (eqn. (19)).

5. We substitute the monitored values of $C_{O_2}^{VB}$ ($=C_{O_2}^{AE}$) and $C_{CO_2}^{VB}$ ($=C_{CO_2}^{AE}$) into eqns. (25) and (31), to obtain the values of $P_{O_2}^{AE}$ and $P_{CO_2}^{AE}$.

6. Now, in order to determine the values of the lung gas-exchange parameters $D_{O_2}$ and $D_{CO_2}$, we substitute into eqns. (3) and (4) for $Q$ from eqn. (32), $P_{O_2}^{AE}$ from eqn. (14), $P_{CO_2}^{AE}$ from eqn. (19), $P_{O_2}^{VB}$ from eqn. (26), and $P_{CO_2}^{VB}$ from eqn. (31).
3.5 Determining $D_{O_2}$ and $D_{CO_2}$

Figure 7 illustrates the variation of $\Delta P^{O_2} (= P^{al}_{O_2} - P^{cap}_{O_2} = P^{al}_{O_2} - P^{AB}_{O_2})$ along the length ($l$) of the capillary bed.

Let $l^* = l / l_m$.

Then we can express:

$$\Delta P^{O_2} = \Delta P^{O_2}_{max} f_{O_2}(l^*).$$  \hspace{1cm} (35)

Then,

$$\Delta P^{O_2}_{av} = \Delta P^{O_2}_{max} \left( \int_0^1 f_{O_2}(l^*) \, dl^* \right) = \Delta P^{O_2}_{max} (F_{O_2}).$$  \hspace{1cm} (36)

Based on data [3], since $\Delta P^{O_2}_{av} = 12$ mmHg for $\Delta P^{O_2}_{max} = 65$ mmHg, we have $F_{O_2} = 0.185$.

We can similarly determine the average value of $\Delta P^{CO_2}_{av}$ from Fig. 8 as:

Let $l^* = l / l_m$.

Then, we can represent Fig. 8 as:

$$\Delta P^{CO_2} = \Delta P^{CO_2}_{max} f_{CO_2}(l^*).$$  \hspace{1cm} (37)

Then,

$$\Delta P^{CO_2}_{av} = \Delta P^{CO_2}_{max} \left( \int_0^1 f_{CO_2}(l^*) \, dl^* \right) = \Delta P^{CO_2}_{max} (F_{CO_2}).$$  \hspace{1cm} (38)

Figure 7: Uptake of oxygen by the pulmonary capillary blood. (The curve in this figure was constructed from data in Mhorn and Pulley: Biophys. J., 8: 337, 1968). [from Guyton (1971), p. 434.]
Based on data [3], since $\Delta P_{av}^{CO_2} = 0.5$ mmHg for $\Delta P_{max}^{CO_2} = 5$ mmHg, we have $F_{CO_2} = 0.1$.

From the $\Delta P_{av}^{O_2}$ and $\Delta P_{av}^{CO_2}$ expressions, we can determine the $O_2$ consumption and the $CO_2$ production rates, as follows:

$$D_{O_2} = \frac{\text{Total } O_2 \text{ consumed}}{\Delta P_{av}^{O_2}} = \frac{\dot{V}_{O_2}}{\Delta P_{av}^{O_2}} = \frac{Q (C_{O_2}^{AB} - C_{O_2}^{VB})}{\Delta P_{av}^{O_2}}$$

$$D_{CO_2} = \frac{\text{Total } CO_2 \text{ produced}}{\Delta P_{av}^{CO_2}} = \frac{\dot{V}_{CO_2}}{\Delta P_{av}^{CO_2}} = \frac{Q (C_{CO_2}^{VB} - C_{CO_2}^{AB})}{\Delta P_{av}^{CO_2}}.$$  \hspace{1cm} (39)

\hspace{1cm} (40)

4 Case studies

(A) We monitor the partial pressures blood concentrations of $O_2$ and $CO_2$ as:

$$C_{O_2}^{AE} = C_{O_2}^{VB} = 0.13, \quad C_{O_2}^{VE} = C_{O_2}^{AB} = 0.18, \quad C_{CO_2}^{AE} = C_{CO_2}^{VB} = 0.525,$$

$$C_{CO_2}^{VE} = C_{CO_2}^{AB} = 0.485.$$

From eqn. (26), we obtain:

$$P_{O_2}^{VB} = 30.5 \ln \left[ \frac{0.2}{0.2 - C_{O_2}^{VB}} \right] = 29.72 \ln \left[ \frac{0.2}{0.2 - 0.13} \right]$$

$$= 32.02 \text{ mmHg}. \hspace{1cm} (41)$$
From eqn. (31), we obtain:

\[
P_{\text{CO}_2}^{\text{VB}} = 37.94 \ln \left( \frac{0.8}{0.8 - C_{\text{CO}_2}^{\text{VB}}} \right) = 37.94 \ln \left( \frac{0.8}{0.8 - 0.525} \right) = 40.51 \text{ mmHg.} \tag{42}
\]

We now also monitor \( Q = 51 \text{ l/min}, \hat{V} = 0.1 \text{ and } \hat{V} = 51 \text{ l/min.} \)

Then, from eqn. (33):

\[
\hat{V}_{\text{O}_2}(t) = Q \left( C_{\text{O}_2}^{\text{AB}} - C_{\text{O}_2}^{\text{VB}} \right),
\]

so that from the above data,

\[
\hat{V}_{\text{O}_2}(t) = 5000 \times 0.05 = 250 \text{ ml O}_2/\text{min Consumption rate} \tag{43}
\]

From eqn. (34):

\[
\hat{V}_{\text{CO}_2}(t) = Q \left( C_{\text{CO}_2}^{\text{VB}} - C_{\text{CO}_2}^{\text{AB}} \right) = 5000 \times 0.04 = 200 \text{ ml CO}_2/\text{min production rate.} \tag{44}
\]

Now, from eqn. (14). For \( \hat{V} = 0.1 \text{ and } \hat{V}_{\text{O}_2} = 0.25 \text{ l, we obtain } P_{\text{O}_2}^{\text{al}}: \)

\[
P_{\text{O}_2}^{\text{al}} = 140 \left[ 1 - e^{-4.18 \left( \frac{\hat{V}}{\hat{V}_{\text{O}_2}} \right)} \right],
\]

\[
= 140 \left[ 1 - e^{-4.18 \left( 0.1/0.25 \right)} \right] = 113.7 \text{ mmHg.} \tag{45}
\]

From eqn. (19), for \( \hat{V} = 0.1 \text{ and } \hat{V}_{\text{CO}_2} = 0.20 \text{ l, we obtain } P_{\text{CO}_2}^{\text{al}}: \)

\[
P_{\text{O}_2}^{\text{al}} = 107.18 e^{-2.19 \left( \frac{\hat{V}}{\hat{V}_{\text{CO}_2}} \right)} = 107.18 e^{-2.19 \left( 0.1/0.20 \right)} = 35.86 \text{ mmHg.} \tag{46}
\]

Now, we can evaluate the diffusion coefficients:

From eqns. (3), (36), (41), and (45):

\[
D_{\text{O}_2} = \frac{Q \left( C_{\text{O}_2}^{\text{AB}} - C_{\text{O}_2}^{\text{VB}} \right)}{\Delta P_{\text{O}_2}^{\text{al}}} = \frac{5000 \left( 0.18 - 0.13 \right)}{(113.7 - 31.2) \times 0.18} = 16.84 \text{ ml O}_2/\text{min/mmHg.} \tag{47}
\]
From eqn. (4):

\[
D_{\text{CO}_2} = \frac{Q}{\Delta P_{\text{av}}^{\text{CO}_2}} \left( C_{\text{CO}_2}^{\text{VB}} - C_{\text{CO}_2}^{\text{AB}} \right)
\]

\[
= \frac{5000(0.04)}{(40.51 - 35.86) \times 0.1} = 430.11 \text{ ml CO}_2/\text{min}/\text{mmHg}. \quad (48)
\]

(B) Alternately, we derive data from:

(i) the inspired and expired air analysis (such as that carried out in Section 2.3):

- O\textsubscript{2} consumption rate = 283.2 ml/min,
- CO\textsubscript{2} production rate = 226.8 ml/min,
- \(P_{\text{al}}^{\text{O}_2} = 103.03 \text{ mmHg and } P_{\text{al}}^{\text{CO}_2} = 38.41 \text{ mmHg}\)

and (ii) venous blood gas analysis:

\(C_{\text{O}_2}^{\text{VB}} = 0.13, C_{\text{CO}_2}^{\text{VB}} = 0.548.\)

Then, as per eqn. (41),

\[P_{\text{O}_2}^{\text{VB}} = 31.2 \text{ mmHg}, \quad (49)\]

corresponding to \(C_{\text{O}_2}^{\text{VB}} = 0.13\) and, as per eqn. (42):

\[P_{\text{CO}_2}^{\text{VB}} = 37.94 \ln \left( \frac{0.8}{0.8 - C_{\text{CO}_2}^{\text{VB}}} \right) = 37.94 \ln \left[ \frac{0.8}{0.8 - 0.548} \right] \]

\[= 43.84 \text{ mmHg}. \quad (50)\]

We obtain, from air-composition analysis, that \(\dot{V}_{\text{O}_2}(t) = 283.3 \text{ ml/min} \quad (51)\)

and \(\dot{V}_{\text{CO}_2}(t) = 226.8 \text{ ml/min}. \quad (52)\)

Hence,

\[D_{\text{O}_2} = \frac{\dot{V}_{\text{O}_2}}{\Delta P_{\text{av}}^{\text{O}_2}} \]

\[= \frac{283.2}{(103.03 - 31.2) \times 0.18} = 21.90 \text{ mlO}_2/\text{min}/\text{mmHg}, \quad (53)\]

and

\[D_{\text{CO}_2} = \frac{\dot{V}_{\text{CO}_2}}{\Delta P_{\text{av}}^{\text{CO}_2}} \]

\[= \frac{226.8}{(43.84 - 38.41) \times 0.1} = 417.68 \text{ mlCO}_2/\text{min}/\text{mmHg}. \quad (54)\]

The advantage of this method (B) over (A) is that it does not require monitoring of the cardiac output, and is hence simpler to implement clinically.
References


3.1 Motivation behind the Project

Chronic obstructive pulmonary disease (COPD) is a chronic, progressive disease of the lungs that gradually reduces airflow. It is characterized by phlegmy coughing, wheezing and shortness of breath. As the disease progresses, quality of life may be severely compromised.

COPD is one of the five most lethal diseases in the world. Both its mortality and its frequency are increasing. The disease is closely associated with cigarette smoking. Studies have shown that smoking is associated with up to a 20-fold increase in the risk of death from COPD. Smoking can lead to the two most common forms of this disease, emphysema and chronic bronchitis. COPD is largely a disease of the elderly. Although symptoms may begin to occur in the 40s, the disease is generally not diagnosed until the patient has reached his or her 60s.

There is no known cure for COPD, so it is very important to learn how to effectively manage the disease. Strategies for managing COPD include making lifestyle changes (e.g., quitting smoking) and taking medications (e.g., bronchodilators). In more severe cases, physicians commonly recommend oxygen-replacement therapy, in which patients breathe oxygen from either oxygen cylinders/tanks or electric concentrators that take the oxygen directly from the air. In extreme cases, surgery might be necessary to reduce the volume of the lungs or even lung transplantation.

In terms of prevalence, hospitalization, disability and death, COPD is a major health problem in Singapore. Prevalence of moderate to severe COPD is estimated at 2.3%, or a population of 3 million or absolute number of 69,000 patients in the community [40].
Table 3.1 Model projections of the prevalence of moderate to severe COPD in those 30 years and older for 12 countries in the Asia-Pacific region [Respiratory, 8, 192-198].

<table>
<thead>
<tr>
<th>Country</th>
<th>Moderate/Serve COPD cases</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Australia</td>
<td>558 000</td>
<td>4.7</td>
</tr>
<tr>
<td>2. China</td>
<td>38 160 000</td>
<td>6.5</td>
</tr>
<tr>
<td>3. Hong Kong</td>
<td>139 000</td>
<td>3.5</td>
</tr>
<tr>
<td>4. Indonesia</td>
<td>4 806 000</td>
<td>5.6</td>
</tr>
<tr>
<td>5. Japan</td>
<td>5 014 000</td>
<td>6.1</td>
</tr>
<tr>
<td>6. South Korea</td>
<td>1 467 000</td>
<td>5.9</td>
</tr>
<tr>
<td>7. Malaysia</td>
<td>448 000</td>
<td>4.7</td>
</tr>
<tr>
<td>8. Philippines</td>
<td>1 691 000</td>
<td>6.3</td>
</tr>
<tr>
<td>9. Singapore</td>
<td>64 000</td>
<td>3.5</td>
</tr>
<tr>
<td>10. Taiwan</td>
<td>636 000</td>
<td>5.4</td>
</tr>
<tr>
<td>11. Thailand</td>
<td>1 502 000</td>
<td>5.0</td>
</tr>
<tr>
<td>12. Vietnam</td>
<td>2 068 000</td>
<td>6.7</td>
</tr>
<tr>
<td>Total</td>
<td>56 553 000</td>
<td>6.3</td>
</tr>
</tbody>
</table>

According to routine official statistics in Singapore, it is the 8th leading cause of death (0.9% of all deaths) and 9th leading cause of hospitalization (1.7% of total hospitalization). Note, these figures from routine official statistics are likely to be under-estimates as they “reported” cases only.

World-wide, it ranks as the 4th leading cause of death alongside HIV. The World Health Organization (WHO) estimates that the trend in the social burden of COPD (a composite measure which factors in death, and disability) would rise from 12th highest in 1990 to 5th highest in year 2020.

We do not have published figures in Singapore, but it can be inferred that the relative importance is similar to that in other developed countries by Prof Tan [40]. Please refer to Tables 2 and 3. Health care cost (due largely to hospitalization) for COPD is twice that of asthma in the USA.

The burden is expected to increase with increasing trends of smoking in the young and with the increase in the population of the aged in the population. The present population of persons aged 65 plus (7% of the population) is expected to increase to 20% by 2030.
Table 3.2 Direct and indirect costs of lung diseases, 1993 (US $ Billions). Compares the estimated costs of various lung disorders in the US 1993. In 1993, the annual economic burden of COPD in the US was estimated at 23.9 billion, including $14.7 billion in direct expenditures for medical care services [GOLD workshop report 2003 update].

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total Cost</th>
<th>Direct Medical Cost</th>
<th>Mortality-Related Indirect Cost</th>
<th>Morbidity-Related Indirect Cost</th>
<th>Total Indirect Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>23.9</td>
<td>14.7</td>
<td>4.5</td>
<td>4.7</td>
<td>9.2</td>
</tr>
<tr>
<td>Asthma</td>
<td>12.6</td>
<td>9.8</td>
<td>0.9</td>
<td>0.9</td>
<td>2.8</td>
</tr>
<tr>
<td>Influenza</td>
<td>14.6</td>
<td>1.4</td>
<td>0.1</td>
<td>13.1</td>
<td>13.2</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>7.8</td>
<td>1.7</td>
<td>4.6</td>
<td>1.5</td>
<td>6.1</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1.1</td>
<td>0.7</td>
<td>-</td>
<td>-</td>
<td>0.4</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>25.1</td>
<td>5.1</td>
<td>17.1</td>
<td>2.9</td>
<td>20.0</td>
</tr>
</tbody>
</table>
Table 3.3 *WHO projection of total social burden world-wide. Leading causes of Disability-Adjusted Life Years (DALYs) lost world-wide, 1990 & 2020 (projected)* [GOLD workshop report 2003 update].

<table>
<thead>
<tr>
<th>Disease or injury</th>
<th>Rank</th>
<th>Percent of Total DALYs</th>
<th>Rank 2020</th>
<th>Percent of Total DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower respiratory Infections</td>
<td>1</td>
<td>8.2</td>
<td>6</td>
<td>3.1</td>
</tr>
<tr>
<td>Diarrheal diseases</td>
<td>2</td>
<td>7.2</td>
<td>9</td>
<td>2.7</td>
</tr>
<tr>
<td>Perinatal period conditions</td>
<td>3</td>
<td>6.7</td>
<td>11</td>
<td>2.5</td>
</tr>
<tr>
<td>Unipolar Major depression</td>
<td>4</td>
<td>3.7</td>
<td>2</td>
<td>5.7</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>5</td>
<td>3.4</td>
<td>1</td>
<td>5.9</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>6</td>
<td>2.8</td>
<td>4</td>
<td>4.4</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>7</td>
<td>2.8</td>
<td>7</td>
<td>3.1</td>
</tr>
<tr>
<td>Measles</td>
<td>8</td>
<td>2.6</td>
<td>25</td>
<td>1.1</td>
</tr>
<tr>
<td>Road traffic accidents</td>
<td>9</td>
<td>2.5</td>
<td>3</td>
<td>5.1</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>10</td>
<td>2.4</td>
<td>13</td>
<td>2.2</td>
</tr>
<tr>
<td>Malaria</td>
<td>11</td>
<td>2.3</td>
<td>19</td>
<td>1.5</td>
</tr>
<tr>
<td>COPD</td>
<td>12</td>
<td>2.1</td>
<td>5</td>
<td>4.1</td>
</tr>
<tr>
<td>Trachea, bronchus, lung cancer</td>
<td>33</td>
<td>0.6</td>
<td>15</td>
<td>1.8</td>
</tr>
</tbody>
</table>

COPD encompasses two groups of lung disease, chronic bronchitis and emphysema. Chronic bronchitis refers to a productive cough for at least 3 months of each of 2 successive years for which other causes have been ruled out. Emphysema describes destruction of the lung architecture with enlargement of the airspaces and loss of alveolar surface area.

COPD prevalence increases with age, but there is a dramatic synergy with smoking such that smokers have higher COPD prevalence and mortality and lung function losses as a function of amount smoked are dose-dependent. Unlike heart disease, quitting smoking does not produce substantial reversal of tobacco-harmful effects once COPD is established. As a result, in much of the developed world, COPD is increasing as a cause of death as cardiovascular death rates fall.

As with other tobacco-associated adverse health effects, smoking either cigarettes or cigars increases risks of COPD. Thus, cigar smokers are reported to have a 45% higher risk of COPD when compared to nonsmokers.
3.2 Pulmonary System

The lung, as seen in Figure 3.1 consists of the collection of alveoli and three branching tubular networks; first the bronchial tree which carries air to and from the alveoli, next the pulmonary arterial tree which carries blood to the pulmonary capillaries, then the pulmonary venous tree which returns the oxygenated blood to the heart. The main bronchus, arteries and veins all enter the lung and are divided into parallel networks to reach the alveoli.

The primary function of the lung is gas exchange between the air and the blood via the alveoli. Air diffuses through the thin air-blood barrier in the alveolar walls (next chapter will describe the process and modeling in details), which is lined with blood capillaries. The lungs, chest wall and diaphragm are described as a balloon mounted inside a mechanical bellows. During spontaneous breathing, the respiratory muscles are responsible for the contraction and the pressure difference in the lungs, while the bellows will assist in rapid breathing. The muscles and functional group involved:

(a) Inspiratory Muscles - Diaphragm is the major muscle here. Contraction results in flattening of the muscles and elevation of the lower ribs, which enlarge the thorax.

(b) Expiratory muscle - The exhaling process is usually passive and is caused by the elastic recoil of the lungs and chest wall; at high rates of ventilation or with airway obstruction.

(c) The abdominal and intercostals muscles play their part too in generating a pressure gradient.

The lung is a difficult area to study deemed by the difficult access to it in its natural state. Because the working fluid of this system is a gas rather than a liquid, opening the chest destroys the partial vacuum in the space between the chest wall and the lung, as well as an incision will cause lung collapse.
Figure 3.1 The Respiratory System [American Medical Association].
Component of the respiratory system consists of:

(a) The lungs: pulmonary parenchyma, airways and blood vessels;
(b) The chest wall: the rib cage, intercostals muscles and diaphragm;
(c) The abdomen: the diaphragm, abdominal musculature and abdominal contents;
(d) The nervous system inputs.
3.2.1 Lung Volume and Pressures

The gas volume of the in-vivo lung is classified into eight components as seen in Figure 3.3. These varies with body size, age, however, large differences from these normal gas volumes are indicators of pulmonary functional problems [41]:

(a) Tidal Volume (TV), 600 ml - Volume of gas inspired and expired during normal breathing of a resting person.
(b) Inspiratory Reserve (IR), 3 L - Volume which can be inspired starting after a normal inspiration
(c) Inspiratory Capacity (IC), 3.6 L - Sum of TV and IR
(d) Expiratory Capacity (EC), 1.2 L - Volume which can be expired starting after a normal expiration
(e) Residual Volume (RV), 1.2 L - Volume of gas remaining in lung after maximal expiration.
(f) Functional Residual Capacity (FRC), 2.4 L - Sum of RV + ER, gas volume at end of normal expiration.
(g) Vital Capacity (VC), 4.8 L - Sum of ER, TV and IR. Total possible conscious volume change.
(h) Total Lung Capacity (TLC), 6 L - Sum of RV, ER, TV and IR, total gas volume in maximally inflated lung.

![Figure 3.3](image.png) The eight gas volume components
The above figure shows the dynamics of a normal tidal volume breath. The tidal volume loop is spread out over 5 seconds, 12 breaths/min. The inspiratory time, 2 seconds, is shorter than the expiratory time, 3 seconds as airflow resistance is higher during expiration, as indicated by the fact that the maximal alveolar pressure deflection is only 0.8 cmH₂O during inspiration but is 1.2 cmH₂O during expiration, even though peak airflow is 0.5 litre/sec in each phase. The dashed line in the pleural pressure graph represents the pressure necessary to overcome lung elastance, the mirror image of the tidal volume curve above. The alveolar pressure curve is in phase with the airflow curve. When the alveolar pressure swing due to airflow is added to the elastic recoil pressure, one obtained the complex curve shown by the heavy solid line in the bottom graph. The line segments a, b, c and d show four examples in which the resistive pressure has been added to the elastic pressure. The shaded are during inspiration is less than the area during expiration because the work to overcome airflow resistance is less [42].

### 3.2.2 Alveolar Pressure

This is the pressure within the alveoli, the smallest gas exchange units of the lung. Alveolar pressure is given with respect to atmospheric pressure, which is always set to zero. Thus, when alveolar pressure exceeds atmospheric pressure during exhalation, it
is positive; when alveolar pressure is below atmospheric pressure during inspiration, it
is negative. Hence, alveolar pressure determines whether air will flow into or out of
the lungs. When alveolar pressure is negative, as is the case during inspiration, air
flows from the higher pressure at the mouth down the lungs into the lower pressure in
the alveoli. When alveolar pressure is positive, which is the case during expiration, air
flows out. At end-inspiration or end-expiration, when flow temporarily stops, the
alveolar pressure is zero (i.e., the same as the atmospheric pressure).

During breathing, the actions of the respiratory muscles on the chest compress and
expand the gas within the alveoli. The resultant alveolar pressure is the net force that
moves air through the airway. Its measurement is necessary to estimate airway
resistance and can be accomplished using the following form [43]:

\[
\Delta P_{alv} = \frac{(B - P_{H_2O})\Delta V}{V_L}
\]

(3-1)

where

\(\Delta V\) : is measured with a body plethysmograph, \(L\);
\(P_{H_2O}\) : vapour pressure of water, mmHg
\(V_L\) : thoracic lung, \(L\);
\(B\) : barometric pressure, mmHg
### 3.2.3 Pleural Pressure

Pleural pressure is the pressure surrounding the lung, within the pleural space. During quiet breathing, the pleural pressure is negative; that is, it is below atmospheric pressure.

The pleura are a thin membrane, which invests the lungs and lines the walls of the thoracic cavity. During development the lungs grow into the pleural sacs until they are completely surrounded by them. The side of the pleura that covers the lung is referred to as the visceral pleura and the side of the pleura that covers the chest wall is called
the parietal pleura. These two sides are continuous and meet at the hilum of the lung. The two faces of the pleural membranes are directly opposed to one another, and the entire potential space within the pleura contains only a few milliliters of serous pleural fluid.

During active expiration, the abdominal muscles are contracted to force up the diaphragm and the resulting pleural pressure can become positive. Positive pleural pressure may temporarily collapse the bronchi and cause limitation of airflow.

3.3 Pulmonary Mechanics

The function of the conducting airways, chest wall and the respiratory muscles is to supply fresh oxygen to and remove carbon dioxide from the alveolar capillaries, they function like the respiratory "pump" while gas exchange is accomplished within the alveoli. Pulmonary mechanics is the study of the elastic and flow-resistive properties of the respiratory system components, and their interactions. Several common human disease states can be best understood physiologically as an alteration in the static or dynamic properties of the pulmonary system. We will briefly discuss the mechanical alterations, which result from emphysema, asthma, pulmonary fibrosis, and the respiratory distress syndromes. Finally, it is important to understand that the pulmonary system functions as an integrated whole to accomplish efficient gas exchange at minimal energy cost to the organism.
3.3.1 Components of Total Airflow Resistance

During tidal breathing the elastic and resistive properties of the total respiratory system determine the pressure required to inflate the lungs. This pressure (\( \Delta P \)) can be divided into its elastic component (pressure required to change volume, \( V \)) and resistive component (\( P_{\text{res}} \), pressure required to generate flow, \( V \)) by the simplified equation of motion of the lungs:

\[
\Delta P = E \cdot V + R \cdot \dot{V}
\]

where \( E \) is elastance (the reciprocal of compliance) and \( R \) is resistance. The relevant elastic properties can be divided into two components, those of the lungs and those of the chest wall, which are arranged in series. Similarly the resistive pressure can be defined as the total pressure drop in phase with flow through the separate segments of the tracheobronchial tree and across the lung tissue and chest wall, which are arranged in series. While the pressure drop through the airways is a classic ohmic resistance and proportional to flow, pressure drops across the lung tissue and chest wall are not proportional to flow, but rather depend on lung volume, tidal volume, and frequency. Although usually regarded as small in normal subjects, they are included in measurements of total lung resistance (\( R_L \)) or total respiratory resistance (\( R_{rs} \)) (refer to the figure below). Resistance of some of the individual airway segments can be measured by catheters or needles but this is rarely done (except for the nose).

Table 3.4 Abbreviations [21]

<table>
<thead>
<tr>
<th>Segmental resistance [cmH₂O.L⁻¹]’s</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOUTH (NOSE)</td>
<td>pharyngeal catheter</td>
</tr>
<tr>
<td>LARYNX</td>
<td></td>
</tr>
<tr>
<td>TRACHEA</td>
<td></td>
</tr>
<tr>
<td>CONDUCTING AIRWAYS</td>
<td></td>
</tr>
<tr>
<td>ALVEOLI</td>
<td></td>
</tr>
<tr>
<td>LUNG TISSUE</td>
<td>body plethysmography</td>
</tr>
<tr>
<td>CHEST WALL</td>
<td>airflow interruption*</td>
</tr>
<tr>
<td></td>
<td>esophageal balloon catheter</td>
</tr>
<tr>
<td>TOTAL R̄</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: \( R_{\text{no}} \) – oral airway resistance; \( R_{\text{na}} \) – nasal airway resistance; \( R_{\text{u}} \) – upper airway resistance; \( R_{\text{a}} \) – airway resistance above the upper end of the trachea; \( R_{\text{lw}} \) – airway resistance of intrathoracic airways (above) to trachea; \( R_{\text{olv}} \) – total airway resistance; \( R_l \) – total pulmonary resistance; \( R_t \) – lung tissue resistance; \( R_{cw} \) – flow resistance of chest wall; \( R_{rs} \) – total respiratory resistance.

The total resistance is the sum of all the segments arranged in series.

* Value when breathing through a large caliber mouthpiece. During nasal breathing \( R_{cw} \) would be 1–2 cmH₂O.L⁻¹’s higher.

* Values are usually higher than for \( R_{cw} \) but in some circumstances measure \( R_{cw} \) accurately.
3.3.2 Methods for Measuring Airflow Resistance

There are four methods in clinical use. They have different strengths and weaknesses and measure slightly differently parts of the total resistive pressure drop.

3.3.2.1 Body plethysmography to measure airway resistance (Raw) [44]

The body plethysmograph is the only available method for directly measuring airway resistance in humans and has the added advantage that absolute lung volume can readily be measured, allowing the calculation of a volume corrected (specific) resistance or its reciprocal, conductance. The technique has been particularly valuable for studies of airway pharmacology in normal subjects and subjects with mild asthma, and, suitably modified, in infants. Its disadvantages are its bulk and expense and a relative difficulty in using it for different maneuvers or breathing different gas mixtures.

Figure 3.6 Body plethysmography method. The subject, seated in a whole-body plethysmograph ('box') breathes through a pneumotachograph back into the box (V).

The above figure shows the setup for the Body plethysmography method. The mass movement of gas from the lungs to box itself results in no change in total volume (provided there are no changes in temperature), and so the change in box pressure ($P_{box}$) during breathing is due to volume change of the lungs caused by compression and rarefaction of alveolar gas; if the volume of alveolar gas is known, the observed change in box pressure can be calibrated in terms of change of alveolar pressure. Dividing change in alveolar pressure by change in flow at the mouth gives airway resistance ($Raw$).

This method assumes a constant volume; so that any change in thoracic volume which is not simply due to mass transfer from lungs to box results in reciprocal changes in box pressure (i.e. box pressure rises if there is rarefaction of alveolar gas). To
calibrate changes in box pressure in terms of change in volume, a pump is used to inject and withdraw repetitively a small volume of gas into the box, while the subject to be studied holds his breath. (A large subject occupies more of the plethysmographic volume, so that a standard primp volume results in a bigger box pressure change than when a small subject is studied.) Alternatively a correction based on subject’s body weight can be used and the box calibration performed when empty.

Changes in box pressure on expiration can occur; mainly because of cooling of expired air transferred from lungs to box (Instability of box pressure can be caused by heating of box air after the subject enters. Some plethysmographs are air-conditioned to hold the temperature more stable. there are also small effects from the respiratory exchange ratio being < 1.0.) This is minimized either by shallow panting through a heated pneumotachograph (this also has the advantage of abducting the cords and minimizing glottal resistance) or by rebreathing into a bag heated to 37° or with computerized simulated correction for the change in temperature and humidity as gas is transferred from lungs to box during tidal breathing.

The subject is connected by caliber mouthpiece to the pneumotachograph shutter assembly. In the first part of the procedure changes in box are plotted against flow rate on an oscilloscope and the angle (\( \Delta P_{\text{box}} / \Delta V \)) measured usually around zero flow or from 0 to 0.5 Ls\(^{-1}\) inspiratory flow. The shutter is then closed to allow ‘calibration’ of the \( P_{\text{box}} \) signal in terms of \( P_{\text{alv}} \) by measuring \( P_{\text{mo}} \) during panting against an occlusion (when it will normally equal \( P_{\text{alv}} \)) and plotting this against \( P_{\text{box}} \) on an oscilloscope, and measuring the \( \Delta P_{\text{mo(alv)}} / \Delta P_{\text{box}} \) slope. Then multiplying the two slopes:

\[
\frac{\Delta P_{\text{box}}}{\Delta V} \times \frac{\Delta P_{\text{alv}}}{\Delta P_{\text{box}}} = \frac{\Delta P_{\text{alv}}}{\Delta V} = \text{Raw}
\]
Figure 3.7 Changes in (a) airways resistance ($R_{aw}$), and (b) conductance ($G_{aw}$) with changes in lung volume in a normal individual. Whereas $R_{aw}$ has a curvilinear relation to lung volume, $G_{aw}$ shows a linear increase as lung volume is increased from residual volume ($RV$) to total lung capacity ($TLC$). Specific airway conductance ($sG_{aw}$) at any lung volume equals $G_{aw}/V_L$, where $V_L$ is the absolute lung volume (L). Because of the intercept of $G_{aw}$ on the volume axis at $RV$, $sG_{aw}$ is lower at functional residual capacity ($FRC$) than at a larger lung volume (as indicated by the dashed lines from the origin). (c) In chronic obstructive pulmonary disease (COPD) $G_{aw}$ increases less than normal as $V_L$ is increased, and there is a large $RV$.

### 3.3.2.2 Esophageal Balloon Catheter Technique to Measure Total Lung Resistance

Pleural surface pressure can be estimated by placing a small balloon catheter in the lower esophagus. During tidal inspiration, changes in pleural (in practice, esophageal) pressure are required to oppose the elastic properties of the lung (measured as dynamic compliance, $C_{Ldyn}$) and the resistive properties of the lungs and lung tissue (total lung resistance, $R_L$). By simultaneous measurement of flow at the mouth ($\dot{V}$) and change in lung volume ($\Delta V$), it is possible to subdivide the change in esophageal pressure into $C_{Ldyn}$ and $R_L$.

Esophageal Balloon Catheter Technique is the only method that directly measures intrathoracic pressure, but its invasiveness means that it is not often used solely to measure $R_L$ (and $C_{Ldyn}$) in humans. Once an esophageal balloon catheter has been placed, a full analysis of pulmonary mechanics can be made with additional measurements such as the static pressure-volume curve of the lung and the mechanical work of breathing on the lungs and chest.
During quiet breathing in normal subjects, most of the tidal change in pleural (esophageal) pressure is overcoming the elastic properties of the lungs and a much smaller proportion the resistive properties; in addition there is often a notable cardiac artifact on the esophageal pressure trace. As a consequence, measurement of $C_{L_{dyn}}$ is more reliable than $R_{L}$. One way to improve the signal-noise ratio is to ask the subject to breathe rapidly, with tidal volume similar to that used during quiet breathing; this increase in flow accentuates the resistive component of the total pressure change. The signal-noise ratio for $R_{L}$ is much better when airways obstruction is present. All calculations of the resistive pressure drop assume dynamic compliance to be constant during the breath and identical on inspiration and expiration. Alinearities in dynamic compliance occur when breathing with large tidal volumes or close to TLC and when dynamic compliance is severely reduced, as in fibrosing alveolitis; these alinearities result in errors in the calculation of $R_{L}$.

Measurements of esophageal pressure may be distorted in the supine position because of the effects of gravity on the heart and mediastinal contents and the position of the diaphragm.

An esophageal balloon catheter is positioned in the lower esophagus and connected to a differential pressure transducer which measures the difference between esophageal and mouth pressure ($\Delta P$). The subject wearing a nose clip, breathes through a pneumotachograph which measures instantaneous flow ($\dot{V}$) which is integrated to give tidal volume ($\Delta V$). Data are collected over at least 10 breaths during quiet breadth (as shown in the figure below).
For normal subjects, it may be useful to breathe with increased frequency of breathing but with a similar tidal volume because this increases the resistive component of $\Delta P$ in the above figure.

Although records against time can be used to calculate $R_L$ and $C_{L_{\text{dyn}}}$, the interrelations between the two relations and the calculation of work of breathing can be
demonstrated better by plotting the relation between pressure and volume during each breath as shown in the above figure. On inspiration pressure becomes more negative until end inspiration. On expiration esophageal pressure rises (becomes less negative).

The dynamic compliance \( (C_{Ldyn}) \) is obtained by dividing tidal volume \( (\Delta V) \) by the difference in esophageal pressure between points of no flow (end inspiration), distance on pressure axis being equivalent to change in dynamic lung elastic pressure \( (\Delta P_{Ldyn}) \).

The total lung resistance \( (R_L) \) is obtained by measuring the width of the esophageal pressure volume loop at iso-volume; this indicates the resistive pressure drop \( (\Delta P_{Pre}) \) which can be divided into inspiratory (to the left of the diagonal line) and expiratory (to the right of the diagonal line) components and related to the corresponding flow at that volume. Usually however the total \( \Delta P_{Pre} \) is used and related to the sum of inspiratory and expiratory flow at this volume, \( R_L = \Delta P_{Pre}(V_{insp} + V_{exp}) \).

Values of \( R_L \) in normal subjects are usually slightly higher than values of \( R_{aw} \), presumably reflecting tissue resistance of the lungs. When airway narrowing is induced in normal subjects the increment in \( R_L \) may be larger than that in \( R_{aw} \); this may be because \( R_L \) is measured at a lower breathing frequency than \( R_{aw} \) or because \( R_L \) also measures an increase in 'tissue resistance' (see later). Few studies have compared values of \( R_L \) and \( R_{aw} \) in patients with airways obstruction. Although the method is potentially suitable for long-term monitoring of \( R_L \) (and \( C_{Ldyn} \)), in practice this is only used in intensive care units; in the pulmonary function laboratory, forced oscillation is a more acceptable non-invasive technique for monitoring airflow resistance during tidal breathing over long periods. The esophageal balloon - catheter technique is the best method for measuring resistance during the high flows of exercise.

### 3.3.2.3 Forced Oscillation Techniques to Measure Total Respiratory Resistance \( (R_{\omega}) \) [45, 46]

The forced oscillation technique for measuring air flow resistance was introduced in 1950s at the same time as body plethysmography, but did not become as widely established in clinical physiology because the technical requirements for obtaining accurate pressure and flow signals and the subsequent signal processing were more demanding. Advances in pressure transducer and microcomputer technology have removed earlier problems with signal collection and analysis. Oscillation methods require less cooperation from the subject and less bulky apparatus than body
plethysmography, and so the oscillation technique is now becoming more widely used.

Forced oscillation techniques deduce the mechanical properties of the respiratory system from the response to small, externally produced oscillatory forces. From the response measured as the instantaneous pressure flow relationship (impedance) - flow resistance and the reactance (the combined effect of elastance and inertance) of the respiratory system can be computed. These mechanical properties of the lungs are non-linear so it is important that only small external forces (1-2 cmH₂O) are applied. During quiet breathing the elastic properties (compliance) and resistive properties account for all the pressure required to expand the respiratory system. A third property, inertance, which is related to the pressure required to accelerate flow, is only important in very rapid breaths but becomes significant when oscillation is applied at high frequencies.

The main current application in clinical physiology of the forced oscillation technique is as a simple method for obtaining the flow resistive properties of the respiratory system at different frequencies during tidal breathing. Usually results are presented at an oscillation frequency of 4 or 6 Hz and as frequency dependence of $R_{rs}$ at higher frequencies within a breath.

In patients with COPD (and asthma) $R_{rs}$ is increased at the lower applied frequencies but falls with increasing applied frequencies (as shown in the following figure). Reactance ($X_{rs}$) is lower than in healthy subjects and becomes positive only at higher frequencies, so that resonant frequency is increased. In the presence of inhomogeneity of mechanical properties of the lungs, resistance falls with increasing frequency, but this fall is exaggerated by increased dissipation of the applied oscillatory signal in the upper airway (chiefly the cheeks and floor of mouth). The contribution of the cheeks and mouth (sometimes called upper airway shunt) to total impedance can be reduced, but not eliminated, by firm support of the cheeks and floor of the mouth with the palms and fingers.
Figure 3.10 Typical changes in total respiratory resistance at different applied oscillation frequencies. In a patient with airways obstruction resistance is higher at all frequencies than in a normal subject and decreases with increasing frequency; reactance is lower at all frequencies and resonant frequency is increased. The tidal breathing pattern can be monitored during measurement by integrating $V_{mo}$ and absolute volume determined by measuring inspiratory capacity at the end of the measurement period to calculate specific $R_{rs}$. 

(Modified from Pride NB. Thorax 1992; 47:317-320)
Figure 3.11 Forced oscillation method for measuring input impedance during tidal breathing. The loudspeaker is driven to generate a sinusoidal oscillation at one frequency, a sequential series of sinusoidal oscillations at different single frequencies. The flow signal can be integrated to give tidal volume and at the end of the measurement period, inspiratory capacity.
3.3.2.4 Airflow interruption technique to measure resistance ($R_{int}$) [47]

The interruption technique is the simplest technique for measuring airflow resistance. Spontaneous breathing is interrupted by occluding the mouthpiece, and the flow immediately before occlusion is related to an estimate of alveolar pressure ($P_{alv}$) shortly after occlusion which is derived from the trace of mouth pressure ($P_{mo}$) (measured on the alveolar side of the closed mouthpiece) versus time. The method requires minimal subject cooperation (the ability to use a flanged mouthpiece), can now be measured by simple portable devices, and does not require full inflation or unusual breathing maneuvers.

Figure 3.12 Airflow Interruption Apparatus. The subject with nosed clipped breaths tidally through the interrupter device which comprises a tube with a fast-closing value and a flow measuring device, usually a pneumotachograph screen. Valve closure may be triggered at a given flow or randomly and typically lasts 100ms. $P_{mo}$ before occlusion ($P_{pre}$) is proportional to screen resistance and is used to measure flow.
Figure 3.13 Analysis of $P_{	ext{mouth}}$ versus time record. During expiratory flow, month pressure ($P_{mo}$) is greater than alveolar pressure ($P_{alv}$) because of the resistance of the airways. $P_{mo}$ indicates the pressure drop across the pneumotachograph screen ($P_{pre}$) and measures flow ($V$). When the disk valve closes, flow ceases and $P_{mo}$ rises rapidly to equilibrate with $P_{alv}$. Following flow interruption, three distinct phases in the $P_{mo}$ versus time curve occur.

In most comparisons, values of $R_{int}$ have been higher than those of $R_{aw}$ and of $R_L$, in normal subjects but the precise reasons for this difference were undetermined. If $P_{mo}$ is back-extrapolated to time of half-closure of the valve, then $R_{int}$ is similar to $R_{aw}$ in normal subjects but is lower than $R_{aw}$ when there is airway obstruction. This underestimate is probably caused by slow equilibration of $P_{alv}$ with $P_{mo}$. Interpretation of the later increase in $P_{mo}$ on the $P_{mo}$ versus time curve is less clear because it is not possible to distinguish the roles of continuing respiratory muscle activity, stress recovery of lung and chest wall tissues, and redistribution of gas - either between intra-and extrathoracic airways or between parallel intrathoracic airways. Despite these limitations in physiological interpretation, measurement of $R_{int}$ has proved useful for the empirical detection of airway narrowing.
3.4 Comparison of Different Methods for Assessing Airflow Resistance

Forced oscillation and airflow interruption are more convenient and require less subject cooperation than esophageal balloon and body plethysmography methods, but unfortunately they are less sensitive than the last two methods and tend to underestimate resistance. Only the esophageal balloon catheter directly measures intrathoracic pressure, and the measurement is subject to noise. The other three methods rely on the measurement of $P_{mo}$, changes in which tend to be increasingly underestimated as airway obstruction becomes more severe. This is because pressure is dissipated in the compliant extrathoracic airway, which is important in the forced oscillation technique; in addition there is slow equilibration of alveolar and mouth pressure which leads to underestimates of resistance with the airflow interruption technique and, in the plethysmographic method, overestimates of lung volume and consequent underestimates of $R_{aw}$ (measurements of $sR_{aw}$ or $sG_{aw}$ are not affected). Standard techniques for measuring $R_i$, $R_{aw}$, and $R_{rs}$ all average resistance over a whole breath, but $R_{int}$ is usually derived from a single inspiratory or expiratory measurement.

In normal subjects resistance values are relatively similar with all four methods, although forced oscillation usually gives slightly higher values.

3.4.1 Lung Diseases with Resistance Issues

Airway resistance is the opposition to flow caused by the forces of friction. It is defined as the ratio of driving pressure to the rate of airflow. Resistance to flow in the airways depends on whether the flow is laminar or turbulent, on the dimensions of the airway, and on the viscosity of the gas.

A relatively large driving pressure is required to sustain turbulent flow. Driving pressure during turbulent flow is in fact proportional to the square of the flow rate such that to double the flow rate one must quadruple the driving pressure.

$$\Delta P = k V^2$$

(3-1)

where:

$\Delta P$ : driving force;

$k$ : constant; and
Laminar flow is of low velocity and through narrow tubes, it tends to be more orderly and streamlined and to flow in a straight line. This type of flow is called laminar flow. Unlike turbulent flow, laminar flow is directly proportional to the driving pressure, such that to double the flow rate, one needs only double the driving pressure.

Most of the resistance to airflow is in the large airways, which includes the mouth, glottis, the trachea and bronchi (>2mm in diameter). While a single small airway provides more resistance than a single large airway, resistance to air flow depends on the number of parallel pathways present. Smaller airways rapidly branch to produce a large total cross sectional area; therefore the flow velocity is very low and the flow is laminar, so the resistance to flow is small as seen in the figure below.

**Figure 3.14** The Resistance to airflow profile along the airways [J. F. Perkins et. al].

In addition to the anatomy of the respiratory tree, there are also dynamic factors, which influence total respiratory system resistance to flow:

(a) Lung volume - Airway resistance decreases as lung volume increases as shown in the figure below, because the airways expand as the lungs inflate, and wider airways have lower resistance.
Figure 3.15 Resistance against Volume profile [J. F. Perkins et. al].

(b) Internal airway obstruction (in cases of asthma or tumor obstruction);
(c) Dynamic airway compression;
(d) Constriction or relaxation of the bronchial smooth muscle.

Under conditions of laminar flow, the airways are rigid. Airway diameter and the viscosity of the gas flowing through them would be the only important determinants of airway resistance. However, if the airways are compressible, the external pressure in the lungs and pleura is transmitted to the airways. In addition, the internal airway pressure that drives air into or out of the lung is dissipated by frictional losses along the airway. The transmural pressure (the pressure inside - pressure outside) determines whether the airway will narrow. The pressure surrounding the intrathoracic airways is close to intrapleural pressure. Dynamic airway compression, the narrowing of an airway from negative transmural pressure is an important determinant of the flow rate in any particular airway passage. During exhalation, the transmural pressure across the airway becomes smaller, the airway narrows and the airflow is limited by this mechanism. Whereas during inhalation, the airway enlarges hence decreases flow resistance.
3.5 Lung Volumes and Elasticity

The respiratory system is an elastic structure changing volume when pressures are generated by inspiratory or expiratory muscles. If the muscles are relaxed the respiratory system returns to its relaxation volume ($V_r$) (referred to in the pediatric literature as the elastic equilibrium volume [EEV]), which in normal subjects is the end-expired volume or functional residual capacity, FRC, where alveolar pressure is equal to atmospheric pressure.

When an anesthetist hand-ventilates a paralyzed patient at this volume by applying a positive pressure at the proximal end of the airway and measures the change in volume per unit change in applied pressure ($\Delta V/\Delta P$) the 'stiffness' or compliance of the total respiratory system ($C_{rs}$) is measured and shown by figures as below. Some of the applied pressure inflates the lungs and some the chest wall. Thus, the total respiratory compliance is less than the compliance of either structure individually. For example, if the compliance of the lungs ($C_L$) is 0.2LcmH$_2$O$^{-1}$ and that of the chest wall ($C_{cw}$) is similarly 0.2LcmH$_2$O$^{-1}$, then to increase the volume of both together by 0.2 L requires a total applied pressure of 2cmH$_2$O (Figure 3.10). Hence, in this situation the total respiratory compliance ($C_{rs}$) is 0.1 L.cmH$_2$O$^{-1}$ or, more generally,

$$\frac{1}{C_{rs}} = \frac{1}{C_L} + \frac{1}{C_{cw}}$$

Although in health $C_L$ and $C_{cw}$ are similar in the tidal range, the resting volume (volume when any distending or collapsing force is removed) of the chest wall is much larger than that of the lungs which collapse down to a small volume in the absence of distending forces.

Note that the analysis in Figures 3.16 and 3.17 relates only to gas volume of the lungs and that tissue and fluid volumes are ignored. In some diseases (cardiac failure, adult respiratory distress syndrome) the fluid volume in the lungs increases markedly and may complicate analysis of the balance of pressures across the respiratory system. Similarly the volume of a pleural effusion or a pneumothorax is ignored if only pulmonary gas volume is considered.
Figure 3.16 Static PV curve of respiratory system with maximal pressures generated by respiratory muscles. Static PV curve of the total respiratory system ($P_{rs}$ – broken line) compliance in the tidal range ($C_{rs}$) and functional residual capacity (FRC), and the pressures recorded during maximal inspiratory $P_{mus_{insp}}$ (left side) and expiratory efforts $P_{mus_{exp}}$ (right side) at various lung volumes in a healthy young adult (dotted line). Solid lines show alveolar pressure ($P_{alv}$, i.e. mouth pressure when efforts are made against a closed airway). $P_{alv}$ represents the sum of $P_{rs}$ and $P_{mus}$. Total lung capacity (TLC) is set by the balance between $P_{rs}$ and inspiratory muscle effort, i.e. at TLC, $P_{rs}$ is equal and opposite to inspiratory $P_{mus}$. Residual volume (RV) is set by the balance between $P_{rs}$ (negative because at low volumes net recoil of the respiratory system is outward) and expiratory $P_{mus}$.
Figure 3.17 Static PV curves of respiratory system, lungs and chest wall. ‘Rahn diagram’ [50] showing how static PV curve of respiratory system \((P_{rs}\text{-broken line})\) shown in Figure 3.9 relates to PV curves of its two components, the lungs and chest wall. Scale on pressure axis is expanded. \(P_L, P_{cw}, P_{rs}\) represent recoil pressures and \(C_L, C_{cw}, C_{rs}\) static compliance of lungs, chest wall, and respiratory system respectively. Compliance is represented by the slope of the respective PV curve over the approximate tidal range (heavy lines). Note: (1) at FRC \(P_L = -P_{cw}\); (2) \(C_{rs}\) is less than either \(C_L\) or \(C_{cw}\) alone; (3) \(P_L\) increases disproportionately towards TLC; (4) \(P_{cw}\) becomes increasingly negative towards RV; (5) resting volume \((P_{cw} = 0)\) of chest wall greatly exceeds that of lungs \((RV)\).

3.5.1 Method for Measuring Lung Compliance

In most clinical circumstances the compliance of the chest wall is of little importance. Measurement of total respiratory compliance is difficult in the adult conscious subject, and so it is rarely measured in the pulmonary function laboratory.

On the other hand, the static compliance of the lungs is of considerable interest and is frequently abnormal in disease [48-49]. In practice, however, it is measured infrequently because it involves the subject swallowing a tube into the esophagus and lengthy breathing maneuvers and analysis.
3.5.1.1 Static Pressure-Volume (PV) curve of the lungs

To construct the static PV relationship of the lungs requires measurement of the difference between alveolar and pleural pressures (transpulmonary pressure) at several lung volumes. This is obtained during breath-holding with a balloon-catheter system or a small pressure transducer in the lower esophagus to approximate pleural pressure. This pressure is compared to the pressure at the airway opening which during breath-holding reflects alveolar pressure.

Volume change measured either with a spirometer or with the subject seated in a variable volume body plethysmograph [50-51], which allows direct measurement of changing thoracic gas volume. An esophageal balloon or appropriate miniature pressure transducer is swallowed, usually via the nose, into the lower third of the esophagus. When using a balloon-catheter system a small volume of air is introduced with the aim of producing a bubble at the upper end of the balloon. The volume of air used needs to be neither too large to distend the esophagus, nor too small to cause the balloon itself to develop a negative recoil. In practice this is usually between 0.2 and 0.5 ml. The position of the balloon or transducer is adjusted up and down to give the most negative values of pressure at FRC, usually by trial and error. Alternatively the depth of the balloon may be standardized in relation to the height of the subject by using the formula of Zapletal et al [52], based on which the tip of a 10 cm balloon should be positioned at a depth of (height[cm]/5 + 9) cm from the nostril.

Measurements of transpulmonary pressure (mouth minus esophageal pressure, $P_L$) at various volumes are usually made during deflation after a standard sequence (volume history) of three full inflations. If expired volume is used, either the subject needs to maintain an inspiratory effort and open airway during breath-holding at each volume or, if allowed to relax against a shutter, a correction to the volume is necessary due to the resulting small changes in thoracic volume associated with the positive pressure which accompanies relaxation (Boyle's law). With a variable volume plethysmograph (with the door closed) no correction is needed as the effects of gas compression are measured directly.
Figure 3.18 Measurement of lung PV curve and compliance. Record against time of volume ($\Delta V$) expired during interrupted expiration from total lung capacity (TLC), and transpulmonary pressure (mouth - esophageal pressure). During bieolla-holding (plateaux of volume and pressure) mouth = alveolar pressure and thus transpulmonary pressure = lung recoil pressure (PL). Irregularities on pressure record are due to cardiac pulsation. Gain on pressure amplifier doubled at point indicated by converging arrows.
3.6 Lung Diseases with Compliance Issues

The three important mechanical characteristics of the lung are its compliance, flow resistance and uniformity of various airways paths. Diseases are caused by the alteration of each of these three, else by the interference with gas exchange at the alveolar walls.

Obstructive lung disease is a respiratory abnormality characterized by a slow rate of forced expiration. In those with active asthma or emphysema, a high residual volume and functional residual capacity and a low vital capacity are usually seen as well. Asthma, bronchitis, and emphysema are all considered obstructive conditions, but the way each results in an obstructive defect is quite different. Asthma, a disease characterized by airway mucosal swelling, hyperirritability of the bronchial smooth muscle, and excessive bronchial mucus production is a disease of flow limitation. Asthmatics often have normal lung compliances and suffer from an inability to generate normal airflow velocities. Thus this increases the work of breathing.

Chronic Obstructive pulmonary disease is another common obstructive disease. In such cases, patients lost the elastic recoil in large parts of their lungs through destruction of elastin, which means they are unable to empty their lungs. The radial distending forces on smaller airways are destroyed so airflow limitation is even more profound if there were only changes in the compliance.

Emphysema is a disease in which there is destruction of the walls of the air sacs of the lung, and it is frequently preceded by chronic bronchitis. Emphysema adds to the breathlessness suffered by the patient with chronic bronchitis. Compliance of the lung is significantly above normal; the lung becomes easy to distend but empties slowly. This results in a chronically over inflated lung (high total lung capacity, functional residual capacity, and residual volume), which reduces the curvature of the diaphragm, making it less efficient in generating even the small swings in pleural pressure necessary for breathing. Pulmonary function tests on a patient with emphysema will reveal a compromised expiratory flow (due to their low lung recoil).

Restrictive disease is a condition marked most obviously by a reduction in total lung capacity. A restrictive ventilatory defect may be caused by a pulmonary deficit, such as pulmonary fibrosis (abnormally stiff, non-compliant lungs), or by non-pulmonary deficits, including respiratory muscle weakness, paralysis, and deformity or rigidity of the chest wall.
In pulmonary tests, an individual with a restrictive ventilatory defect demonstrates a low total lung capacity, a low functional residual capacity, and a low residual volume. Because large drops in pleural pressure are required to inflate the lungs, deep breaths are difficult for individuals with restrictive defects, and they tend to breathe shallowly and rapidly.

The figure below shows the relationship between pressure and volume for the obstructive and restrictive lung diseases as compared to the normal lung. For lungs diagnosed with Emphysema it distends but empties slowly. While fibrosis lungs is unable to inflate hence results in a low total lung capacity.

![Figure 3.19 Volume-Pressure profile for different lung diseases](image)

**3.6.1 Lung Distensibility**

In response to a pressure differential, elasticity causes the lungs to return to its original size by resisting inflation and promotes lung emptying. The reciprocal of elastance is compliance. Compliance refers to the distensibility of an elastic structure and is defined as the change in volume of that structure produced by a change in pressure across the structure. It is important to understand that the lung (or any other elastic structure) will not increase in size if the pressure within it and around it is increased equally at the same time.

In a normal healthy lung at low volume, relatively little negative pressure outside (or positive pressure inside) needs to be applied to blow up the lung quite a bit. However lung compliance decreases with increasing volume. Therefore as the lung increases in size, more pressure must be applied to get the same increase in volume. This can be
seen from the following pressure-volume curve of the lung: Lung compliance and the slope are the same and it is non-linear:

![Lung Pressure Volume curve](image)

**Figure 3.20** Lung Pressure Volume curve [J F. Perkins et. al].

The compliance of the lungs is critical to breathing:

(a) The lungs are hard to inflate if the compliance is too low. Therefore, the work of breathing is increased. An example of this is pulmonary fibrosis (damaged lung tissue grows back as scar tissue), where the thoracic wall is pulled in (the lungs win the tug-of-war) and inspiration is difficult.

(b) Too great a compliance and there is little recoil once the lungs are inflated.Expiration is difficult as it is caused by the passive recoil of the lungs. Also, the thoracic wall wins the tug-of-war and the lung and thoracic volume expands so that the diaphragm flattens and becomes inefficient. An example of this is pulmonary emphysema (one of the possible terminal stages of death by smoking). These people have barrel chests because of the expanded volume.
3.7 Literature Review

3.7.1 The Alveolus Model - A prediction of the pressure-volume behavior of the lung

The alveolus model is used to describe the mechanical stability of the inflated lung from its microstructure. The alveolus is modeled as a distensible spherical bubble on the end of a rigid tube representing the alveolar duct as shown in Figure 3.21.

![Figure 3.21 Model of an alveolus at the end of an airway. The alveolar wall tissue is subjected to equal biaxial stretch [6].](image)

The inflating pressure is balanced by the surface tension, $\gamma$, in the liquid lining of the bubble and by the tension, $T$, in the alveolar walls [6]. The bubble size in radius, $R_s$ relates to the transmural pressure, $P$, using Laplace's formula:

$$P = \frac{2(\gamma + T)}{R_s}, \text{ or } T_s = \frac{PR_s - 2\gamma}{2} \quad (3-1)$$

The stresses, $\sigma$ and the wall thickness, $t$ affect the tissue tension. Since there is only one tissue wall between adjacent alveoli, the wall stresses are shared by two alveoli. Hence the volume of the alveoli determines the magnitude of the stresses. The tissue tension in one alveolar wall is related to the stresses and wall thickness, by:

$$\sigma_s = \frac{T_s}{t_s} = \frac{PR_s - 2\gamma}{2t_s} \quad (3-2)$$
From the above relationship, the surface tension, $\gamma$ in the liquid lining of the bubble, reduces with the tissue stress, $\sigma$.

The alveolar duct, which is the shape of a cylinder, is modeled as a rigid tube that is collapsible at a pressure below a critical value, $P_{cr}$ and gas is trapped in the alveolar bubble, otherwise it is open and rigid above $P_{cr}$. The collagen and elastin fibers that encircle the alveolar mouths give the tube tissue its rigidity [8]. The pressure is equal to the tension, $T_c$ in the fiberous rings and the surface tension of the alveolar and tube lining as shown in the Laplace's equation below for a cylinder:

$$\sigma_c = \frac{T_c}{t_c} = \frac{PR}{t_c}$$  \hspace{1cm} (3-3)

Similar to equation (3-2), the surface tension, $\gamma$ in the liquid lining of the bubble reduces with the tissue stress, $\sigma$ in the alveolar duct.

During deflation, $R_c$ remains constant while $T_c$, $\gamma$ and $P$ decreases. At $T_c = 0$, critical pressure occurs and the surface tension, $\gamma$ is at its minimum, as given by:

$$P_{cr} = \frac{2\gamma_{min}}{R_c}$$  \hspace{1cm} (3-4)

The volume of gas trapped in the collapsed bubble can be determined from the critical radius of the sphere, $R_{cr}$. Since the tissue stresses are zero at this small volume, pressure and surface tensions are equal in the bubble and the cylinder, we have:

$$R_{cr} = 2R_c$$  \hspace{1cm} (3-5)

In this situation when $R_s$ reaches the critical value of $2R_c$, instability occurs and there are two possible bubble volumes, one a segment smaller than a hemisphere (for which $R_s = R_c$) and one larger than the hemisphere (for which $R_s > R_c$). Lung morphology [8] indicates that the smaller volume, which corresponds to a minimum value of $R_s$, occurs at the end of expiration, before inflation. Now, inflation occurs when the pressure exceeds $P_{cr}$ (of equation 3.4), and the bubble starts becoming bigger. The bubble will grow without bound if the surface tension and tissue stresses do not change i.e. the bubble in Figure 3.22 is unstable until the tissue stresses become large. Changing the surface tension (due to surfactant lining) helps maintain the alveolus in shape, prevents it from collapsing as well as overstretching. Alveoli vary in size
throughout the lungs; some have a radius 3 - 4 times that of others. If surface tension were the same in all alveoli, regardless of their size, the pressure required to keep air spaces inflated against surface tension would also vary 3 - 4 times.

As all alveoli communicate with one another, there cannot be a huge pressure difference in the alveoli of the lung; pressure must be the same in all. However, Laplace's law shows that if the air pressure were equal in bubbles of different sizes, the smaller bubbles would collapse and the larger ones would over-expand. The tension, $T$, in the wall of a spherical bubble tends to contract the bubble, and the pressure inside the bubble tends to expand it. Referring to equation (3-1), if the surface tension in the bubble remains the same regardless of the radius of the bubble, the air pressure to inflate the bubble increases as the tension increases. A low surface tension requires a low air pressure to maintain a given radius or volume, whereas one with a high surface tension requires a large counter-pressure. This explains why small bubbles have a high pressure and large bubbles have low pressure and why small bubbles can empty into larger ones as depicted in the figure below.

![Figure 3.22 Dynamics of soap bubbles [9].](image)

A real lung contains a distribution of alveolar and alveolar duct diameters hence lung behavior is represented by bubbles of different dimensions acting in parallel. The variations in surface tension and tissue tensions enable different sizes of alveoli to co-exist. However, if surface tension were equal, the inflating pressures would be unequal and air would flow out of the smaller alveoli into the larger ones:
If $\gamma_1 = \gamma_2$ during inflation, $R_{s1} = \frac{2(\gamma + T_{s1})}{P_1}$ and $R_{s2} = \frac{2(\gamma + T_{s2})}{P_2}$  

(3-6)

As a result we would have an inhomogeneous lung with a mixture of collapsed and maximally extended alveoli. This does not occur in healthy lungs, because firstly the surface tension of the alveolar lining is significantly less than that of plasma, and secondly the surface tension of the alveolar lining decreases as the film is compressed; this probably occurs during expiration when the alveoli becomes smaller. Avery et. al. [9] has calculated that this factor, acting in conjunction with elastic elements of the tissue, is sufficient to ensure the stability and prevent the collapse of small alveoli during expiration, and lead to a stable balance between small and large alveoli. The combined effect of alveolar size and surface tension on tranpulmonary pressure is required to maintain lung inflation is required.

This alveolar bubble model is valid only for static and quasi-static conditions, as it does not take into consideration of the airflow resistance, which is an important parameter in a respiratory model. Besides that, it assumes that all alveoli are exposed to an inflating pressure equal to the transmural pressure, while only a small amount of the alveoli are at the lung's surface. Mead [10] has proved that this is the case for a uniformly inflated lung. The alveolar wall tissue transmits pressure without changing the pressure into the lung as long as the spatial density of the alveolar walls is uniform. However, a stress concentration occurs if one section of the lung is over-inflated or under-inflated. This is caused by the variation in tissue wall elongation, which tends to return the abnormal region to the average inflation of the entire lung. Thus the lung structure as well as the surface tension acts as a mechanical stabilizing mechanism.

### 3.7.2 Lung Compliance and Flow Resistance

According to [11], the dynamic lung compliance, $C_{dyn}$ and resistance $R_{dyn}$ while breathing at any frequency if total airflow and transmural pressure are measured simultaneously. Compliance is estimated by taking the ratio of the change in lung volume $\Delta V$ and the change in transmural pressure $\Delta P$ at zero airflow condition:

$$C_{dyn} = \frac{\Delta V}{\Delta P}$$  \hspace{1cm} (3-7)
Likewise, the flow resistance in the pulmonary airways during breathing can be estimated by taking the ratio of the change in transmural pressure, $\Delta P$ and the change in airflow, $\Delta V$ at a certain level of lung volume:

$$R_{dyn} = \frac{\Delta P}{\Delta V} \quad (3-8)$$

As this is a linear model, it does not reflect the complex flow patterns within the branching airways of the lung. Therefore, our work in the next section we will formulate models that incorporates $\dot{V}$ and $\ddot{V}$. The reason being the inertia of the lung tissue must be overcome during rapid and big volume changes. This explains why the acceleration term $\ddot{V}$ is added into the governing equation.

Some models include Compliance, $C$, Resistance of the first compartment, $R_1$ and Resistance of the second compartment, $R_2$, such as the theory developed by Otis et al [13], which states that uneven ventilation of the lungs is manifested by a decrease in $C_{dyn}$ and $R_{dyn}$ with increasing frequency due to the time-constant imbalance between parallel lung units. The equation below represents the model [13]:

$$C_{dyn} = \frac{\omega^2 (\tau_2 C_1 + \tau_1 C_2)^2 + (C_1 + C_2)^2}{\omega^2 (\tau_1^2 C_2 + \tau_2^2 C_1) + (C_1 + C_2)} \quad (3-9)$$

where frequency $\omega = 2\pi f$; $\tau_1 = R_1 C_1$ and $\tau_2 = R_2 C_2$.

If $\tau_1 = \tau_2$:

$$C_{dyn} = C_1 + C_2 \quad (3-10)$$

$$R_{dyn} = \frac{\omega^2 \tau_1 \tau_2 (\tau_2 C_1 + \tau_1 C_2) + (\tau_1 C_1 + \tau_2 C_2)}{\omega^2 (\tau_1^2 C_2 + \tau_2^2 C_1) + (C_1 + C_2)} \quad (3-11)$$

Similarly if $\tau_1 = \tau_2$:

$$R_{dyn} = \frac{R_1 R_2}{(R_1 + R_2)} \quad (3-12)$$
As can be seen above, $C_{\text{dyn}}$ and $R_{\text{dyn}}$ are independent of frequency unless $\tau_1$ and $\tau_2$ are unequal. Since $C_{\text{dyn}}$ can be measured under static condition ($f = 0$), it is a better assessment of frequency dependence for airway obstruction compared to $R_{\text{dyn}}$ which is limited to breathing frequencies. In emphysema, the site of obstruction to airflow appears to be in the peripheral airways.

### 3.7.3 The Bronchial Tree Model

The actual analysis of the airflow in the bronchial tree is very complex. The air travels through a network of continuously branching tubes of various lengths with diameter, cross-sectional area and direction changes at each branch.

Each of these tubes has flexible and collapsible walls and diameters, which vary with the regional variations in the transmural pressure difference. Most studies of bronchial airflow are based on the regularized dichotomy geometric model developed by Weibel [8]. This model states that each airway divides into two airways of smaller diameter as seen in Figure 3.23, with trachea divides into the two main bronchi which divides into eight.

There are 23 generations or branching between the trachea (generation zero) and the alveolar sacs (generation 23). Total cross-sectional area increases by factor of 5000 from trachea to alveolar sacs. Weibel [8] has developed empirical exponential relationship between generation number and average airway dimensions in terms of diameter and length. The main characteristic of this model is that all the airways of a generation act in parallel for airflow. Thus the total volume flow rate divided by the total cross-sectional area of one generation gives the average velocity in that generation. For example, in the n-th generation, the flow rate and average velocity in one airway are:

\[
V_N^* = \frac{4Q_N}{\pi D_N^2}
\]

(3-12)

where $V_N^*$ is the volume flow rate of the lung and $D_N$ is the diameter of the n-th generation. The maximum flow velocities and resistance occur in generations 2 - 4, where the area is the smallest. These being some of the longest airways also increase the pressure loss and flow resistance. Airways are generally classified as large or small airways [14], with a diameter of 2 - 3 nun (generation 6 - 7) being the division
point. In large airways, most of the flow resistance and pressure drop occur due to having less parallel airways [15]. Clinical tests measure the flow resistance of only the large airways, yet several small diseases affect the small airways [15].

![Regular airway branching model](image)

**Figure 3.23** Regular airway branching model [9].

As mentioned above, resistance due to Poiseuille flow (also known as laminar flow) changes very slowly, and yields the smallest possible pressure drops in the bronchial trees. For one airway,

\[ P_N = \frac{32\mu^2 L_N}{D_N^2} \]  \hspace{1cm} (3-14)

where \( \mu = \) gas viscosity; \( L = \) tube length; \( D = \) tube diameter. For the entire bronchial tree, the Poiseuille pressure loss (using equation (3.14)) between the trachea and alveoli is:

\[ P_N = V \left( \frac{128\mu}{\pi} \right) \sum_{N=1}^{23} \frac{L_N}{2^N D_N^4} \]  \hspace{1cm} (3-15)

However the above model is only for small airways where laminar flow is present and Reynolds number is below 900 [16]. If turbulent flow (\( Re \geq 900 \)) is present (in the largest bronchi), it contributes to the high resistance of these airways. The
Womersley number \( (\alpha) \) is a frequency parameter used to distinguished quasi-steady flows from oscillatory pulsatile flow. For oscillatory airflow in the bronchial tube, the Womersley number [17] can be used:

\[
\alpha = \left( \frac{D_N}{2} \right) \left( \frac{\omega \rho}{\mu} \right)^{\frac{1}{2}}
\]  

(3-16)

If the frequency, \( \alpha \) is \( \leq 1 \), the flow is quasi-steady; if \( \alpha \geq 1 \), the flow pulsates, for in-between the flow is transitional. Oscillatory flows have different boundary layer thickness and velocity profiles than steady flows. Womersley numbers have been calculated for bronchial trees at several breathing rates. The maximum value is \( \alpha = 5 \) in the trachea during exercise (40 breaths/min) [18]. The frequency has the same pattern as the Re number, it decreases down the bronchial tress and is always less than one beyond the 4th or 5th generation. The large airways' flow is transitions between steady and pulsatile, while the small airways have quasi-steady flow.

On large-scaled models of the bronchial tree, it is indicated that the direction changes produce eddy currents and distortion of the velocity profiles from the Poiseuille flow patterns. This increases the viscous energy losses and flow resistance. Pedley, et al. [30] have experimentally develop an index; \( Z_N \) for the Poiseuille equation to account for the direction and area changes for inflation only.

\[
Z_N = 0.33 \left( \frac{D_N^2 V_N P}{\mu L_N} \right)
\]  

(3-7)

or \( Z_N = 1.0 \), whichever is larger.  

(3-18)

The branching effects, when \( Z_N \geq 1 \), are significant in the first ten generations [13]. They extend further down the bronchial tree, but are negligent in small airways of diameter less than 1 mm. Along with the occurrence of Poiseuille flow near generation 10, there is a change of the means of oxygen transport from convection to diffusion.

The flexibility of the walls of the bronchi and bronchioles also plays an important role in flow resistance. All bronchi have alveolar wall tissue connected to the outside of their walls. The forces of these tissue act to distend the bronchi, especially during exhalation. Based on studies done on the pressure-volume behavior of bronchial segments [6, 19], the small airways have the same compliance as the alveolar tissue,
whereas the large airways are stiffer in comparison. This is because of the cylindrical shape of the bronchi, the forces of the alveolar wall tissue may not produce the same uniform tri-axial expansion that they do on the alveoli [20].

During lung inflation, the pleural and alveolar pressures are below tracheal and bronchial airway pressures. The airways are subjected to a positive transmural pressure difference, and are distended, which lowers airway resistance. With positive transmural pressure, the airways remain open and cylindrical. These trends are reversed for the case of lung deflation. The negative pressure difference decreases the tube diameter, increases resistance and tends to make the tube structure unstable, and thus collapsible. During deflation, air is trapped in the alveoli by collapsed airways, which produces huge compressive pressures.

3.7.4 Multi-Component Model of Lung

It is difficult to develop a general theoretical description, as there are some limitations:

(a) The flow in some regimes cannot be accurately described except empirically;
(b) The bronchial tree model describes only the average geometry;
(c) The variety of flow patterns cause mathematical complexity and that the tissues' mechanical stiffness, elasticity and the airflows are interrelated.

In multi-component model, (including our own model in this chapter), an important characteristic of the lung is that the parallel airways leading to all the alveoli are fluid mechanically nearly identical. Whichever path the air molecule takes to an alveolus, it will encounter the same resistance.

The model in Fig. 3-4 illustrates a set of balloons (alveoli) with separate tubes (airways), connected to one common tube (trachea) enclosed in a bellows (thorax). Each balloon has its own stiffness and each tube has its own resistance. Thus the governing equation:

$$\Delta P = \left( \frac{1}{C_i} + \frac{R_i}{V} \right) \quad (3-19)$$
Normal breathing can be represented as a small sinusoidal pressure ($\Delta P \sin(\omega t)$) or volume ($\Delta V \cos(\omega t)$) oscillation [21], so that:

$$\Delta P = P_0 + \Delta P \sin(\omega t) \quad (3-20)$$

$$V = V_0 + \Delta V \sin(\omega t) \quad (3-21)$$

where $\omega = 2\pi f$, $f =$ breathing frequency. The above representation will not work practically, as having the sine term alone is insufficient to accurately represent the clinical data parametrically. For that reason, we have added a cosine term in our model, so as to yield a more accurate and clinically representative lung volume response (as discussed later in the chapter).

The normal lung is represented by the special case of having all of the $C$ and $R$ values identical and all the balloons of equal size. Hence equation (3-19) reduces to, upon division of each term by $M$, lung mass:

$$\Delta P = \left( \frac{V}{MC_i} + \frac{RV_i}{M} \right) \quad (3-22)$$

and the lung can be modeled as equivalent one balloon with one airway. During sinusoidal or periodic oscillations, there is a phase lag between the pressure extrema (maxima or minima) and the volume extrema (as depicted in the figure below). The magnitude of the phase lag for each alveolus depends on the values of $R$ and $C$. At the

**Figure 3.24** Single component (a) and multi-component (b) models of the lung [W.R. Powell].
volume extrema, the tracheal airflow rate is zero; with equal values of \( C \) and \( R \), the flow rates in all airways are zero. When all values are the same, the phase lag for every alveolus is the same as in the case for a normal lung inflated in-vitro. In vivo, there is a small vertical variation in alveolar size, which causes small but detectable variations in phase lags [22]. The effect of differing phase lags can cause crossflow of air, to increase the flow resistive work and decrease the efficiency of breathing. However, the problem is insignificant in the in-vivo lungs, due to weight bearing stresses. The lung is designed to smoothen the process of gas exchange in millions of alveoli effortlessly, by ensuring minimum work is required for breathing through adjusting the compliance of the lung, as well as to provide equal transit time by appropriate tuning of the airways resistance during exercise. When the oxygen demand increases, the lung has an enormous reserve capacity available to cope with the increase oxygen demands of exertion. These factors work together to ensure that the lung obtains sufficient oxygen at minimal exertion and at vastly different rates required by different physical activity levels.
Figure 3.25 The flow rates in the total lung model, the upper compartment, and the lower compartment as a function of time.

3.8 Work of Breathing

For air to flow from the mouth into the alveoli, the tissues of the lungs and the thorax must be stretched by both muscular and ventilator forces. The greater the force applied, the greater the volume change in inspiration. These forces in the respiratory system can be measured in terms of pressure differences. The following relationship shows the work done during a breathing cycle, where it is represented as an area on the pressure-volume diagram:

\[ W = \int PdV \]  

(3-23)
Otis et al. [12] were the first to calculate the mechanical work done by a ventilator of a volume-controlled breath and a pressure-controlled breath, where there is no patient's effort. A volume control breath maintains a distinct flow wave shape: sinusoidal, constant or triangular decreasing waveform during the inspiratory phase of a cycle. On the other hand, a pressure control breath maintains a preset airway pressure level during the inspiratory phase of a cycle; the waveform has no regular shape and varies in-between breaths. They concluded that the area bounded by the relaxation pressure curve (see curve ADC in below) and the volume axis represents work done to overcome the elastic forces of the lung; $W_{elas}$. The area bounded by the relaxation pressure and the mouth pressure curve represents the work done to overcome the resistive forces of the respiratory system; $W_{res}$ with $W_{elas}$ and $W_{res}$ being both expressed in equation (3-26).

\[
W = \int_0^T \left( \frac{V}{C} - RV \right) dV = \int_0^T \left( \frac{V}{C} - RV \right) dV
\]
(3-24)

\[
W = \frac{1}{C} \int_0^T V \dot{V} dt + R \int_0^T \ddot{V} dt
\]
(3-25)

\[
W = \frac{1}{2C} \int_0^T \left( \frac{V^2}{dt} \right) dt + \int_0^T \ddot{V} dt
\]
(3-26)

Figure 3.26 Pressure-Volume curve of a volume control breath (without patient effort) [24].
In the above figure, the area bounded by the ventilator driving pressure and the volume axis represents the total work of breathing (by the ventilator):

\[ W_{vent} = \int_0^T (P_m(t) - P_{atm})dV \]  

(3-27)

According to Otis et al. who has reviewed the work of normal breathing, the elastic work and the work done to overcome lung elasticity decrease with decreasing tidal volumes and result in increased breathing rates. At large tidal volume, it exerts a non-linear elastic behavior (which we will discuss later), whereas the flow resistive work is independent of the volume rate as long as the minute volume is constant.

To calculate the work performed in a volume-controlled breath, Martini et al. [23] came up with a method, which involves comparing a volume-controlled breath with no patient effort with another volume-controlled breath for the same flow settings. Based on the identical flow waveforms generated, the difference in ventilator work in the two breaths provides the work performed by the patient as shown in Figure 3.26. For example, the ventilator performs the total work of breathing in the case of one breath while both the ventilator and the patient perform the work in the other breath. Then the difference in the ventilator work of the two breaths provides the patient's work in the second breath. However, there are drawbacks to this method:

(a) Measuring patient's work in pressure-controlled breaths and spontaneous breaths cannot be done, and the inspiratory flow waveform of both types of breaths has no regular shape and may vary between any two similar breaths.

(b) The patient's work can only be calculated for volume-controlled breaths. Every time the inspiratory volume changes or flow waveform changes, it has to be compared with different breaths with no patient's effort and identical flow waveform.

To overcome the drawbacks, a mathematical measurement is developed. Let \( P_m^*(t) \) be the mouth pressure of a breath which has no patient's involvement, and \( P_m(t) \) be the mouth pressure of another breath of identical flow waveform. The patient's work can be written as the difference in ventilator work of the two breaths [24]:

\[ W = \int_0^T P_m^*(t)\dot{V}(t)dt - \int_0^T P_m(t)\dot{V}(t)dt \]  

(3-28)
Since $\dot{V}$ is identical in both breaths:

$$P_{\text{mus}}^* = P_m(t) + P_{\text{mus}}$$  \hspace{1cm} (3-29)

where $P_{\text{mus}}$ is the reduction in pressure created by the muscle respiration.

$$W = \int_0^T P_{\text{mus}}(t) dt$$  \hspace{1cm} (3-30)

Using the same equation as equation (3-27), which provides the ventilator's work component, the above equation represents the volume integral of the respiratory driving pressure signal, and provides the patient's component of work. $P_{\text{mus}}(t)$ can then calculated as:

$$P_{\text{mus}}(t) = R_{av} \dot{V} + \frac{1}{C} \int_0^T \dot{V}(t) dt - P_m(t) + P_{\text{atm}}$$  \hspace{1cm} (3-31)

Where $P_m(t) - P_{\text{atm}} + P_{\text{mus}}(t) = R_{av} \dot{V} + \frac{1}{C} \int_0^T \dot{V}(t) dt$  \hspace{1cm} (3-32)

and $R_{av}$ is airway resistance.

Similarly for the work done in our work, we have validated the concept of Otis [12], that the work done during a respiratory cycle, is given by the area of the loop generated by plotting lung volume ($V$) against net driving pressure ($P$). The larger the phase shift between the volume-pressure curve, the larger the area, and hence higher the WOB. The area can be obtained graphically. At the same time, we can determine the WOB by integration of the derived $V(P)$ expression. All of this will be discussed later.
3.9 Model of Diseased Lung

3.9.1 Large Airway Problems

The diameters of the large bronchi produce significant changes in the pulmonary airflow resistance. This problem characterizes bronchitis and asthma. Bronchitis is an inflammation of the bronchial tubes, while asthma is a spasmodic contraction of the tube diameters. During an asthma attack, the muscle contraction can reduce bronchial diameters and increase resistance by a factor of seven. The diameter reductions cause increases in velocity, flow-resistance and pressure-drop between the trachea and alveoli. Should the body need to maintain the air volume flow rate as the airway diameter decreases, the air velocity must increase. Therefore, this is to be accompanied by increased pressure drops and an enlargement of the turbulent flow regions. To increase the pressure drop, it needs large mechanical work (large chest wall motions) as the pleural and alveolar pressures need to be further below atmospheric. An alternative to maintaining the flow-rates is maintaining the pressure-drops as the bronchi constrict. This will reduce the air velocities, flow rates and tidal volumes and increase the breathing frequencies. To describe this mathematically, two breathing patterns having different frequencies ($\omega_2 > \omega_1$) and tidal volumes ($TV_2 < TV_1$) with equally large airway losses are compared. Modeling breathing by sinusoidal volume changes [25],

$$\Delta V = \frac{1}{2} TV \sin \omega t$$  \hspace{1cm} (3-33)

The pressure drop depends on volume flow rate:

$$\Delta V = \frac{1}{2} \omega TV \cos \omega t$$ \hspace{1cm} (3-34)

Thus, for equal pressure drops:

$$\omega_1 TV_1 = \omega_2 TV_2$$ \hspace{1cm} (3-35)

The resting minute volume ($RMV$) depends on frequency and tidal volume minus the unchanging dead volume ($DV$),

$$RMV = \omega (TV - DV)$$ \hspace{1cm} (3-36)
Therefore:

\[ RMV_1 - RMV_2 = \omega_1 (TV_1 - DV) - \omega_2 (TV_2 - DV) = (\omega_2 - \omega_1) DV \]  \hspace{1cm} (3-37)

Since \( \omega_2 > \omega_1 \); \( TV_2 < TV_1 \); \( RMV_2 < RMV_1 \), this illustrates rapid shallow breathing.

Actual responses involve changes in both tidal volume and breathing rate. The sound of wheezing in asthma and bronchitis is an indication of the increase in flow rate and therefore breathing work.

### 3.9.2 Alveolar Wall Problems

In this problem, the alveolar wall and hence the lung compliance is affected; an emphysema diseased lung is one example. It has large holes caused by destroyed alveolar walls. This reduces gas exchange by reducing the surface area available for exchange. It also increases the tissue stresses in the remaining walls. The expanding pressure \( P \) is balanced by the restraining wall tension \( T \); as the number of walls decreases \( t \), the tension in each remaining wall must increase in order to maintain the force equilibrium [10]. The increased tensions mean increased tissue strains and lung volumes, resulting in lower compliance and increased mechanical work of breathing [24, 25]:

\[ P_{alv} = \frac{(\gamma + T)}{t} \]  \hspace{1cm} (3-38)

\[ P_{alv}(t) = \frac{1}{C} \int_0^t \dot{V}(t) dt + P_{amb} \]  \hspace{1cm} (3-39)

\[ W = \frac{1}{C} \int_0^t \dot{V} \dot{V} dt \]  \hspace{1cm} (3-40)

where \( \gamma \) = surface tension in the liquid lining of the bubble.

\[ \sigma = \frac{T}{t} \]  \hspace{1cm} (3-41)
The bronchial tree can also be affected, as the tissue stresses on the outside of the tube walls deviate from the uniform distribution found in normal lungs. Unsupported regions are prone to instability and airway collapse. The enlarged alveoli, lung inhomogeneity and airway instability cause increased lung volumes and decreased compliance found in emphysema, thereby destroying respiratory function by destroying lung structure.

Pulmonary fibrosis diseases produce similar dysfunction of stiffening the alveolar wall tissue. If the lung compliance is reduced, the pressure changes needed to maintain tidal volume increase, and hence the work of breathing increases. Even though fibrosis and emphysema produce similar functional problems, they can be distinguished by chest x-rays; this is because fibrosis increases tissue density, while emphysema decreases it.

3.9.3 Small Airway Obstruction

The mechanical manifestations of changes in the small airways although are not as significant as those due to changes in large airway resistance or compliance. However, its links to air pollution and emphysema make small airway obstruction a major health concern. One identified cause of small airway obstruction is exposure to low levels of nitrogen oxides, which is a major component of automobile exhausts. Long-term exposures to low concentrations irritate the cells lining and small airways. Small airways obstruction is characterized by localized and large reductions in the diameters of the small airways, hence causing non-uniformity of airflow. Its clinical name, chronic-obstructive-respiratory-disease (CORD) creates inhomogeneity in the lung's airflow patterns and inspired gas distribution, along with detrimental changes in the phase lags between pressure and flow and in the mechanical work of breathing.

The effects of the obstruction are larger during expiration. The alveolar volume increases as the gas is trapped inside; however, its compliance decreases and its contribution to gas exchange is reduced:

\[
\Delta P = \frac{V}{C_i}
\]  

(3-42)

The remaining alveoli with normal airways must undergo larger tidal volumes to maintain the minute volume. The over-extended alveolar walls sometimes begin to disintegrate, and emphysema results. There are two major effects of obstruction and
increased flow resistance: First, the lung compliance ceases to be independent of the breathing frequency, where viscous pressure losses occur in the lung. Thus, the compliance of a lung with obstructed small airways will decrease with the frequency. The second effect is a change in the phase lags [26] between pressure and flow, where the phase lags are larger for lungs with small airway obstruction. This means the time delay between the pressure-maxima and the volume-maxima is larger for these lungs. Figure 3.27 shows why the compliance and phase-lags change when one set of airway is obstructed.

**Figure 3.27** Multi component model of lung reduced to two components: one with normal airways and one with obstructed airways. The difference in airway diameters causes the component's volume changes to be non-synchronous [W. R. Powell].

The analysis of Otis et al. [12] uses pressure as a sinusoidal driving function with the volume lagging behind:

\[ \Delta P = P_0 + \Delta P \sin(\omega t) \]  \hspace{1cm} (3-43)

\[ V_i = V_0 + \Delta V_i \sin(\omega t + \phi) \]  \hspace{1cm} (3-44)
Combining the above two equations with equations (3-19), (3-43) and (3-44), we obtain:

\[
P_0 + \Delta P \sin(\omega t) = \left( \frac{1}{C_i} (V_0 + \Delta V_i \sin(\omega t + \phi_i)) + R_i \Delta V_i \omega \cos(\omega t + \phi_i) \right)
\]  

(3-45)

Then using \( V = V_1 + V_2 \), the values of \( C, R \) and \( \phi \) are determined:

\[
R = \frac{\omega^2 R_1 R_2 (R_1 + R_2)(C_1 C_2)^2 + R_1 C_1^2 + R_2 C_2^2}{\omega (R_1 + R_2)^2 (C_1 C_2)^2 + (C_1 + C_2)^2}
\]  

(3-46)

\[
C = \frac{\omega^2 (R_1 + R_2)^2 (C_1 C_2)^2 + R_1 C_1^2 + R_2 C_2^2 + (C_1 + C_2)^2}{\omega^2 (C_1 C_2)(R_1^2 C_1 + R_2^2 C_2)^2 + (C_1 + C_2)}
\]  

(3-47)

\[
\phi = \tan^{-1}\left( \frac{1}{\omega R C} \right)
\]  

(3-48)

All the above three parameters above depend on \( \omega \), the breathing frequency. This is the case for obstructed lung. If the compliances and resistances of the two compartments are made equal, then the equations for \( R \) and \( C \) simplify to

\[
C = 2C_1 = 2C_2; \quad R = \frac{R_1}{2} = \frac{R_2}{2}
\]  

(3-49)

Figure 3.28 Shows the behavior of this model, using compliance and resistance values against frequency. For the obstructed lung, \( R_2 \) is twice as large as \( R_1 \). The effective compliance and resistance both decrease with increasing frequency. But at all frequencies, the obstructed model has more resistance and less compliance than the normal one with the phase-lag changing approximately 8° from the normal to the obstructed model [26].
One major weakness of this two-compartment model for small airway [26] obstruction is its simplified treatment of airflow, whereas a more detailed model uses a more realistic description of flow-resistance and concentrates all the obstruction in the respiratory bronchioles. Another weakness is that it assumes independence of the two compartmental model. However, in a real lung, a single tissue wall may separate alveoli with obstructed and normal airways. For our proposed two-compartmental model, we have assumed an independent relationship between the two compartments, otherwise it will greatly complicates our model analysis. When we talk about a non-independent relationship, the model behavior depends on the amount of diameter reduction, the percent of the airways involved, as well as the size of the obstructed alveoli. These are minute details that may not produce significant insight into the behavior of the lungs.

3.10 Ventilation Distribution Model with Non-linear Components

Shykoff et al. [27] presented a model, shown in Figure 3-9 that differed from many other respiratory models by incorporating non-linearities into its respiratory components. The intention of the model is to determine what difference in gas distribution within the lung could be expected from variation of pleural pressure in different parts of the lung. The unequal time constants in different portions of the lung
are attributed to unequal lung filling. However, some experimental data suggests that
the variation in lung filling could be caused by the uneven distribution of pleural
pressure between the upper and lower chest. To test the possibility of a connection
between pleural pressure differences and lung filling, Shykoff et al proposed a two-
compartment lung model. The upper and lower compartments were treated in a
parallel arrangement, and each was considered to be represented by a resistance and
compliance in series. Each was exposed to a different variable pleural pressure. The
model equations for the common pathway are:

\[ P_m - P_b = R_c \dot{V} \]  
\[ \text{Where} \]
\[ P_m = \text{pressure at the entrance to the common airway, N/m}^2 \]
\[ P_b = \text{pressure at exit from common airway, N/m}^2 \]
\[ R_c = \text{common airway resistance, N.sec/m}^5 \]
\[ \dot{V} = \text{volumetric flow rate, m}^3/\text{s} \]

and flow rate to compartment:

\[ \dot{V}_i = \dot{V}_1 + \dot{V}_2 \]  
\[ \text{For each compartment:} \]

\[ P_b - P_i = R_i \dot{V}_i \]  
\[ dV_i = C_i d \left( P_i - P_{pli} \right) \]

\[ \text{Where} \]
\[ V_i = \text{volume of compartment } i, \text{ m}^3 \]
\[ P_{pli} = \text{pleural pressure on compartment } i, \text{ N/m}^2 \]
\[ C_i = \text{compliance of compartment } i, \text{ m}^5/\text{N} \]

The equation for compliance is:

\[ C_i = \frac{\left( V_{\text{max}} - V \right)^2 \left( V_{\text{min}} - V \right)^2}{\lambda_1 \left( V_{\text{min}} - V \right)^2 + \lambda_2 \left( V_{\text{max}} - V \right)^2} \times \frac{VC}{100} \]  

\[ \text{(3-54)} \]
where

\[ V_{\text{max}}, V_{\text{min}} = \text{constants, dimensionless} \]
\[ \lambda_1, \lambda_2 = \text{constant, N/m}^2 \]
\[ \text{VC} = \text{vital capacity, m}^3 \]
\[ \text{RV} = \text{residual volume, m}^3 \]

The resistance is given by:

\[
R = \frac{k_1 + k_2 V}{k_3 + k_4 V} \tag{3-55}
\]

where

\[ R = \text{resistance, N.sec/m}^5 \]
\[ k_1 = \text{constant, N.sec/m}^5 \]
\[ k_2 = \text{constant, N.sec/m}^8 \]
\[ k_3 = \text{constant, dimensionless} \]
\[ k_4 = \text{constant, m}^3 \]

Airflow into these compartments was driven by sinusoidal, square, or triangular waveforms, superimposed on a static pressure difference. The amplitudes of the pressures were independently varied on the two compartments: a range of static pressures and frequencies was used, and a phase-lag between compartments was introduced for sinusoidal and square wave pleural pressure variations. In our two-compartmental model, the amplitudes of the pressures vary independently as well.

It was found from this model that at low pleural pressure amplitudes and frequencies, there was no difference between results using constant compliance and resistance values and those using non-linear values. On the other hand, at higher frequencies the difference becomes greater at lower amplitudes and vice versa. Compliance non-linearities are more important at low flow rates, but resistance non-linearities are increasingly more important at higher flow rates.

The ratio of volumes in compartments 1 and 2 does not change significantly for sinusoidal, square, or triangular pleural pressure waveform. Thus Shykoff et al. conclude that the waveform of the pleural pressure swing has no effect on the distribution of tidal volumes.
Although this model is simple in structure with a limited scope, it succeeds in highlighting the effects of non-linearities. Figure 3.30 shows the instantaneous flow rates as a function of time in the total lung volume, the upper compartment, and the lower compartment. It can be observed that the lower compartment fills first, followed by emptying into the upper compartment.

Figure 3.29 Two-compartmental model of the lung. Resistance and compliances are considered to be non-linear [Skykoff et. al].
3.11 Characterization of the Branching Structure of the Lung

This model describes an asymmetric tree model with a predicted pressure-volume relationship connected to the distribution $\Pi (n)$ of the generation number $(n)$ of the trees terminal segments [28]. The purpose of this model is to analyze the problem of fluid flow (liquid or gas) in a bifurcating structure containing random blockages, from the information of the asymmetric structure of the lung obtained through macroscopic (noninvasive) pressure-volume measurements. This relation explores the branching structure of the lung, by analyzing experimental pressure-volume data from dog lungs. The $\Pi (n)$ extracted from the data using the model agrees well with experimental data on the branching structure.

The problem of fluid flow through bifurcating structures is of considerable interest [28]. So far, the case when the structure contains random blockages that can be
removed by the fluid pressure has been studied only for the simple case of symmetric branching, whereas the real lung is asymmetrical [29]. Such cases are often encountered during fluid flow in an organ system, such as for circulation of blood or flow of air in the lung where the pathways can be blocked, leading to potentially lethal situations [30]. Here, the pressure-volume curve of the lung is modeled to obtain a correlation between lung inflation and its branching structure. Next, fitting the model to experimental pressure-volume ($P-V$) data provides information about a key microscopic property of the airway tree, namely, the distribution of the generation numbers of the tree's terminal segments. Since experiments measuring the $P-V$ curves of an inflating lung are noninvasive, this method provides a way to study "microscopic" branching structures from "macroscopic" $P-V$ data without the use of invasive techniques.

During expiration, peripheral airways in a diseased lung tend to collapse, thereby blocking the flow of air, if the surface tension of the lining fluid is abnormally high [31]. The lung is assumed to be empty of air with all the airways blocked at the beginning of the inspiratory cycle. These blockages can be removed during inflation if the pressure ($P$) reaches the critical opening threshold of the segment [32]; it then increases, until all closed segments open. Since the airways are arranged in a treelike branching structure, the opening of one segment is not possible until all segments connecting it to the root of the tree are opened. If the threshold pressure of a daughter segment is smaller than that of its parent, the daughter opens simultaneously with the parent. This mechanism also applies to subsequent generations, leading to avalanches of opening of airways [33].

The volume of inhaled air during inspiration in a symmetrical branching follows a simple power law, and the numerical value of the exponent was shown to be equal to the generation number ($n_o$) of the terminal segments [34]:

$$V \propto P^{n_o}$$

(3-56)

The $P-V$ curves of the two isolated dog lung lobes (A&B) are determined experimentally [28]. The lobes are thoroughly inflated through the main bronchus. Over 90% of the air volume recruited into a lung is contained in the terminal alveoli (air sacs) [35-39]. Assuming that all alveoli are identical and inelastic, the volume of air at any pressure is proportional to the number of ventilated alveoli.
Next we discuss the model to account for the asymmetric branching of the airway tree. Herein, each air sac is labeled with an index \( k \) going from 1 to \( N \) (the total number of air sacs in the lung). The state of being open or closed for each air sac \( k \) at pressure \( P \) is then described by a variable, \( \sigma_k \), which is normalized to enable the sum of it to be unity when all air sacs are open) that represents \( l/N \) (if the air sac is open) or 0 (if it is closed). The depth for air sac, \( n_k \), is the number of generations between the air sac and the root of the tree as well as the blockages. The variable \( \sigma_k \) is dependent upon the threshold pressures of all the segments along this path. Each segment along the path is denoted by a pair of indices \( (j, k) \), where (i) the index \( k \) identifies the air sac \( k \) it connects, whereas (ii) \( j \) describes the number of generations separating the segment from the air sac \( (j = 1, ..., n_k) \). A segment \( (j, k) \) is open only if its threshold pressure, \( T_{jk} \), is less than the pressure \( P \). The threshold pressure of all segments, independent of generation, is drawn from a uniform distribution between 0 and 1 \([29]\), with a threshold pressure of 1 being the pressure at the inflection point. This amounts to saying that all air sacs are open when \( P \) reaches the inflection point. Since the air sac \( k \) is open only if all segments \( j \) are open, \( \sigma_k \) is given by:

\[
\sigma_k = \frac{1}{N} \prod_{j=1}^{n_k} \Theta(P - T_{jk})
\]

(3-57)

where \( \Theta(x) \) is the unit step function.

The volume, \( V(P) \), contained in the lung at pressure, \( P \) is thus given by the averaged count of all the open air sacs,

\[
V(P) = \sum_{k=1}^{N} \sigma_k
\]

(3-58)

Combining equations (3-57) and (3-58), we obtained:

\[
V(P) = \frac{1}{N} \prod_{j=1}^{n_k} \int_{0}^{1} \Theta(P - T_{jk})dT_{jk} = \frac{P_{n_k}}{N}
\]

(3-59)

Equation (3-59) expresses \( \sigma_k \) in terms of the number of segments along the path from air sac \( k \) to the root of the tree. Next using equations (3-58) and (3-59), we obtain an average volume as a function of inspiratory pressure:
\[ V(P) = \sum_{k=1}^{N} \frac{P_{n_k}}{N} = \sum_{n} \Pi(n) P^n \] (3-60)

where \( \Pi(n) \) is the distribution of generation number of the terminal segments.

The expression equation (3-60) for the volume is a polynomial containing different powers of \( P \), unlike the result for a symmetric tree in equation (3-56) where a unique exponent corresponds to the single depth \( n_o \). The degree of asymmetry is thus manifested in the width of the distribution \( \Pi(n) \). Equation (3-60) incorporates the effects of the tree structure, as characterized by the depth distribution \( \Pi(n) \) and the dynamics characterized by \( P^n \). The experimental data is then fitted with polynomials of order 48, which is the known maximum depth in a dog lung [35]. It is found that the distributions obtained have two distinct regions: (i) a narrow peak for \( n < 5 \), which corresponds to the P-V curve at small \( P \) when very few air sacs are ventilated, and (ii) a broad distribution for \( 15 < n < 40 \), which has two main peaks in \( 22 < n < 30 \).

To conclude, when applied to the \( P-V \) curve of the lung, this model is able to estimate the terminal structure of the airway tree from noninvasive measurement made at the top of the tree.

Conventionally, the \( P-V \) curve represents a measurement of the elastic (compliance) properties of the lung tissue. This model take advantage of the fact that fluid blockages have a profound influence on the characteristics of the \( P-V \) curve, which allows us a direct representation of the lung structure from data. This approach can be useful to other development work done in asymmetrically branched biological and physical systems.
3.12 Author’s work Lung Ventilation Model [3]

We have developed a lung ventilation model by modeling the lung volume response
to mouth minus pleural driving pressure (by means of first and second order
differential equations) in terms of resistance-to-airflow ($R$) and the lung compliance
($C$). The lung volume solution of the differential equation is matched with the clinical
volume data, to evaluate the parameters, $R$ and $C$. These parameters values can help
us to distinguish obstructive lung and lung with stiffened parenchyma from the
normal lung, and hence diagnose lung diseases such as asthma and emphysema. We
have also formulated a nonlinear compliance lung model, and demonstrated deceased
lung compliance with filling volume. We then formulated a non-dimensional lung-
ventilatory index ($VTI$), incorporating the parameters $R$ and $C$ as well as the lung
breathing rate. When the $VTI$ is evaluated for various lung diseases, it will
conveniently enable us to diagnose lung diseases in terms of just one $VTI$ number.
Finally, we have shown how to model a two-lobe lung, and differentiate between
normal and diseased lobes.

3.12.1 Role of Lung Ventilation

Lung ventilation constitutes inhalation of appropriate air volume under driving
pressure (=mouth pressure-pleural pressure), so as to: (i) provide adequate alveolar $O_2$
amount at appropriate partial pressure, (ii) oxygenate the pulmonary blood, and (iii)
thereby provide adequate metabolic oxygen to the cells. Hence, ventilatory function
and performance assessment entails determining how much air volume is provided to
the alveoli, to make available adequate alveolar oxygen for blood oxygenation and
cellular respiration.

Based on the below figure 1, we get:  
(i) $(P_a - P_p) - P_{el} = 0$
(ii) $P_{el} = (2a h) / R r = 2 T / r = V/C + P_{el0}$
(iii) $(P_m - P_o) = R(dV/dt)$
(iv) $P_L = P_m - P_p$
(v) $R(dV/dt) + VIC = P_L - P_{el0}$
(lung elastic recoil pressure at end-expiration)
3.12.2 Lung Ventilation Performance using a Linear First-order Model

We first analyze Lung Ventilation function by means of a very simple model represented by a first-order differential equation ($D_{v_h}$) in lung-volume ($V$) dynamics in response to the driving pressure ($P_d = $ atmospheric pressure – pleural pressure), as displayed in Figure 3.31. The clinical pressure-volume data is in Figure 3.32.

Figure 3.31 Alveolar model.

Figure 3.32 Lung ventilatory model and lung-volume & pleural-pressure data. Curve 1 on the curve represents $P_{el}$, the pressure required to overcome lung elastance (=V/C). Curve 2 represents $P_p$, the summation of $P_{el}$ and $P_a$. The pressure $P_n(t)$ in equation 1a equals $P_p$ minus $P_{el}$ at end-expirartion.
The model governing equation (shown derived in Figure 3.31) \cite{1,2} is as follows:

\[ RV + \frac{V}{C} = P_L(t) - P\ell_0 = P_N(t) \]  

(1-a)

wherein:

(i) the values of pressure are obtained from the given \(P_L (= P_m - P_p)\) data

(ii) the parameters of this Governing Eq. are lung compliance \((C)\) and airflow-resistance \((R)\); in the equation both \(R\ & C\) are instantaneous values

(iii) \(V = V(t) - V_0\) (the lung volume at the end-expiration

(iv) \(P\ell_0\) is the lung elastic-recoil pressure at the end of expiration, and

\[ P\ell_0 = P_el - \frac{V}{C} \]  

(1-b)

At end-expiration when \(\omega t = \omega T, \ P_L = P\ell_0=P_N(t)\), which is represented by

\[ P_N(t) = \sum_{i=1}^{3} P_i \sin(\omega_i t + c_i) \]

and the governing equation (1) becomes:

\[ RV + \frac{V}{C} = P_N(t) = \sum_{i=1}^{3} P_i \sin(\omega_i t + c_i) \]  

(2-a)

where the right-hand side represents the net driving pressure minus pleural pressure. \(P_N = (P_m - P_p) - P\ell_0\). This \(P_N\) is in fact the driving pressure \((P_m - P_p)\) normalized with respect to its value at end-expiration. Equation (2-a) can be rewritten as follows:

\[ \frac{V}{RC} + \frac{V}{C} = \frac{1}{R} \sum_{i=1}^{3} P_i \sin(\omega_i t + c_i) \]  

(2-b)

wherein the \(P(t)\) clinical data (displayed in Figure 3.32) is assumed to be represented by:

\[ P(t) = \sum_{i=1}^{3} P_i \sin(\omega_i t + c_i) \]  

(3)

\[ P_1 = 1.581 \text{ cm H}_2\text{O}, \quad P_2 = -5.534 \text{ cm H}_2\text{O}, \quad P_3 = 0.5523 \text{ cm H}_2\text{O} \]

\[ \omega_1 = 1.214 \text{ rad/s}, \quad \omega_2 = 0.001414 \text{ rad/s}, \quad \omega_3 = 2.401 \text{ rad/s} \]

\[ c_1 = -0.3132 \text{ rad}, \quad c_2 = 3.297 \text{ rad}, \quad c_3 = -2.381 \text{ rad} \]
The pressure curve (in Figure 3.33) represented by the above equation (3) closely matches the pressure data of Figure 3.32. If, in equation (1), we designate $R_a$ and $C_a$ as the average values ($R$ & $C$) for the ventilatory cycle, then the solution of equation (1) is given by:

$$V(t) = \sum_{i=1}^{3} \frac{PC_a \left[ \sin(\omega t + c_i) - b_i R_a C_a \cos(\omega t + c_i) \right]}{(1 + \omega_i^2 (R_a C_a)^2)} - He^{-\frac{t}{R_a C_a}}$$  \hspace{1cm} (4)

wherein the term $(R_a C_a)$ is denoted by $\tau_a$. We need to have $V = 0$ at $t = 0$. Hence, putting $V$ at $t = 0 = 0$, gives us:

$$H = \sum_{i=1}^{3} \frac{PC_a \left[ \sin(\omega t + c_i) - b_i R_a C_a \cos(\omega t + c_i) \right]}{(1 + \omega_i^2 (R_a C_a)^2)}$$  \hspace{1cm} (5)

Then from equations (4) and (5), the overall expressions for $V(t)$ becomes

$$V(t) = \sum_{i=1}^{3} \frac{PC_a \left[ \sin(\omega t + c_i) - b_i R_a C_a \cos(\omega t + c_i) \right]}{(1 + \omega_i^2 (R_a C_a)^2)} - \frac{H}{\tau_a}$$  \hspace{1cm} (6)

We also want that $dV / dt = 0$ at $t = 0$, implying no air-flow at the start of inspiration. So then by differentiating (6), we get:

$$\dot{V} = \sum_{i=1}^{3} \frac{PC_a \left[ \omega_i \cos(\omega t + c_i) + \omega_i^2 \tau_a \sin(\omega t + c_i) \right]}{(1 + \omega_i^2 \tau_a^2)} \left[ 1 - e^{-\frac{t}{\tau_a}} \right] - \frac{\dot{H}}{\tau_a}$$  \hspace{1cm} (7)

From (7), we get $\dot{V} \neq 0$ at $t = 0$, thereby also satisfying this initial condition.

Now, by matching the above $V(t)$ expression (6) with the given $V(t)$ data in Figure 3.27, and carrying out parameter-identification, we can determine the invivo values of $R_a$ and $C_a$, to be

$$C_a = 0.2132 \text{ (cmH}_2\text{O)}^{-1} \quad R_a = 2.275 \text{ cmH}_2\text{Osl}^{-1}$$

The computed $V(t)$ curve, represented by equation (6) for the above values of $C_a$ and $R_a$, is shown in Figure 3.37. We can however analytically evaluate $R_a$ and $C_a$ by
satisfying some conditions. For this purpose, we first note that \( V \) is maximum (=Tidal Volume, TV) at about \( t=t_V = 2.02s \). At \( t = t_V \), the exponential term \( e^{-\frac{t}{\tau_a}} \) in (6) becomes of the order of \( e^{-10} \), and hence negligible. Then by putting \( \dot{V}(t = 2.02) = 0 \) in (7), without the exponential term we obtain:

\[
\left. V \right|_{t=2.02} = 3 \sum_{i=1}^{3} P_i C_a \left[ \cos(\omega_i t + c_i) + \frac{\omega_i^2 \tau_a^2}{(1 + \omega_i^2 \tau_a^2)} \sin(\omega_i t + c_i) \right] = 0
\]  

(8)

in which the values of \( P_i, \omega_i, \) and \( c_i \) are given by equation (3). Then by solving equation (8), we get \( \tau_a = 0.522s \). We can also put \( \dot{V} = 0 \) at \( t \approx 1.81/2.87s \) and obtain a similar value for \( \tau \).

Then, we also note that at \( t_v = 2.02s \) (at which \( dV/dt = 0 \)) and \( V = 0.55l \). Hence upon substituting into equation (6), and neglecting the exponential term, we get the following algebraic equation:

\[
\left. V(t) \right|_{t=2.02} = 3 \sum_{i=1}^{3} P_i C_a \left[ \cos(\omega_i t + c_i) - \frac{\omega_i^2 \tau_a^2}{(1 + \omega_i^2 \tau_a^2)} \sin(\omega_i t + c_i) \right] = 2.55 C_a
\]  

(9)

By employing the values of \( P_i, \omega_i \) and \( c_i \) from equation (3). Now since \( V(t = 2.02s) = 0.55l \), we get

\[
2.55 C_a = 0.55
\]

\[
C_a = 0.22/(cmH_2O)^{-1}
\]  

(10)

We can substitute, therein, the values of \( P_1 \) & \( P_2 \) from (3), and obtain the value of \( C_a \) as: \( C_a = 0.22/(cmH_2O)^{-1} \). Since we have computed \( \tau_a = 0.485s \), therefore \( R_a = 2.275 \) \( (cmH_2O)s^{-1} \). These are the average values of resistance-to-airflow and lung compliance during the ventilatory cycle shown in Figure 3.27.

Since Lung disease will influence the values of \( R \) and \( C \), these parameters can be employed to diagnose lung diseases. For instance in the case of emphysema, the destruction of lung tissue between the alveoli produces a more compliant lung, and hence results in a larger value of \( C \). In asthma, there is increased airway resistance \( (R) \) due to contraction of the smooth muscle around the airways. In fibrosis of the lung, the membranes between the alveoli thicken and hence lung compliance \( (C) \) decreases.
Thus by determining the normal and diseased ranges of the parameters $R$ and $C$, we can employ this simple Lung-ventilation model for differential diagnosis.

### 3.13 Ventilatory Index

Let us, however formulate just one non-dimensional number to serve as a ventilatory performance index $VTI_1$ (to characterize ventilatory function), as:

$$VTI_1 = \left[ (R_a C_a) (\text{Ventilatory rate in s}^{-1}) 60 \right]^2 = \tau_a^2 (BR)^2 60^2 \tag{11}$$

where $BR$ is the breathing rate.

Now, let us obtain its order-of-magnitude by adopting representative values of $R_a$ and $C_a$ in normal and disease states. Let us take the above computed values of $R_a = 2.275 \text{ (cm H}_2\text{O)s}^{-1}$ and $C_a = 0.2132 \text{ (cm H}_2\text{O)}^{-1}$ and $BR = 12\text{m}^{-1}$ or $0.2\text{s}^{-1}$, computed for the data of figure 2 and equation (3). Then, in a supposed normal situation, the value of $VTI_1$ is of the order of 33.88. In the case of obstructive lung disease, (with increased $R_a$), let us take $R_a = 5\text{cm H}_2\text{Os} \text{l}^{-1}$, $C_a = 0.12l \text{(cm H}_2\text{O)}^{-1}$ and $BR = 0.3\text{s}^{-1}$; then we get $VTI_1 = 116.6$. For the case of emphysema (with enhanced $C_a$), let us take $R_a = 2.0\text{cm H}_2\text{Os} \text{l}^{-1}$, $C_a = 0.5 l\text{(cm H}_2\text{O)}^{-1}$ and $BR = 0.2\text{s}^{-1}$; then we obtain $VTI_1 = 144$. In the case of lung fibrosis (with decreased $C_a$), we take $R_a = 2.0\text{cm H}_2\text{Os} \text{l}^{-1}$, $C_a = 0.08 L\text{(cm H}_2\text{O)}^{-1}$ and $BR = 0.2\text{s}^{-1}$; then we obtain $VTI_1 = 3.7$. We can, hence summarize that $VTI_1$ would be in the range of 2-5 in the case of fibrotic lung disease, 5-50 in normal persons, 50-150 in the case of obstructive lung disease and 150-200 for the case of emphysema. This would of course be needed to be verified by analyzing a big patient population.

Now, all of this analysis requites pleural pressure data, for which the patient has to be intubated. If now we evaluate the patient in an outpatient clinic, in which we can only monitor lung volume and not the pleural pressure, then can we develop a non-invasively obtainable Ventilatory index?

### 3.13.1 Noninvasively determinable Ventilatory index:

In order to formulate a non-invasively determinable Ventilatory index from (1), we need to recognize that in this case $P_N(t)$ (and hence $P_a$, $\omega$ and $C_i$) will be unknowns need to redesignate the model parameters to be and indicate their identification.
procedure. So we make use of the following features from the volume-time data to facilitate evaluation of the following three parameters: \((P_1, C_a)\), \(\omega_i\), and \(c_i\) and \(\tau_a\).

At \(t = t_v = 2.02s\), \(V\) is max and \(dV/dt = 0\); hence we rewrite (9) as:

\[
\frac{d}{dt} V = 3 \sum_{i=1}^{\infty} \left[ \frac{(P_C a) \left[ -\sin(\omega_i t_m + c_i) \omega_i^2 + \omega_i^2 \tau_a^2 \cos(\omega_i t_m + c_i) \right]}{(1 + \omega_i^2 \tau_a^2)} \right] 1 - e^{-\frac{t}{\tau_a}}
\]

Also, at \(t = t_m = 1.82/2.87s\), \(V = 0\). Hence by differentiating equation (7), without the exponential term, we obtain:

\[
\frac{d}{dt} V(t) = \sum_{i=1}^{\infty} \left[ \frac{(P_C a) \left[ -\sin(\omega_i t_m + c_i) \omega_i^2 + \omega_i^2 \tau_a^2 \cos(\omega_i t_m + c_i) \right]}{(1 + \omega_i^2 \tau_a^2)} \right] 1 - e^{-\frac{t}{\tau_a}}
\]

Then, at \(t=1s\), \(V_1 = 2.02\). From equation (6), without the exponential term, this condition yields:

\[
V_1 = \sum_{i=1}^{\infty} \left[ \frac{(P_C a) \left[ -\sin(\omega_i t_m + c_i) \omega_i^2 + \omega_i^2 \tau_a^2 \cos(\omega_i t_m + c_i) \right]}{(1 + \omega_i^2 \tau_a^2)} \right] 1 - e^{-\frac{t}{\tau_a}} = 2.02
\]

In addition, we can utilize data information concerning \(V_j\) at \(t_j\) \((j = 1 to 8)\), and put down:

\[
V_j = \sum_{i=1}^{\infty} \left[ \frac{(P_C a) \left[ -\sin(\omega_i t_j + c_i) \omega_i^2 + \omega_i^2 \tau_a^2 \cos(\omega_i t_j + c_i) \right]}{(1 + \omega_i^2 \tau_a^2)} \right] ; j = 1 to 8
\]

From these equations (12-14), we can obtain the values of \(P_C a\) (but not of \(P_1, P_2\) and \(P_3\) by themselves), \(\omega_i\), \(c_i\) and \(\tau_a\). On the other hand, by also fitting equation (6), (without the exponential term) to the \(V(t)\) data, we obtain:

\[
\begin{align*}
P_1C &= 0.3223 & P_2C &= 0.3143 & P_3C &= -0.02269 \quad (15) \\
\omega_1 &= -1.178 & \omega_2 &= 0.5067 & \omega_3 &= 1.855 \quad (16) \\
c_1 &= 90223 & c_2 &= 0.2242 & c_3 &= -3.961 \quad (17) \\
\tau_a &= 0.5535
\end{align*}
\]
We can now also formulate another noninvasively-determinable non-dimensional ventilatory index (VTI2) in terms of these parameters as follows:

\[ VTI_2 = \frac{(BR)\tau}{[P_1C][P_2C][P_3C]} = \frac{(BR)R[T]}{[P_1P_2P_3C^2]} \]  

(18)

It is seen that VTI2 can in fact be expressed in terms of \( P_1, P_2, P_3 \) and \( R, C \). This VTI2 index can be evaluated by computing the values of \( (BR) \) and \( \tau \), along with \( (P, C) \), as given by (17). Then, after evaluating VTI2 for a number of patients, its distribution can enable us to categorize and differentially diagnose patients with various lung disorders and diseases.
3.14 Variations in $R$ and $C$ during a Respiratory cycle (towards nonlinear $C$)

Thus far, we have adopted the average cyclic values $C_a$ and $R_a$ for our $DE_q$ model parameters. However, we expect that $C$ will vary with lung volume ($V$), and that $R$ will perhaps vary with the airflow-rate or ($\dot{V}$) or even $\omega$. Hence, for a true representation of the lung properties $C$ and $R$, let us determine their values for different times during the ventilatory cycle, and compare them with their average values $C_a$ and $R_a$, so as to make a case for a nonlinear ventilatory-function model.

Let us hence compute the instantaneous value of compliance ($C$) at time ($t = t_m$), when $\dot{V} = 0$. Let us have differentiate equation (2-a), giving:

$$ RV + \frac{V}{C} = \sum_{i=1}^{\infty} P_i C_{a_i} \cos(\omega_{a_i} t + c_i) \quad (19) $$

Now at about mid-inspiration, when $t = t_m = 1.18$ and $\dot{V} = 0.48$ l/s, $\dot{V} = 0$ l/s and $V = 0.29l$ (based on Figure 3.27). By substituting for $\dot{V}$, $\dot{V}$ and $V$ in (19), we obtain, $C=0.486l/cm$ H$_2$O (compared to its $C_a$ value of 0.21). Now, in order to compute $R$, we utilize the data information that at $t = 2.02s$ we substitute $\dot{V} = 0.89 l/s$ and $V = 0.54 l$ (from the Figure 3.27 data) into equation (2-a), to obtain:

$$ RV = \sum_{i=1}^{\infty} P_i \omega_{a_i} \cos(\omega_{a_i} t + c_i) 
R = \frac{\sum_{i=1}^{\infty} P_i \omega_{a_i} \cos(\omega_{a_i} t + c_i)}{V} \quad (20) $$

Substitute $C$ (at $t_m = 1.18s$)=$0.486 l/cmH_2O$ in either equation (6) or 2(b), and obtain $R=1.122 (cmH_2O)s/l$. This gives us some idea of the order of magnitude of $R$ and $C$, in comparison to their average values $C_a$ and $R_a$. We could naturally expect $C$ at $t = t_m$ (which is about mid-inspiration) to be higher than its value at end-inspiration, when the lung is fully inflated. Also, we could expect the flow-resistance to be minimum at peak-inspiration, when $\ddot{V} = 0$.

Because $C$ and $R$ are not constant, but a function of $V$ and $\dot{V}$, we can hence represent lung compliance ($C$) and resistance ($R$) as follows:

$$ C = C_0 e^{-k_c \dot{V}} \quad \text{or} \quad E = \frac{1}{C} = E_0 e^{k_d \dot{V}} \quad (21-a) $$

$$ R = R_0 e^{k_d \dot{V}} \quad (21-b) $$
wherein \( V \) can also be varied by having the subjects breathe at different ventilation frequencies (\( \omega \)).

**Figure 3.33**

A The pressure curve represented by equation (3) matched against the pressure data (represented by dots).

B The volume curve represented by equation (6), for from \( C_u =0.2132 \text{(cmH2O)}^{-1} \) and \( Ra=2.275 \text{ cmH2O} \text{sl}^{-1} \) pp. 3 matched against the volume data represented by dots.
3.14.1 Nonlinear Compliance:

We note as per the conventional formulation of compliance, given by (2) in Figure 3.33 as:

\[
P_{el} = \frac{V}{C} + P_{e0} = VE + P_{e0}
\]  
(22)

In the above formulation, we assume that \(C\) and \(E(=1/C)\) remains constant throughout the ventilation cycle. However at the start of inspiration, \(C=C_0\) at \(t=0\), and it decreases as the lung volume increases, based on the lung (static) volume vs pressure curve. So let us improve upon this (22) model, by making \(P_{el}\) to be a nonlinear function of volume, as follows:

\[
P_{el} = P_{e0} + VE_0e^{KV}
\]  
(23-a)

We can alternatively write equation (23) as:

\[
P_{el} = P_{e0} + V(E_0 + E_1t + E_2t^2)
\]  
(23-b)

Employing the above format of compliance, the governing DEq (1) becomes

\[
RV + VE_0e^{KV} = P_L(t) - P_{el0} = P_{N}(t) = \sum_{i=1}^{3} P_i \sin(\omega_i t + c_i)
\]  
(24)

Again at end-expiration, \(P_{el0} = \) intra-pulmonary pressure=\((P_0+P_1)\). Hence equation (24) becomes:

\[
RV + VE_0e^{KV} = \sum_{i=1}^{3} P_i \sin(\omega_i t + c_i)
\]  
(25-a)

whose RHS is similar to that of (2-a), and the values of \(P_1, P_2,\) and \(P_3\) are given by (3) for the Table 3.5 data.

Solving equation (25-a):
This yields:

\[
V(t) = e^{\frac{i(\omega_0 t + 3E_1 t^2 + 2E_2 t^2)}{6R}} \sum_{i=1}^{\infty} \frac{P_i C a^{\omega_i}}{R} \sin(\omega_i t + c_i) \int_0^\infty e^{\frac{i(\omega_0 t + 3E_1 t^2 + 2E_2 t^2)}{6R}} \sum_{i=1}^{\infty} \frac{P_i C a^{\omega_i}}{R} \sin(\omega_i t + c_i) du
\]  

(25-b)

We could employ this expression for \(V(t)\) to fit the clinical \(V(t)\) to fit the clinical \(V(t)\) data. However, let us try a simpler approach to evaluate these parameters \(k\) & \(E_0\). For this purpose, we again bring to bear the situation that at end-inspiration, for \(t = t_v = 2.02s\), we have \(V = 0\) and \(V_{\text{max}} = TV = 0.55l\). Hence, from Table 3.5 data, and (3) and (25-a), we obtain:

\[
0.55E_0 e^{0.55k} = 2.55
\]

(26)

Let us now employ the volume data point at which \(V = 0\). For this purpose, we differentiate (25-a), to obtain:

\[
V(t) = e^{\frac{i(\omega_0 t + 3E_1 t^2 + 2E_2 t^2)}{6R}} \sum_{i=1}^{\infty} \frac{P_i C a^{\omega_i}}{R} \cos(\omega_i t + c_i) \int_0^\infty e^{\frac{i(\omega_0 t + 3E_1 t^2 + 2E_2 t^2)}{6R}} \sum_{i=1}^{\infty} \frac{P_i C a^{\omega_i}}{R} \cos(\omega_i t + c_i) du
\]  

(27)

From the Table 3.5 data at about mid-inspiration, for which at \(t = t_m = 1.18s\), \(V = 0\), \(V = 0.29\) and \(P = 2.53\), from Table 3.5 data. Substituting these values into (27), we get:

\[
(1 + 0.29k)(E_0 + 1.18E_1 + 1.39E_2) = 2.53
\]

(28)

Now in equations (26) and (28), we have four unknowns to be identified: \(k, E_0, E_1,\) and \(E_2\). Hence we need two more equations, corresponding to two additional time instants. From the values in the following table,
Table 3.5 Data.

<table>
<thead>
<tr>
<th>t</th>
<th>V</th>
<th>( \dot{V} )</th>
<th>( \ddot{V} )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.18</td>
<td>0.29</td>
<td>0.48</td>
<td>0</td>
<td>2.53</td>
</tr>
<tr>
<td>2.02</td>
<td>0.55</td>
<td>0</td>
<td>-0.89</td>
<td>2.55</td>
</tr>
<tr>
<td>2.87</td>
<td>0.29</td>
<td>-0.47</td>
<td>0</td>
<td>0.29</td>
</tr>
<tr>
<td>4.19</td>
<td>-0.03</td>
<td>0.16</td>
<td>-0.15</td>
<td>26</td>
</tr>
<tr>
<td>4.76</td>
<td>-0.02</td>
<td>0.02</td>
<td>0</td>
<td>-0.06</td>
</tr>
</tbody>
</table>

Using Equation 1.18 we can determine the unknowns:

\[ k = -0.13, \quad E_0 = 4.98, \quad E_1 = -2.24 \quad \text{and} \quad E_2 = 0.21 \]

Hence, by employing the nonlinear formulation,

\[ P_{el} = P_{el0} + E_0 e^{-kV} \]

we obtain the following expression for nonlinear lung compliance (or elastance):

\[ \frac{dP_{el}}{dV} = E = \frac{1}{C} = E_0 ke^{kV} = 0.65e^{0.13V} \]

Based on this expression, we obtain, for \( t = t_m \) and \( V = 0.29 \) l:

\[ E = \frac{1}{C} = 0.67 \text{cmH}_2\text{O}/l \quad \text{and} \quad C = 1.48 l/\text{cm H}_2\text{O}. \]

Equation (31) can now provide us a more realistic characterization of lung compliance as follows:

At \( t = 0 \) and \( V = 0 \), we compute \( E = \frac{1}{C} = 0.65 \) and \( C = 1.53 \text{ cmH}_2\text{O}/l \)

At \( t = t_m = 1.18s \) and \( V = 0.029l \), \( E = \frac{1}{C} = 0.67 \) and \( C = 1.48 \text{ cmH}_2\text{O}/l \)

At \( t = t_v = 2.02s \) and \( V = 0.55l \) and \( E = \frac{1}{C} = 0.70 \) and \( C = 1.43 \text{ cmH}_2\text{O}/l \)

which corresponds to the value of \( C_a \).

Our nonlinear formulation of lung compliance, as depicted by (31) and (33), indicates that compliance decreases from 1.53 cmH_2O/l at start-inspiration to 1.48 cmH_2O/l at
about mid-inspiration, and then to 1.43 cm H₂O /l at the end of inspiration. What this also tells us is that the ventilatory model (1) gives the correct reading of the compliance at \( V_{\text{max}} \), i.e. at end-inspiration. At other times of inspiration and expiration, the \( C_a \) parameter underestimates the instantaneous value of lung compliance. Now, we could also obtain an analytical solution of (25) for \( V(t) \), and fit the expression for \( V(t) \) to the lung volume data, to evaluate the parameters

(i) \( R, E_o \) & \( k \) for an intubated patient

(ii) \( R, E_o k \) & \( P_1, P_2 \) and \( P_3 \) for a non-intubated patient in the out patient clinic. However, this is outside the scope of this chapter.
This is an important diagnostic index, especially if it can be obtained without intubating the patient and even without using the ventilator. The premise for determining WOB is that the respiratory muscles expand the chest wall during inspiration, thereby lowering the pleural pressure (i.e., making it more negative) below the atmospheric pressure to create a pressure differential from the mouth to the alveoli during inspiration. Then, during expiration, the lung recoils passively.

Hence, the work done during a respiratory life cycle, is given by the area of the loop generated by plotting lung volume ($V$) versus net driving pressure ($P_p$). This plot is shown in Figure 3.34. Its area can be obtained graphically, as well as analytically as shown below:

\[
WOB = \int_0^T V dP_p(t) = \frac{T}{0} V \frac{dP_p(t)}{dt} dt
\]

\[
= \int_0^T \left( \sum_{i=1}^3 \frac{P_i C_i a \left[ \sin(\omega_i t + c_i) - \omega_i^2 \tau_a^2 \cos(\omega_i t + c_i) \right]}{(1 + \omega_i^2 \tau_a^2)} \right) \sum_{i=1}^3 P_i \omega_i \cos(\omega_i t + c_i) dt
\]

\[
= \sum_{i=1}^3 -P_i C_i a \left[ \cos(\omega_i T + c_i) + \omega_i \tau_a \sin(\omega_i T + c_i) - \cos c_i - \omega_i \tau_a \sin c_i \right] \omega_i (1 + \omega_i^2 \tau_a^2)
\]

The above expression for WOB can be evaluated, once the values of $C_i$ and $\tau$ (or $\omega \tau$) and $P_1$, $P_2$ and $P_3$ and have been computed (as shown in the previous section). So let us substitute into this equation, the following values associated with equation (3).

\[
P_1 = 1.581 \text{ cm H}_2\text{ O}, \quad P_2 = -5.534 \text{ cm H}_2\text{ O}, \quad P_3 = 0.5523 \text{ cm H}_2\text{ O}
\]

\[
\omega_1 = 1.214 \text{ rad/s}, \quad \omega_2 = 0.001414 \text{ rad/s}, \quad \omega_3 = 2.401 \text{ rad/s}
\]

\[
c_1 = -0.3132 \text{ rad}, \quad c_2 = 3.297 \text{ rad}, \quad c_3 = -2.381 \text{ rad}
\]

We compute the value of WOB to be 0.9446 (cm H$_2$O l) in 5s, or 0.19 cm H$_2$O l s$^{-1}$ or 0.14 mmHg l s$^{-1}$ or 0.02 W, which is equivalent to an oxygen consumption of about 0.51 ml/min or about 0.18% of the resting $\dot{V}O_2^*$ of 28.87 ml/min. This value can be verified by calculating the value of the area of the pressure-volume loop in Figure 3.29 which is equal to 0.8 cm H$_2$O l.
3.16 Second-Order model for Single-compartment Lung Model

Let us now consider the dynamic (instead of static) equilibrium of a spherical segment of the lung model in Figure 3.31, obtained as (by dividing throughout by the elemental lung area):

\[ m_s \ u + (P_p - P_a) + P_{elas} = 0 \]  

wherein: \( P_a \) and \( P_p \) are the alveolar and pleural pressures, \( u \) is the alveolar-wall displacement, \( m_s = \text{lung mass (M) per unit surface area} = \frac{M}{4\pi R^2} \),

and

\[ P_{elas} = \frac{2\sigma h}{R} = \frac{V}{C} + P_{el0} \]  

where:

(i) \( C \) is in \((\text{cm H}_2\text{O})^{-1}\)

(ii) \( m_s \) (wall mass per unit surface area or surface density) = \( \rho h \), \( \rho \) is the density (mass per unit volume)

(iii) \( \sigma \) is the wall stress

(iv) \( h \) & \( R \) are the wall thickness and radius of the equivalent-lung model.

Now, the displaced alveolar volume, \( V = \frac{4}{3} \pi (R + u)^3 \),

from which we get

\[ V = 4\pi R^2 u \]  

(39)
Now, from equation (1), by putting

(i) \[ P_p - P_a = (P_o - P_a) + (P_p - P_o) \] and \[ P_L = P_o - P_p \]

so that \[ P_p - P_a = P_o - P_a - P_L = RV - P_L \]  \[ (40) \]

(ii) \[ m_s \omega = \left( \frac{M}{4\pi R^2} \right) \left( \frac{V}{4\pi R^2} \right) = \frac{MV}{16\pi^2 R^4} = M^* \omega; \quad M^* = \frac{M}{16\pi^2 R^4} = \frac{m_s}{4\pi R^2} \]  \[ (41) \]

we obtain, from (1), (2) and (3):

\[ M^* + (P_o - P_a) + \frac{V}{C} = P_L - P_{el \omega}; \quad M^* = \frac{M}{16\pi^2 R^4} \quad (= \frac{m_s}{4\pi R^2}) \]  \[ (42) \]

Now putting \( P_o - P_a = RV \), we obtain:

\[ M^* + RV + \frac{V}{C} = P_L - P_{el 0} = \frac{3}{\sum_{i=1}^3} P_i \sin(\omega_i t + c_i) - P_{el 0} \]

\[ = P_N \]  \[ (43) \]

Since at end-expiration when \( \omega_i t = \omega_i T \) for \( i = 1 \) to 3 and \( P_L = P_{el 0} \) so that \( P_{el 0} = 0 \).

In the above (6), we have:

wherein:

(i) \( M^* = \frac{m_s}{4\pi R^2} = \rho_s h \); \( \rho_s \) is the lung volume-density per unit surface area (in Kgm\(^{-5}\)) and \( M^* \) is in kgm\(^{-4}\);

(ii) the clinical data in Figure 3.27 is assumed to be represented by

\[ P_N(t) = \sum_{i=1}^3 P_i \sin(\omega_i t + c_i) \] with \[ (44) \]

\( P_1 = 1.581 \) cm H\(_2\) O, \( P_2 = -5.534 \) cm H\(_2\) O \( P_3 = 0.5523 \) cm H\(_2\) O

\( \omega_1 = 1.214 \) rad/s \( \omega_2 = 0.001414 \) rad/s \( \omega_3 = 2.401 \) rad/s

\( c_1 = -0.3132 \) rad \( c_2 = 3.297 \) rad \( c_3 = -2.381 \) rad

Then we can rewrite (6) as:

\[ \sum_{i=1}^3 \frac{P_i}{M^*} \sin(\omega_i t + c_i) \]  \[ (45-a) \]
or as:
\[
\dot{V} + 2n \dot{V} + p^2V = \sum_{i=1}^{\infty} Q_i \sin(\omega_i t + \phi_i)
\]  
(45-b)

In the above equation:
(i) the damping coefficient, \(2n = R/M^*\)
(ii) the natural frequency of the lung ventilatory cycle, \(p^2 = 1/CM^*\)
(iii) \(Q_i = P_i / M^*\)  
(45-c)

So the governing (8) of the lung ventilatory response to the inhalation pressure has three parameters: \(M^*, R \& C\) (if the lung pressure is also monitored by intubating the patient). The solution of this equation is given by:

\[
V(t) = \frac{3}{2} \sum_{i=1}^{\infty} \left\{ \frac{Q_i}{4n^2 \omega_i^2 + p^4 - 2p^2 \omega_i^2} \left[ -\frac{1}{2} \left( -\omega_i \sin(\omega_i t + \phi_i) + \omega_i^3 \cos(\omega_i t + \phi_i) \right) \right] e^{\frac{1}{2} \left( -\omega_i^2 - (p-n)\omega_i^2 \right) t} \right\}
\]

We will ignore the exponential terms and perform parameters identification by matching the above expression for \(V(t)\) to the clinical data, shown in Figure 3.33. The matching is illustrated in Figure 3.35, wherein the first and second order differentiate equation solutions for \(V(t)\) are depicted. The computed values of the model parameters are also shown in the table below the figure. Further, the first and second order model values of \(R\) and \(C\) are compared in the table.
Let us compare these values with those obtained by simulating the First-Order Model to the clinical data, as shown below.

<table>
<thead>
<tr>
<th></th>
<th>First Order Model</th>
<th>Second Order Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R \ [cmH_2O/l/s]$</td>
<td>2.28</td>
<td>3.44</td>
</tr>
<tr>
<td>$C \ [l/cmH_2O]$</td>
<td>0.21</td>
<td>0.85</td>
</tr>
<tr>
<td>$M^* \ [cmH_2O/l/s^2]$</td>
<td>3.02</td>
<td></td>
</tr>
<tr>
<td>$n \bigg( = \frac{R}{M^*} \bigg) \ [s^{-1}]$</td>
<td>1.14</td>
<td></td>
</tr>
<tr>
<td>$p^2 \bigg( = \frac{1}{CM} \bigg) \ [s^{-2}]$</td>
<td></td>
<td>0.39</td>
</tr>
</tbody>
</table>

**Figure 3.35** Results of Single Compartmental Model based on differentiate equation formulation, compared with the First Order differential equation model.
3.17 Two-compartmental Linear Model

Now, it is possible that only one of the two lungs (or lung lobes) may be diseased. So, let us develop a procedure to distinguish between the normal lung and the pathological lung? We hence employ the 2-compartment model (based on our first-order differential-equation of lung ventilatory function) to solve the problem of a two-lung model (schematized in Figure 3.36).

For this purpose we make the subject breath at different values of frequency ($\omega$), and monitor the total lung pressure $P_{i}^{T}(t)$ (i.e., $P_{1i}$ and $P_{2i}$) and total lung volume $V_{i}(t)$. Correspondingly, we have $P_{i}^{L}(t)$ and $V_{i}^{L}(t)$ for the left lungs, respectively. The governing equations will be as follows (refer Figure 3.36):

\[ P_{i}^{T} = P_{i}^{l} = P_{i}^{R}, \text{i.e.} \quad P_{i}^{1} = P_{i}^{1} = P_{i}^{2} = P_{i}^{2} \]
\[ V_{i}^{T} = V_{i}^{l} + V_{i}^{r} \]

Correspondingly, we have $P_{i}^{l}(t)$, $V_{i}^{l}(t)$, and $P_{i}^{R}(t)$, $V_{i}^{R}(t)$ for the left and right lungs, respectively. The governing equations will be as follows (refer Figure 3.36):

\[ P_i^T = p_i^l = p_i^r, \text{i.e.} \quad p_i^1 = p_i^1 = p_i^2 = p_i^2 \]
\[ V_i^T = V_i^l + V_i^r \]

Corresponding to $\omega$;

wherein

(i) $V_i^l(t) = f(\omega, R_i^l, C_i, P_i^T(t))$  
(ii) $V_i^r(t) = f(\omega, R_i^r, C_i, P_i^T(t))$

In these equations (20).

(i) the variables $\omega$, $P_i^T(t)$, $V_i^T(t)$ are deemed to be known, i.e. monitored.

(ii) the parameters $R_i^l$, $C_i$, and $R_i^r$, $C_i$ are to be evaluated.

Using the first-order differential equation model, (presented in section 2, as given by equation 6 or 14):

\[ V(t) = \sum_{i=1}^{3} \left( P_i^l C_i^l \right) \left[ -\sin(\omega_i t + c_i) - \frac{\omega_i^2 c_i^2}{1 + \omega_i^2 t^2} \right] \]

We put down the expression for $V_i^T(t) = V_i^L(C_i^L, \tau_i^L) + V_i^R(C_i^R, \tau_i^R)$, match it with the volume data (using parameter-identification technique (software), to obtain the values of $(C_i^L, \tau_i^L)$ and $(C_i^R, \tau_i^R)$ by means of which we can differentially diagnose left and right lung lobes’ ventilatory capacities and associated disorders (or diseases).
3.17.1 Two Compartmental Model Using First Order Ventilatory Model

Using equation (6) without the exponential term, we put down the expression for the total lung volume equal to the sum of left and right lung volumes, as follows:

\[
V(t) = \sum_{i=1}^{3} \frac{P_i C_i}{(1 + \omega_i^2 \tau_i^2)} \left[ \sin(\omega_i t + c_i) - \frac{\omega_i^2 \tau_i^2}{(1 + \omega_i^2 \tau_i^2)} \cos(\omega_i t + c_i) \right]
\]

wherein, for the clinical data, we have:

\[
P_1 = 1.581 \text{ cm H}_2\text{ O}, \quad P_2 = -5.534 \text{ cm H}_2\text{ O}, \quad P_3 = 0.5523 \text{ cm H}_2\text{ O}
\]
\[
\omega_1 = 1.214 \text{ rad/s}, \quad \omega_2 = 0.001414 \text{ rad/s}, \quad \omega_3 = 2.401 \text{ rad/s}
\]
\[
c_1 = -0.3132 \text{ rad}, \quad c_2 = 3.297 \text{ rad}, \quad c_3 = -2.381 \text{ rad}
\]

We further assume that the ratio of \(TV\) of left lung to that of right lung is 0.92.

Now, in order to develop a measure of confidence in our analysis, we first generate the total lung volume data by assuming different values of \(C\) and \(R\) for left and right lung lobes. We then use equation (52) along with the above data on pressure and
frequency, to generate the total lung volume data. We adopt this generated lung volume data as the clinical-volume data.

We now make our volume solution expression (equation (52)) match this generated clinical volume data, by means of the parameter-identification procedures, to evaluate $C$ and $R$ for the left and right lung-lobes and hence $VTL_1$ and $VTL_2$ (equations (11) and (18)) for these lobes. Based on the values of $VTL_1$ and $VTL_2$, we can differentially diagnose the left and right lung lobes.

### 3.17.1.1 Stiff Right Lung (with compliance problems)

We now simulate a normal left lung and stiff right lung, represented by:

$$R^L = R^R = 1.14 \text{ cmH}_2\text{O}^{-1} \text{s} \quad \text{and} \quad C^L = 0.11, \quad C^R = 0.05 \text{ l/cmH}_2\text{O} \quad (53)$$

Substituting these parametric values into equation (52), we generate the total lung volume data, as illustrated in Figure 3.32.

Now our clinical data for this Two-Compartment Model comprises of the pressure data of Figure 3.38 and the generated volume data of Figure 3.31. For this clinical data, we match the volume solution given by equation (52) with the generated volume data, illustrated in Figure 3.32, and carry our parameter identification. The computed values of $R$ and $C$, listed in the table of Figure 3.32, are in close agreement with the initially assumed parametric values of equation (53). This lends credibility to our model and to our use of parameter-identification method.

Now for differential diagnosis, we compute the lung ventilatory indices, as shown in the Table.
Two Compartmental Model

<table>
<thead>
<tr>
<th></th>
<th>First Order Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left Lung</td>
</tr>
<tr>
<td>( R \ [\text{cmH}_2\text{O}^{-1}\text{s}] )</td>
<td>1.137</td>
</tr>
<tr>
<td>( C \ [\text{l}/\text{cmH}_2\text{O}] )</td>
<td>0.1066</td>
</tr>
<tr>
<td>VTL(_1)</td>
<td>2.115</td>
</tr>
<tr>
<td>VTL(_2)</td>
<td>0.2198</td>
</tr>
</tbody>
</table>

**Figure 3.37** Results of the Two-Compartment Model, based on First-Order differential equation model. Based on our assumption of \( TV^L / TV^R = 0.92 \) we have \( TV^L = 0.48 \times 0.48 = 0.2304 \text{l} \) and \( TV^R = 0.52 \times 0.48 = 0.2496 \text{l} \).
3.17.1.2 Right Lung with R problems

Now, we simulate a lung with an obstructive right lung, as represented by:

\[ R^L = 1.14 \text{ and } R^R = 2.28 \text{ cmH}_2\text{O}^{-1}\text{s} \text{ and } C_L = C_R = 0.11 \text{ l/cmH}_2\text{O} \quad (54) \]

![Graph of lung volume vs time](image)

### Two Compartmental Model

<table>
<thead>
<tr>
<th></th>
<th>First Order Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left Lung</td>
</tr>
<tr>
<td>[ R \left[ \text{cmH}_2\text{O}^{-1}\text{s} \right] ]</td>
<td>1.138</td>
</tr>
<tr>
<td>[ C \left[ 1/\text{cmH}_2\text{O} \right] ]</td>
<td>0.1066</td>
</tr>
<tr>
<td>VTL_1</td>
<td>2.1192</td>
</tr>
<tr>
<td>VTL_2</td>
<td>0.3553</td>
</tr>
</tbody>
</table>

**Figure 3.38** Results of the Two-Compartment Model, based on First-Order differential equation model. Based on our assumption of \( TV^L / TV^R = 0.92 \) we have \( TV^L = 0.48 \times 0.61 = 0.2928 \text{l} \ and \ TV^R = 0.52 \times 0.61 = 0.3172 \text{l} \).

As in the case of the stiff right lung, we first generate the lung volume data for the above values of compliance and resistances. We then match the total lung volume solution given by equation (52) with the generated lung volume data, and compute the compliance and flow resistance values of the right and left lung. These are tabulated
in Figure 3.38, and found to have good correspondence with the assumed values of equation (54).
3.18 Two Compartmental Model Using Second Order Ventilatory Model

In the previous section, we have discussed the 2-compartmental model using first order ventilatory model, now let’s derive the second order ventilatory model for the model. We employ the 2-compartment model (based on our second-order differential-equation of lung ventilatory function) to solve the problem of a two-lung model (schematized in Figure 3.36).

For this purpose we make the subject breathe at different values of frequency \( \omega \), and monitor the total lung pressure \( P_i^T(t) \) (i.e., \( P_{1i} \) and \( P_{2i} \)) and total lung volume \( V_i(t) \). Correspondingly , we have \( P_i^L(t) \) and \( V_i^L(t) \) and \( P_i^R(t) \) & \( V_i^R(t) \) for the left and right lungs, respectively. The governing equations will be as follows (refer Figure 3.36)

\[
P^T = P^l = P^R, \text{i.e.} \quad P_1^T = P_1^l = P_1^R \quad \text{&} \quad P_2^T = P_2^l = P_2^R \quad \text{from (47)}
\]

and \( V^T = V^l + V^r \) \quad \text{from (48)}

corresponding to \( \omega \);

wherein

\[
\text{(i)} \quad V^l(t) = f(\omega, Q^l, C^l, P^T(t)) \quad \text{(55)}
\]

\[
\text{(ii)} \quad V^r(t) = f(\omega, Q^r, C^r, P^T(t)) \quad \text{(56)}
\]

Using equations (46) and (52), we put down the expression for the total lung volume equal to the sum of left and right lung volumes, as follows:
\[ V(t) = \sum_{i=1}^{4} \left[ Q_i' \left( -2 \omega_i \cos(\omega t + c_i') n - 2 \sin(\omega t + c_i') (p')^2 - \sin(\omega t + c_i') \omega \right) \right] - \frac{1}{2} Q_i' \left[ \left( n' \right)^2 - (p')^2 \right] \frac{1}{2} c'_i \sin \omega \beta + (p')^2 \left( \left( n' \right)^2 - (p')^2 \right) \frac{1}{2} \sin c'_i - 2 \omega_i \left( n' \right)^2 \cos c'_i + (p')^2 \left( n' \right)^2 \sin c'_i \right] e^t 
\] 

\[ -2 \omega_i \left( n' \right)^2 \frac{1}{2} \frac{1}{2} \frac{1}{2} \sin c'_i - \omega \cos c'_i + \omega \left( n' \right)^2 \sin c'_i + \omega \left( p' \right)^2 \left( n' \right)^2 \sin c'_i \] 

\[ \left( n' \right)^2 - (p')^2 \right] \frac{1}{2} \frac{1}{2} \frac{1}{2} \sin c'_i + \omega \left( p' \right)^2 \left( n' \right)^2 \sin c'_i + \omega \cos c'_i \left( p' \right)^2 \left( n' \right)^2 \sin c'_i \] 

\[ 2 \omega_i \left( n' \right)^2 \cos c'_i + 2 \omega_i \left( n' \right)^2 \left( n' \right)^2 \left( p' \right)^2 \left( n' \right)^2 \sin c'_i + \omega \cos c'_i \left( p' \right)^2 \left( n' \right)^2 \sin c'_i \]
But due to insufficient data points in our clinical model, we are not able to determine the numerical solutions.

3.19 Conclusions

We have demonstrated that we can determine the lung resistance and compliance from a pressure-volume curve obtained by a ventilator. The second-order one-compartmental gives a very accurate result as compared against the first-order one-compartmental model. Due to the complexities involved in the second-order two-compartmental model, the current 32-bit and 64-bit digital computer cannot perform any convergent results. In time, we can try the model on a more powerful computer.
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Anatomy and Physiology, Mathematical Modeling, Numerical Simulation and Applications

Series: Advances in Bioengineering  Volume 3

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Chapter 3
Lung-gas composition and transfer analysis: O\textsubscript{2} and CO\textsubscript{2} diffusion coefficients and metabolic rates .......................... 77
D.N. Ghista, K.M. Loh & D. Ng

1  Introduction ................................................................................................. 77
2  Lung-air composition analysis (and O\textsubscript{2} consumption and CO\textsubscript{2} production rates) .......................................................... 78
   2.1 Calculation of O\textsubscript{2} consumption rate and CO\textsubscript{2} production rate ... 78
   2.2 Dead-space air composition ................................................................. 79
   2.3 Alveolar air composition and partial pressures ................................. 80
3  Lung gas-exchange model and parametric analysis ............................... 81
   3.1 Expressions for $D_{O_2}$ and $D_{CO_2}$ .................................................. 81
   3.2 Alveolar O\textsubscript{2} and CO\textsubscript{2} partial-pressure expressions .............. 85
   3.3 Arterial and venous O\textsubscript{2} and CO\textsubscript{2} partial-pressure expressions .......... 86
   3.4 Sequential procedure to compute $D_{O_2}$ and $D_{CO_2}$ ....................... 88
   3.5 Determining $D_{O_2}$ and $D_{CO_2}$ ......................................................... 89
4  Case studies .................................................................................................. 90

Chapter 4
Lung ventilation modeling and assessment.................................................. 95
D.N. Ghista, K.M. Loh & M. Damodaran

1  Introduction .................................................................................................. 95
   1.1 Role of lung ventilation ........................................................................ 95
2  Lung ventilation performance using a linear first-order model .................. 96
3  Ventilatory Index ......................................................................................... 101
   3.1 Noninvasively determinable ventilatory index ........................................ 101
4  Variations in R and C during a respiratory cycle (towards nonlinear) ....... 103
   4.1 Nonlinear compliance ........................................................................ 104
5  Work of breathing (WOB) ......................................................................... 106
6  Second-order model for single-compartment lung model ......................... 108
7  Two-compartmental linear model ............................................................. 110
   7.1 Two compartmental model using first order ventilatory model .......... 112
      7.1.1 Stiff right lung (with compliance problems) .................................... 115
      7.1.2 Right lung with R problems ......................................................... 115

Chapter 5
Modeling of two-phase flow in the human respiratory system ....................... 117
V.V. Kulish, B. Wijayanto & C.S. Lim

1  Introduction ................................................................................................. 117
2  Methodology .............................................................................................. 118
   2.1 Geometry of the human respiratory duct ............................................ 118
CHAPTER 4

Lung ventilation modeling and assessment

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Abstract

We have developed a lung-ventilation model by modeling the lung-volume response to mouth minus pleural driving pressure (by means of first- and second-order differential equations) in terms of resistance to airflow ($R$) and the lung compliance ($C$). The lung-volume solution of the differential equation is matched with the clinical-volume data, to evaluate the parameters, $R$ and $C$. These parameter values can help us to distinguish an obstructive lung and a lung with stiffened parenchyma from a normal lung, and hence diagnose lung diseases such as asthma and emphysema. We have also formulated a nonlinear compliance lung model, and demonstrated deceased lung compliance with filling volume. We then formulated a nondimensional lung-ventilatory index ($VTI$), incorporating the parameters $R$ and $C$ as well as the lung-breathing rate. When the $VTI$ is evaluated for various lung diseases, it will conveniently enable us to diagnose lung diseases in terms of just one $VTI$ number. Finally, we have shown how to model a two-lobe lung, and differentiate between normal and diseased lobes.

1 Introduction

1.1 Role of lung ventilation

Lung ventilation constitutes inhalation of an appropriate air volume under driving pressure (=mouth pressure − pleural pressure), so as to: (i) provide an adequate alveolar $O_2$ amount at an appropriate partial pressure, (ii) oxygenate the pulmonary blood, and (iii) thereby provide adequate metabolic oxygen to the cells.
Hence, ventilatory function and performance assessment entails determining how much air volume is provided to the alveoli, to make available adequate alveolar oxygen for blood oxygenation and cellular respiration.

Based on Fig. 1, we get:

(i) \((P_a - P_p) - P_{cl} = 0\)
(ii) \(P_{cl} = \frac{2ah}{Rr} = \frac{2T}{r} = V/C + P_{e0}\)
(iii) \((P_m - P_a) = R(dV/dt)\)
(iv) \(P_L = P_m - P_p\)
(v) \(R(dV/dt) + V/C = P_L - P_{e0}\) (lung elastic recoil pressure at end of expiration)

2 Lung-ventilation performance using a linear first-order model

We first analyze the lung-ventilation function by means of a very simple model represented by a first-order differential equation \((D_{eq})\) in lung-volume \((V)\) dynamics in response to the driving pressure \((P_L = \text{atmospheric pressure} - \text{pleural pressure})\), as displayed in Fig. 1. The clinical pressure-volume data is in Fig. 2.

The model-governing equation (shown derived in Fig. 1) is as follows:

\[
R\dot{V} + \frac{V}{C} = P_L(t) - P_{e0} = P_N(t),
\]  

wherein:

(i) the values of pressure are obtained from the given \(P_L(=P_m - P_p)\) data
(ii) the parameters of this governing \(D_{eq}\) are lung compliance \((C)\) and airflow resistance \((R)\); in the equation both \(R\) and \(C\) are instantaneous values
(iii) \(V = V(t) - V_o\) (the lung volume at the end of expiration)
(iv) \(P_{e0}\) is the lung elastic-recoil pressure at the end of expiration, and

\[
P_{e0} = P_{e0} - \frac{V}{C},
\]
Figure 2: Lung-ventilatory model and lung-volume and pleural-pressure data. Curve 1 on the curve represents $P_{cl}$, the pressure required to overcome lung elastance ($=V/C$). Curve 2 curve represents $P_{pl}$, the summation of $P_{cl}$ and $P_a$. The pressure $P_N(t)$ in eqn. (1a) equals $P_p$ minus $P_{cl}$ at end of expiration.

At the end of expiration when $\omega t = \omega T, P_L = P_{cl0} = P_N(t)$, which is represented by

$$P_N(t) = \sum_{i=1}^{3} P_i \sin (\omega_i t + c_i),$$

and the governing eqn. (1a) becomes:

$$R\dot{V} + \frac{V}{C} = P_N(t) = \sum_{i=1}^{3} P_i \sin (\omega_i t + c_i),$$

(2a)

where the right-hand side represents the net driving pressure minus pleural pressure. $P_N = (P_m - P_p) - P_{cl0}$. This $P_N$ is, in fact, the driving pressure $(P_m - P_p)$ normalized with respect to its value at end of expiration. Equation (2a) can be rewritten as follows:

$$\dot{V} + \frac{V}{RC} = \frac{1}{R} \sum_{i=1}^{3} P_i \sin (\omega_i t + c_i).$$

(2b)
wherein the \( P(t) \) clinical data (displayed in Fig. 2) is assumed to be represented by:

\[
P(t) = \sum_{i=1}^{3} P_i \sin (\omega_i t + c_i),
\]

\[
P_1 = 1.581 \text{ cmH}_2\text{O} \quad P_2 = -5.534 \text{ cmH}_2\text{O} \quad P_3 = 0.5523 \text{ cmH}_2\text{O}
\]
\[
\omega_1 = 1.214 \text{ rad/s} \quad \omega_2 = 0.001414 \text{ rad/s} \quad \omega_3 = 2.401 \text{ rad/s}
\]
\[
c_1 = -0.3132 \text{ rad} \quad c_2 = 3.297 \text{ rad} \quad c_3 = -2.381 \text{ rad}.
\]

The pressure curve (in Fig. 3A) represented by the above eqn. (3) closely matches the pressure data of Fig. 2. If, in eqn. (1), we designate \( R_a \) and \( C_a \) as the average values (\( R \) and \( C \)) for the ventilatory cycle, then the solution of eqn. (1) is given by:

\[
V(t) = \sum_{i=1}^{3} \frac{P_i C_a [\sin (\omega_i t + c_i) - b_i R_a C_a \cos (\omega_i t + c_i)]}{(1 + \omega_i^2 (R_a C_a)^2)} - H e^{-\frac{t}{T_a}},
\]

wherein the term \((R_a C_a)\) is denoted by \( r_a \). We need to have \( V = 0 \) at \( t = 0 \). Hence, putting \( V \) (at \( t = 0 \)) = 0, gives us:

\[
H = \sum_{i=1}^{3} \frac{P_i C_a [\sin (\omega_i t + c_i) - b_i R_a C_a \cos (\omega_i t + c_i)]}{(1 + \omega_i^2 (R_a C_a)^2)}.
\]

Then from eqns. (4) and (5), the overall expressions for \( V(t) \) becomes

\[
V(t) = \sum_{i=1}^{3} \frac{P_i C_a [\sin (\omega_i t + c_i) - \omega_i^2 r_a^2 \cos (\omega_i t + c_i)]}{(1 + \omega_i^2 r_a^2)}
\]

\[- \sum_{i=1}^{3} \frac{P_i C_a [\sin (\omega_i t + c_i) - \omega_i^2 r_a^2 \cos (\omega_i t + c_i)]}{(1 + \omega_i^2 r_a^2)} e^{-\frac{t}{T_a}}
\]

\[= \sum_{i=1}^{3} \frac{P_i C_a [\sin (\omega_i t + c_i) - \omega_i^2 r_a^2 \cos (\omega_i t + c_i)]}{(1 + \omega_i^2 r_a^2)} [1 - e^{-\frac{t}{T_a}}].
\]

We also want that \( dV/dt = 0 \) at \( t = 0 \), implying no airflow at the start of inspiration. So, by differentiating eqn. (6), we get:

\[
\dot{V} = \sum_{i=1}^{3} \frac{P_i C_a [\omega_i \cos (\omega_i t + c_i) + \omega_i^2 r_a \sin (\omega_i t + c_i)]}{(1 + \omega_i^2 r_a^2)} [1 - e^{-\frac{t}{T_a}}]
\]

\[+ \sum_{i=1}^{3} \frac{P_i C_a [\sin (\omega_i t + c_i) - \omega_i^2 r_a \cos (\omega_i t + c_i)]}{(1 + \omega_i^2 r_a^2) r_a} e^{-\frac{t}{T_a}}.
\]

From eqn. (7), we get \( \dot{V} \neq 0 \) at \( t = 0 \), thereby also satisfying this initial condition.
Figure 3: A The pressure curve represented by eqn. (3) matched against the pressure data (represented by dots). B The volume curve represented by eqn. (6), for from \( C_a = 0.2132 \text{ (cmH}_2\text{O)}^{-1} \) and \( R_a = 2.275 \text{ cmH}_2\text{O} \text{s}^{-1} \) pp. 3 matched against the volume data represented by dots.
Now, by matching the above \( V(t) \) expression \((6)\) with the given \( V(t) \) data in Fig. 2, and carrying out parameter identification, we can determine the in vivo values of \( R_a \) and \( C_a \), to be

\[
C_a = 0.2132 \text{ (cmH}_2\text{O)}^{-1}, \quad R_a = 2.275 \text{ cmH}_2\text{O sl}^{-1}
\]

The computed \( V(t) \) curve, represented by eqn. \((6)\) for the above values of \( C_a \) and \( R_a \), is shown in Fig. 3B. We can however analytically evaluate \( R_a \) and \( C_a \) by satisfying some conditions. For this purpose, we first note that \( V \) is maximum (= tidal volume, TV) at about \( t = t_V = 2.02 \text{ s} \). At \( t = t_V \), the exponential term \( e^{-\frac{t}{\tau}} \) in \((6)\) becomes of the order of \( e^{-10} \), and hence negligible. Then by putting \( \dot{V}(t=2.02) = 0 \) in eqn. \((7)\), without the exponential term we obtain:

\[
\dot{V}_{\mid t=2.02} = \sum_{i=1}^{3} P_i C_a \left[ \omega_i \cos \left( \omega_i \times 2.02 + c_i \right) + \omega_i^2 \tau_a \sin \left( \omega_i \times 2.02 + c_i \right) \right] \left( 1 + \omega_i^2 \tau_a^2 \right) = 0,
\]

in which the values of \( P_i, \omega_i \), and \( c_i \) are given by eqn. \((3)\). Then by solving eqn. \((8)\), we get \( \tau_a = 0.522 \text{ s} \). We can also put \( \dot{V} = 0 \) at \( t \approx 1.81 \text{ or } 2.87 \text{ s} \) and obtain a similar value for \( \tau \).

Then, we also note that at \( t = t_v = 2.02 \text{ s} \) (at which \( dV/dt = 0 \)) and \( V = 0.551 \). Hence upon substituting into eqn. \((6)\), and neglecting the exponential term, we get the following algebraic equation:

\[
V(t)_{\mid t=2.02} = \sum_{i=1}^{3} P_i C_a \left[ \sin \left( \omega_i t + c_i \right) - \omega_i \tau_a^2 \cos \left( \omega_i t + c_i \right) \right] \left( 1 + \omega_i^2 \tau_a^2 \right) = 2.55C_a,
\]

by employing the values of \( P_i, \omega_i \) and \( c_i \) from eqn. \((3)\). Now since \( V(t = 2.02 \text{ s}) = 0.551 \), we get

\[
2.55C_a = 0.55 \Rightarrow C_a = 0.221 \text{ (cmH}_2\text{O)}^{-1}.
\]

We can substitute, therein, the values of \( P_1 \) and \( P_2 \) from eqn. \((3)\), and obtain the value of \( C_a \) as: \( C_a = 0.221 \text{ (cmH}_2\text{O)}^{-1} \). Since we have computed \( \tau_a = 0.485 \text{ s} \), therefore \( R_a = 2.275 \text{ (cmH}_2\text{O) sl}^{-1} \). These are the average values of resistance to airflow and lung compliance during the ventilatory cycle shown in Fig. 2.

Since lung disease will influence the values of \( R \) and \( C \), these parameters can be employed to diagnose lung diseases. For instance in the case of emphysema, the destruction of lung tissue between the alveoli produces a more compliant lung, and hence results in a larger value of \( C \). In asthma, there is increased airway resistance \((R)\) due to contraction of the smooth muscle around the airways. In fibrosis of the lung, the membranes between the alveoli thicken and hence lung compliance \((C)\) decreases. Thus, by determining the normal and diseased ranges of the parameters \( R \) and \( C \), we can employ this simple lung-ventilation model for differential diagnosis.
3 Ventilatory index

Let us, however, formulate just one non dimensional number to serve as a ventilatory-performance index \( VTI_1 \) (to characterize ventilatory function), as:

\[
VTI_1 = [(R_a C_a) (\text{Ventilatory rate in s}^{-1}) 60]^2 = \tau_a^2 (BR)^2 60^2,
\]

where \( BR \) is the breathing rate.

Now, let us obtain its order of magnitude by adopting representative values of \( R_a \) and \( C_a \) in normal and disease states. Let us take the above computed values of \( R_a = 2.275 \text{ (cmH}_2\text{O} \text{sl}^{-1}) \) and \( C_a = 0.21321 \text{ (cmH}_2\text{O})^{-1} \) and \( BR = 12 \text{ m}^{-1} \) or \( 0.2 \text{ s}^{-1} \), computed for the data of Fig. 2 and eqn. (3). Then, in a supposed normal situation, the value of \( VTI_1 \) is of the order of 33.88. In the case of obstructive lung disease, (with increased \( R_a \)), let us take \( R_a = 5 \text{ (cmH}_2\text{O} \text{sl}^{-1}) \), \( C_a = 0.121 \text{ (cmH}_2\text{O})^{-1} \) and \( BR = 0.3 \text{ s}^{-1} \), then we get \( VTI_1 = 116.6 \). For the case of emphysema (with enhanced \( C_a \)), let us take \( R_a = 2.0 \text{ cmH}_2\text{O} \text{sl}^{-1} \), \( C_a = 0.51 \text{ (cmH}_2\text{O})^{-1} \) and \( BR = 0.2 \text{ s}^{-1} \); then we obtain \( VTI_1 = 144 \). In the case of lung fibrosis (with decreased \( C_a \)), we take \( R_a = 2.0 \text{ cmH}_2\text{O} \text{sl}^{-1} \), \( C_a = 0.081 \text{ (cmH}_2\text{O})^{-1} \) and \( BR = 0.2 \text{ s}^{-1} \); then we obtain \( VTI_1 = 3.7 \). We can hence summarize that \( VTI_1 \) would be in the range of 2–5 in the case of fibrotic lung disease, 5–50 in normal persons, 50–150 in the case of obstructive lung disease and 150–200 for the case of emphysema. This would of course need verification by analyzing a big patient population.

Now, all of this analysis requires pleural-pressure data, for which the patient has to be intubated. If now we evaluate the patient in an outpatient clinic, in which we can only monitor lung volume and not the pleural pressure, then can we develop a non invasively obtainable ventilatory index?

3.1 Noninvasively determinable ventilatory index

In order to formulate a non-invasively determinable ventilatory index from eqn. (1), we need to recognize that in this case \( P_N(t) \) (and hence \( P_t, \omega_i \) and \( c_i \)) will be unknown and we need to redesignate the model parameters and indicate their identification procedure. So we make use of the following features from the volume–time data to facilitate evaluation of the following three parameters:

\((P_t, C_a), \omega_i, c_i, \) and \( \tau_a.\)

At \( t = t_v = 2.02 \text{ s} \), \( V \) is max and \( dV/dt = 0 \); hence we rewrite eqn. (9) as:

\[
\dot{V}_{I_2=2.02} \sum_{i=1}^{3} \frac{(P_i C_a) [\omega_i \cos (2.02 \times \omega_i + c_i) + \omega_i^2 \tau_a \sin (2.02 \times \omega_i + c_i)]}{(1 + \omega_i^2 \tau_a^2)} = 0.
\]

(12)
Also, at \( t = t_m = 1.82/2.87\ s \), \( \dot{V} = 0 \). Hence by differentiating eqn. (7), without the exponential term, we obtain:

\[
\dot{V}(t) = \sum_{i=1}^{3} (P_i C_a) \left[ -\sin(\omega_i t_m + c_i) \omega_i^2 + \omega_i^3 \tau_a^2 \cos(\omega_i t_m + c_i) \right] \left[ 1 - e^{-\frac{t_m}{\tau_a}} \right] \\
+ 2 \sum_{i=1}^{3} (P_i C_a) \left[ \omega_i \cos(\omega_i t_m + c_i) - \omega_i^2 \tau_a \sin(\omega_i t_m + c_i) \right] \frac{e^{-\frac{t_m}{\tau_a}}}{\tau_a (1 + \omega_i^2 \tau_a^2)} \\
- \sum_{i=1}^{3} (P_i C_a) \left[ \sin(\omega_i t_m + c_i) - \omega_i \tau_a^2 \cos(\omega_i t_m + c_i) \right] \frac{e^{-\frac{t_m}{\tau_a}}}{\tau_a^2 (1 + \omega_i^2 \tau_a^2)} = 0. \tag{13}
\]

Then, at \( t = 1\ s \), \( V_1 = 2.02l \). From eqn. (6), without the exponential term, this condition yields:

\[
V_1 = \sum_{i=1}^{3} (P_i C_a) \left[ -\sin(\omega_i + c_i) \omega_i^2 + \omega_i^3 \tau_a^2 \cos(\omega_i + c_i) \right] \left( 1 + \omega_i^2 \tau_a^2 \right) = 2.02.
\]

In addition, we can utilize data information concerning \( V_j \) at \( t_j \) (\( j = 1 \) to 8), and put down:

\[
V_j = \sum_{i=1}^{3} (P_i C_a) \left[ -\sin(\omega_i t_j + c_i) \omega_i^2 + \omega_i^3 \tau_a^2 \cos(\omega_i t_j + c_i) \right] \left( 1 + \omega_i^2 \tau_a^2 \right); \quad j = 1 \quad \text{to} \quad 8. \tag{14}
\]

From eqns. (12)–(14), we can obtain the values of \( P_i C_a \) (but not of \( P_1, P_2 \) and \( P_3 \) by themselves), \( \omega_i, c_i \), and \( \tau_a \). On the other hand, by also fitting eqn. (6), (without the exponential term) to the \( V(t) \) data, we obtain:

\[
P_1 C = 0.3223 \quad P_2 C = 0.3143 \quad P_3 C = -0.02269 \tag{15}
\]

\[
\omega_1 = -1.178 \quad \omega_2 = 0.5067 \quad \omega_3 = 1.855 \tag{16}
\]

\[
c_1 = 90223 \quad c_2 = 0.2242 \quad c_3 = -3.961 \tag{17}
\]

\[
\tau_a = 0.5535.
\]

We can now also formulate another noninvasively determinable nondimensional ventilatory index (\( VT_{I2} \)) in terms of these parameters as follows:

\[
VT_{I2} = \frac{(BR)R[TV]^2}{|P_1 C||P_2 C||P_3 C|} = \frac{(BR)R[TV]^2}{|P_1 P_2 P_3 C^2|}. \tag{18}
\]

It is seen that \( VT_{I2} \) can in fact be expressed in terms of \( P_1, P_2, P_3 \) and \( R, C \). This \( VT_{I2} \) index can be evaluated by computing the values of \( (BR) \) and \( \tau \), along with \( (P_i C) \), as given by eqn. (17). Then, after evaluating \( VT_{I2} \) for a number of patients, its distribution can enable us to categorize and differentially diagnose patients with various lung disorders and diseases.
4 Variations in $R$ and $C$ during a respiratory cycle (towards nonlinear)

Thus far, we have adopted the average cyclic values $C_a$ and $R_a$ for our $DE_q$ model parameters. However, we expect that $C$ will vary with lung volume ($V$), and that $R$ will perhaps vary with the airflow rate or ($\dot{V}$) or even $\omega$. Hence, for a true representation of the lung properties $C$ and $R$, let us determine their values for different times during the ventilatory cycle, and compare them with their average values $C_a$ and $R_a$, so as to make a case for a nonlinear ventilatory-function model.

Let us hence compute the instantaneous value of compliance ($C$) at time ($t = t_m$), when $\ddot{V} = 0$. Let us differentiate eqn. (2a), giving:

$$R\ddot{V} + \frac{\dot{V}}{C} = \sum_{i=1}^{3} P_i C \omega_i \cos (\omega_i t + c_i).$$  \hspace{1cm} (19)

Now at about mid-inspiration, when $t = t_m = 1.18$ and $\dot{V} = 0.48$ l/s, $\ddot{V} = 0$ l/s and $V = 0.291$ (based on Fig. 2). By substituting for $\ddot{V}$, $\dot{V}$ and $V$ in eqn. (19), we obtain, $C = 0.486$ l/cmH$_2$O (compared to its $C_a$ value of 0.21). Now, in order to compute $R$, we utilize the data information that at $t = 2.02$ s we substitute $\ddot{V} = 0$ l/s, $\dot{V} = -0.89$ l/s and $V = 0.541$ (from the Fig. 2 data) into eqn. (2a), to obtain:

$$R\ddot{V} = \sum_{i=1}^{3} P_i C \omega_i \cos (\omega_i t + c_i)$$

$$R = \frac{\sum_{i=1}^{3} P_i \omega_i \cos (\omega_i t + c_i)}{\ddot{V}}.$$  \hspace{1cm} (20)

Substitute $C$ (at $t_m = 1.18$ s) = 0.486 l/cmH$_2$O in either eqns. (6) or (2b), and obtain $R = 1.122$ (cmH$_2$O)/s$^{-1}$. This gives us some idea of the order of magnitude of $R$ and $C$, in comparison to their average values $C_a$ and $R_a$. We could naturally expect $C$ at $t = t_m$ (which is about mid-inspiration) to be higher than its value at the end of inspiration, when the lung is fully inflated. Also, we could expect the flow resistance to be minimum at the peak of inspiration, when $\dot{V} = 0$.

Because $C$ and $R$ are not constant, but a function of $V$ and $\dot{V}$, we can hence represent lung compliance ($C$) and resistance ($R$) as follows:

$$C = C_0 e^{-k_v V} \quad \text{or} \quad E = \frac{1}{C} = E_0 e^{k_v V}$$  \hspace{1cm} (21a)

$$R = R_0 e^{k_v \dot{V}},$$  \hspace{1cm} (21b)

wherein $\dot{V}$ can also be varied by having the subjects breathe at different ventilation frequencies ($\omega$).
4.1 Nonlinear compliance

We note as per the conventional formulation of compliance, given by eqn. (2) in Fig. 1 as:

\[ P_{el} = \frac{V}{C} + P_{e0} = VE + P_{e0}. \]  

(22)

In the above formulation, we assume that \( C \) and \( E(\approx -1/C) \) remains constant throughout the ventilation cycle. However, at the start of inspiration, \( C = C_0 \) at \( t = 0 \), and it decreases as the lung volume increases, based on the lung (static) volume vs pressure curve. So let us improve upon this (22) model, by making \( P_{el} \) a nonlinear function of volume, as follows:

\[ P_{el} = P_{e0} + VE_0 e^{kV}. \]  

(23a)

We can alternatively write eqn. (23) as:

\[ P_{el} = P_{e0} + V(E_0 + E_1 t + E_3 t^2). \]  

(23b)

Employing the above format of compliance, the governing \( DE_q \) (1) becomes

\[ R\dot{V} + VE_0 e^{kV} = P_I(t) - P_{e0} = P_N(t) = \sum_{i=1}^{3} P_i \sin(\omega_i t + c_i). \]  

(24)

Again at the end of expiration, \( P_{e0} = \) intrapulmonary pressure = \( (P_0 + P_1) \). Hence eqn. (24) becomes:

\[ R\dot{V} + VE_0 e^{kV} = \sum_{i=1}^{3} P_i \sin(\omega_i t + c_i) \]  

(25a)

whose RHS is similar to that of eqn. (2a), and the values of \( P_1, P_2, \) and \( P_3 \) are given by eqn. (3) for the Fig. 2 data.

Solving eqn. (25a):

\[ R\dot{V} + VE_0 e^{kV} = \sum_{i=1}^{3} P_i \sin(\omega_i t + c_i), \]

or,

\[ \dot{V} + \frac{VE_0}{R} e^{kV} = \sum_{i=1}^{3} \frac{P_i}{R} \sin(\omega_i t + c_i), \]

or, based on eqn. (23b),

\[ \dot{V} + \frac{V}{R} [E_0 + E_1 t + E_2 t^2] = \sum_{i=1}^{3} \frac{P_i}{R} \sin(\omega_i t + c_i). \]
This yields:

\[ V(t) = e^{\frac{-sl_0 + 3E_1 + 2\pi^2 t^2}{sk}} \int_0^t e^{\frac{-sl_0 + 3E_1 + 2\pi^2 u^2}{sk}} \sum_{i=1}^3 \frac{P_i}{R} \sin(\omega_i u + c_i) du. \] (25b)

We could employ this expression for \( V(t) \) to fit the clinical \( V(t) \) data. However, let us try a simpler approach to evaluate these parameters \( k \) and \( E_0 \). For this purpose, we again bring to bear the situation that at the end of inspiration, for \( t = t_e = 2.02 \) s, we have \( \ddot{V} = 0 \) and \( V = V_{\text{max}} = TV = 0.551 \). Hence, from Fig. 2 data, and eqns. (3) and (25a), we obtain:

\[ 0.55E_0 e^{0.55k} = 2.55. \] (26)

Let us now employ the volume data point at which \( \dddot{V} = 0 \). For this purpose, we differentiate eqn. (25a), to obtain:

\[ \dddot{V} + \frac{E_0}{R} e^{kV} (1 + kV) + \sum_{i=1}^3 \frac{P_i C_i \omega_i}{R} \cos(\omega_i t + c_i) \]

\[ \dddot{V} + \frac{(1 + kV)}{R} \left[ E_0 + E_1 t + E_2 t^2 \right] = \sum_{i=1}^3 \frac{P_i C_i \omega_i}{R} \cos(\omega_i t + c_i). \] (27)

From the Fig. 2 data at about mid-inspiration, for which at \( t = t_m = 1.18 \) s, \( \dddot{V} = 0 \), \( \dot{V} = 0.29 \) and \( P = 2.53 \), from Fig. 2 data. Substituting these values into eqn. (27), we get:

\[ (1 + 0.29k)(E_0 + 1.18E_1 + 1.39E_2) = 2.53. \] (28)

Now, in eqns. (26) and (28), we have four unknowns to be identified: \( k, E_0, E_1, \) and \( E_2 \). Hence we need two more equations, corresponding to two additional time instants. From the values in the following table,

<table>
<thead>
<tr>
<th>( t )</th>
<th>( V )</th>
<th>( \dot{V} )</th>
<th>( \dddot{V} )</th>
<th>( P )</th>
<th>Using eqn.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.18</td>
<td>0.29</td>
<td>0.48</td>
<td>0</td>
<td>2.53</td>
<td>26</td>
</tr>
<tr>
<td>2.02</td>
<td>0.55</td>
<td>0</td>
<td>-0.89</td>
<td>2.55</td>
<td>26</td>
</tr>
<tr>
<td>2.87</td>
<td>0.29</td>
<td>-0.47</td>
<td>0</td>
<td>0.29</td>
<td>28</td>
</tr>
<tr>
<td>4.19</td>
<td>-0.03</td>
<td>0</td>
<td>0.16</td>
<td>-0.15</td>
<td>26</td>
</tr>
<tr>
<td>4.76</td>
<td>-0.02</td>
<td>0.02</td>
<td>0</td>
<td>-0.06</td>
<td>28</td>
</tr>
</tbody>
</table>

we can determine the unknowns:

\[ k = -0.13, E_0 = 4.98, E_1 = -2.24 \text{ and } E_2 = 0.21. \] (29)

Hence, by employing the nonlinear formulation,

\[ P_{el} = P_{el0} + E_0 e^{-kV}, \] (30)
we obtain the following expression for nonlinear lung compliance (or elastance):
\[
\frac{dP_{el}}{dV} = E = \frac{1}{C} = E_0 ke^{kV} = 0.65 e^{0.13V}.
\] (31)

Based on this expression, we obtain, for \( t = t_m \) and \( V = 0.29 \text{l} \):
\[
E = \frac{1}{C} = 0.67 \text{cmH}_2\text{O/l} \text{ and } C = 1.48 \text{l/cm H}_2\text{O}.
\] (32)

Equation (31) can now provide us a more realistic characterization of lung compliance as follows:
\[
\begin{align*}
\text{At } t &= 0 \text{ and } V = 0, \text{ we compute } E = \frac{1}{C} = 0.65 \text{ and } C = 1.53 \text{ cmH}_2\text{O/l} \\
\text{At } t &= t_m = 1.18 \text{s and } V = 0.29 \text{l}, E = \frac{1}{C} = 0.67 \text{ and } C = 1.48 \text{ cmH}_2\text{O/l} \\
\text{At } t &= t_v = 2.02 \text{s and } V = 0.551 \text{l and } E = \frac{1}{C} = 0.70 \text{ and } C = 1.43 \text{ cmH}_2\text{O/l}
\end{align*}
\] (33)

which corresponds to the value of \( C_a \).

Our nonlinear formulation of lung compliance, as depicted by eqns (31) and (33), indicates that compliance decreases from 1.53 cm H\textsubscript{2} O/l at the start of inspiration to 1.48 cm H\textsubscript{2} O/l at about mid-inspiration, and then to 1.43 cm H\textsubscript{2} O/l at the end of inspiration. What this also tells us is that the ventilatory model (1) gives the correct reading of the compliance at \( V_{max} \), i.e. at the end of inspiration. At other times of inspiration and expiration, the \( C_a \) parameter underestimates the instantaneous value of lung compliance. Now, we could also obtain an analytical solution of eqn. (25) for \( V(t) \), and fit the expression for \( V(t) \) to the lung-volume data, to evaluate the parameters

(i) \( R, E_0 \) and \( k \) for an intubated patient
(ii) \( R, E_0, k \) and \( P_1, P_2 \) and \( P_3 \) for a non-intubated patient in the out-patient clinic.

However, this is outside the scope of this chapter.

5 Work of breathing (WOB)

This is an important diagnostic index, especially if it can be obtained without intubating the patient and even without using the ventilator. The premise for determining WOB is that the respiratory muscles expand the chest wall during inspiration, thereby lowering the pleural pressure (i.e., making it more negative) below the atmospheric pressure to create a pressure differential from the mouth to the alveoli during inspiration. Then, during expiration, the lung recoils passively.

Hence, the work done during a respiratory life cycle, is given by the area of the loop generated by plotting lung volume (\( V \)) versus net driving pressure (\( P_p \)).
Figure 4: Plot of pressure versus volume. The area under the curve provides the work done.

This plot is shown in Fig. 4. Its area can be obtained graphically, as well as analytically as shown below:

\[
WOB = \int_0^T V dP_p(t) = \int_0^T V \frac{dP_p(t)}{dt} dt
\]  \hspace{1cm} (34)

\[
= \int_0^T \left( \sum_{i=1}^{3} P_i C_a \left[ \sin(\omega_i t + c_i) - \omega_i \tau_a \cos(\omega_i t + c_i) \right] \right) \left( 1 + \omega_i^2 \tau_a^2 \right) dt
\]

\[
= \sum_{i=1}^{3} -P_i C_a \frac{\cos(\omega_i t + c_i) + \omega_i \tau_a \sin(\omega_i t + c_i) - \cos c_i - \omega_i \tau_a \sin c_i}{\omega_i \left( 1 + \omega_i^2 \tau_a^2 \right)}.
\]  \hspace{1cm} (35)

The above expression for WOB can be evaluated, once the values of \( C_1 \) and \( \tau \) (or \( \omega \tau \)) and \( P_1 \), \( P_2 \) and \( P_3 \) and have been computed (as shown in the previous section). So let us substitute into this equation, the following values associated with eqn. (3).

\[
P_1 = 1.581 \text{ cmH}_2\text{O} \hspace{1cm} P_2 = -5.534 \text{ cmH}_2\text{O} \hspace{1cm} P_3 = 0.5523 \text{ cmH}_2\text{O}
\]

\[
\omega_1 = 1.214 \text{ rad/s} \hspace{1cm} \omega_2 = 0.001414 \text{ rad/s} \hspace{1cm} \omega_3 = 2.401 \text{ rad/s}
\]

\[
c_1 = -0.3132 \text{ rad} \hspace{1cm} c_2 = 3.297 \text{ rad} \hspace{1cm} c_3 = -2.381 \text{ rad}.
\]
We compute the value of WOB to be 0.9446 (cmH₂O) in 5 s, or 0.19 cmH₂O 1 s⁻¹ or 0.14 mmHg 1 s⁻¹ or 0.02 W, which is equivalent to an oxygen consumption of about 0.51 ml/min or about 0.18% of the resting \( \dot{V}_{O_2} \) of 28.87 ml/min. This value can be verified by calculating the value of the area of the pressure-volume loop in Fig. 4 which is equal to 0.8 cmH₂O.

6 Second-order model for single-compartment lung model

Let us now consider the dynamic (instead of static) equilibrium of a spherical segment of the lung model in Fig. 1, obtained as (by dividing throughout by the elemental lung area):

\[
m_s \ddot{u} + (P_p - P_a) + P_{elas} = 0,
\]

wherein: \( P_a \) and \( P_p \) are the alveolar and pleural pressures, \( u \) is the alveolar-wall displacement, \( m_s = \text{lung mass (M) per unit surface area} = M/4\pi R^2 \), (1b) and

\[
P_{elas} = \frac{2\sigma h}{R} = \frac{V}{C} + P_{elb},
\]

where:

(i) \( C \) is in l (cmH₂O)⁻¹
(ii) \( m_s \) (wall mass per unit surface area or surface density) = \( \rho \), \( \rho \) is the density (mass per unit volume)
(iii) \( \sigma \) is the wall stress
(iv) \( h \) and \( R \) are the wall thickness and radius of the equivalent-lung model.

Now, the displaced alveolar volume, \( V = \frac{4}{3}\pi (R + u)^3 \),

from which we get \( \ddot{V} \approx 4\pi R^2 \ddot{u} \).

Now, from eqn. (1), by putting

(i) \( P_p - P_a = (P_0 - P_0) + (P_p - P_0) \) and \( P_L = P_0 - P_p \),

so that \( P_p - P_a = P_0 - P_a - P_L = R\dot{V} - P_L \),

(ii) \( m_s \ddot{u} = \left( \frac{M}{4\pi R^2} \right) \left( \frac{\ddot{V}}{4\pi R^2} \right) = \frac{M \ddot{V}}{16\pi^2 R^4} = M^* \dot{V}; \quad M^* = \frac{M}{16\pi^2 R^4} \)

\[
= \frac{m_s}{4\pi R^2},
\]
we obtain, from eqns. (1), (2) and (3):

\[
M^* \ddot{V} + \left( P_0 - P_a \right) + \frac{V}{C} = P_L - P_{el_0}; \quad M^* = \frac{M}{16\pi^2 R^4} \left( = \frac{m_s}{4\pi R^2} \right). \quad (40)
\]

Now, putting \( P_0 - P_a = R \dot{V} \), we obtain:

\[
M^* \ddot{V} + R \dot{V} + \frac{V}{C} = P_L - P_{el0} = \sum_{i=1}^{3} P_i \sin (\omega_i t + c_i) - P_{el0}
\]

\[= P_N. \quad (41)\]

Since at the end of expiration when \( \omega_i T \) for \( i = 1 \) to \( 3 \) and \( P_L = P_{el0} \) so that \( P_{el0} = 0 \). In eqn. (6), we have:

wherein:

(i) \( M^* = m_s/4\pi R^2 = \rho_s h; \) \( \rho_s \) is the lung volume-density per unit surface area (in Kgm\(^{-3}\)) and \( M^* \) is in Kgm\(^{-4}\);

(ii) the clinical data in Fig. 2 is assumed to be represented by

\[
P_N(t) = \sum_{i=1}^{3} P_i \sin (\omega_i t + c_i) \quad \text{with} \quad (42)
\]

\[P_1 = 1.581 \text{ cmH}_2\text{O} \quad P_2 = -5.534 \text{ cmH}_2\text{O} \quad P_3 = 0.5523 \text{ cmH}_2\text{O}\]

\[\omega_1 = 1.214 \text{ rad/s} \quad \omega_2 = 0.001414 \text{ rad/s} \quad \omega_3 = 2.401 \text{ rad/s}\]

\[c_1 = -0.3132 \text{ rad} \quad c_2 = 3.297 \text{ rad} \quad c_3 = -2.381 \text{ rad}.\]

Then we can rewrite eqn. (6) as:

\[
\ddot{V} + \left( \frac{R}{M^*} \right) \dot{V} + \frac{V}{CM^*} = \sum_{i=1}^{3} \frac{P_i}{M^*} \sin (\omega_i t + c_i), \quad (43a)
\]

or as:

\[
\ddot{V} + 2n \dot{V} + p^2 V = \sum_{i=1}^{3} Q_i \sin (\omega_i t + c_i). \quad (43b)
\]

In the above equation:

(i) the damping coefficient, \( 2n = R/M^* \)

(ii) the natural frequency of the lung-ventilatory cycle, \( p^2 = 1/CM^* \)

(iii) \( Q_i = P_i/M^*. \quad (43c)\)

So the governing eqn. (8) of the lung-ventilatory response to the inhalation pressure has three parameters: \( M^*, R \) and \( C \) (if the lung pressure is also monitored by
intubating the patient). The solution of this equation is given by:

\[
V(t) = \sum_{i=1}^{3} \left\{ \left[ \frac{Q_i(-2\omega_i \cos(\omega_i t + c_i)n + \sin(\omega_i t + c_i)p^2 - \sin(\omega_i t + c_i)\omega_i^2)}{4n^2\omega_i^2 + p^4 - 2p^2\omega_i^2} 
- \frac{1}{2}Q_i \left( -n^2 - p^2 \right)^{1/2} c_i \sin(\omega_i^2 + p^2(n^2 - p^2)^{1/2} \sin c_i - 2\omega_i n^2 \cos c_i 
+ p^2 n \sin c_i - 2\omega_i n(n^2 - p^2)^{1/2} \cos c_i - \omega_i^3 \cos c_i + \omega_i^2 n \sin c_i 
+ \omega_i p^2 \cos c_i \right] e^{-\left( -\left( \frac{-p^2(n^2 - p^2)^{1/2}}{2} \right) \right)} \right\}
\]

\[
= \sum_{i=1}^{3} 1/2 \left[ \left[ -p^2(n^2 - p^2)^{1/2} \sin c_i + np^2 \sin c_i + \omega_i \cos c_i \omega_i^2 
+ \omega_i^2 n \sin c_i - 2\omega_i n^2 \cos c_i + 2\omega_i n(n^2 - p^2)^{1/2} \cos c_i 
+ \omega_i^2 (n^2 - p^2)^{1/2} \sin c_i - \omega_i^3 \cos c_i \left( -\left( \frac{-p^2(n^2 - p^2)^{1/2}}{2} \right) \right) \right] e^{-\left( -\left( \frac{-p^2(n^2 - p^2)^{1/2}}{2} \right) \right)} \right\}.
\]

We will ignore the exponential terms and perform parameters identification by matching the above expression for \(V(t)\) to the clinical data, shown in Fig. 2. The matching is illustrated in Fig. 5, wherein the first- and second-order differential equation solutions for \(V(t)\) are depicted. The computed values of the model parameters are also shown in the table below the figure. Further, the first- and second-order model values of \(R\) and \(C\) are compared in the table.

Let us compare these values with those obtained by simulating the first-order model to the clinical data.

7 Two-compartmental linear model

Now, it is possible that only one of the two lungs (or lung lobes) may be diseased. So, let us develop a procedure to distinguish between the normal lung and the pathological lung? We hence employ the 2-compartment model (based on our first-order differential equation of lung ventilatory function) to solve the problem of a two-lung model (schematized in Fig. 6).

For this purpose we make the subject breath at different values of frequency \((\omega)\), and monitor the total lung pressure \(P(t)\) (i.e., \(P_1\) and \(P_2\)) and total lung volume \(V(t)\). Correspondingly, we have \(P_1(t)\) and \(V_1(t)\) and \(P_2(t)\) and \(V_2(t)\) for the left and right lungs, respectively. The governing equations will be as follows
First order model  Second order model

\[ R \ [\text{cmH}_2\text{O}1^{-1}\text{s}] \quad 2.28 \quad 3.44 \]
\[ C \ [\text{l/cmH}_2\text{O}] \quad 0.21 \quad 0.85 \]
\[ M^* \ [\text{cmH}_2\text{O}1^{-1}\text{s}^2] \quad 3.02 \]
\[ n \left( = \frac{R}{M^*} \right) [\text{s}^{-1}] \quad 1.14 \]
\[ p^2 \left( = \frac{1}{CM^*} \right) [\text{s}^{-2}] \quad 0.39 \]

Figure 5: Results of single compartmental model based on differentiate equation formulation, compared with the first-order differential equation model.

(refer to Fig. 3)

\[ p^T = p^l = p^R, \quad \text{i.e.} \quad p^T_1 = p^l_1 = p^R_1 \quad \& \quad p^T_2 = p^l_2 = p^R_2 \quad (45) \]
\[ V^T = V^l + V^r \quad (46) \]

corresponding to \( \omega \); wherein

(i) \[ V^l(t) = f(\omega, R^l, C^l, P^T(t)) \quad (47) \]
(ii) \[ V^R(t) = f(\omega, R^r, C^r, P^T(t)). \quad (48) \]

In these equations (20),

(i) the variables \( \omega, P^T(t), V^T(t) \) are deemed to be known, i.e. monitored.
(ii) the parameters \( R^l, C^l, \) and \( R^r, C^r \) are to be evaluated.
Using the first-order differential equation model, (presented in sect. 2, as given by eqn. (6) or (14):

\[ V(t) = \sum_{i=1}^{3} \left( P_i C_l \frac{\left[ -\sin(\omega_l t + c_l) + \omega_l^2 \right] + \omega_l^2 \tau_l^2 \cos(\omega_l t + c_l)}{1 + \omega_l^2 \tau_l^2} \right). \]  \hspace{1cm} (49)

We put down the expression for \( V(t) = V^L(C_L, \tau_L) + V^R(C_R, \tau_R) \), match it with the volume data (using a parameter-identification technique (software), to obtain the values of \((C_L, \tau_L)\) and \((C_R, \tau_R)\) by means of which we can differentially diagnose left and right lung lobes' ventilatory capacities and associated disorders (or diseases).

### 7.1 Two compartmental model using first-order ventilatory model

Using eqn. (6) without the exponential term, we put down the expression for the total lung volume equal to the sum of left and right lung volumes, as follows:

\[ V(t) = \sum_{i=1}^{3} \left( P_i C_l \frac{\left[ \sin(\omega_l t + c_l) - \omega_l \tau_l \cos(\omega_l t + c_l) \right]}{1 + \omega_l^2 \tau_l^2} \right) \]

\[ + \sum_{i=1}^{3} \left( P_i C_l \frac{\left[ \sin(\omega_l t + c_l) - \omega_l \tau_l \cos(\omega_l t + c_l) \right]}{1 + \omega_l^2 \tau_l^2} \right). \]  \hspace{1cm} (50)
Two compartmental model

First order model

<table>
<thead>
<tr>
<th></th>
<th>Left lung</th>
<th>Right lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R ) [cmH(_2)O 1(^{-1}) s]</td>
<td>1.137</td>
<td>1.137</td>
</tr>
<tr>
<td>( C ) [l/cmH(_2)O]</td>
<td>0.1066</td>
<td>0.0533</td>
</tr>
<tr>
<td>( VTL_1 )</td>
<td>2.115</td>
<td>0.5289</td>
</tr>
<tr>
<td>( VTL_2 )</td>
<td>0.2198</td>
<td>1.0320</td>
</tr>
</tbody>
</table>

Figure 7: Results of the two-compartment model, based on the first-order differential equation model. Based on our assumption of \( TV^L / TV^R = 0.92 \) we have \( TV^L = 0.48 \times 0.48 = 0.2304 \) l and \( TV^R = 0.52 \times 0.48 = 0.2496 \) l.

wherein, for the clinical data, we have:

\[
\begin{align*}
P_1 &= 1.581 \text{ cmH}_2\text{O} \\
P_2 &= -5.534 \text{ cmH}_2\text{O} \\
P_3 &= 0.5523 \text{ cmH}_2\text{O} \\
\omega_1 &= 1.214 \text{ rad/s} \\
\omega_2 &= 0.001414 \text{ rad/s} \\
\omega_3 &= 2.401 \text{ rad/s} \\
c_1 &= -0.3132 \text{ rad} \\
c_2 &= 3.297 \text{ rad} \\
c_3 &= -2.381 \text{ rad}.
\end{align*}
\]

We further assume that the ratio of \( TV \) of the left lung to that of the right lung is 0.92.

Now, in order to develop a measure of confidence in our analysis, we first generate the total lung-volume data by assuming different values of \( C \) and \( R \) for left
Two compartmental model

First order model

<table>
<thead>
<tr>
<th></th>
<th>Left lung</th>
<th>Right lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R$ [cmH$_2$O 1$^{-1}$ s]</td>
<td>1.138</td>
<td>2.276</td>
</tr>
<tr>
<td>$C$ [l/cmH$_2$O]</td>
<td>0.1066</td>
<td>0.1066</td>
</tr>
<tr>
<td>$VTL_1$</td>
<td>2.1192</td>
<td>8.4766</td>
</tr>
<tr>
<td>$VTL_2$</td>
<td>0.3553</td>
<td>0.8341</td>
</tr>
</tbody>
</table>

Figure 8: Results of the two-compartment model, based on the first-order differential equation model. Based on our assumption of $TV^L/TV^R = 0.92$ we have $TV^L = 0.48 \times 0.61 = 0.2928 \text{l}$ and $TV^R = 0.52 \times 0.61 = 0.3172 \text{l}$.

and right lung lobes. We then use eqn. (50) along with the above data on pressure and frequency, to generate the total lung-volume data. We adopt this generated lung volume data as the clinical-volume data.

We now make our volume-solution expression (eqn. (50)) match this generated clinical-volume data, by means of the parameter-identification procedures, to evaluate $C$ and $R$ for the left and right lung-lobes and hence $VTL_1$ and $VTL_2$ (eqns. (11) and (18)) for these lobes. Based on the values of $VTL_1$ and $VTL_2$, we can differentially diagnose the left and right lung lobes.
7.1.1 Stiff right lung (with compliance problems)

We now simulate a normal left lung and stiff right lung, represented by:

\[ R^L = R^R = 1.14 \text{ cmH}_2\text{O l}^{-1} \text{ s and } C^L = 0.11, C^R = 0.051/\text{cmH}_2\text{O}. \]  (51)

Substituting these parametric values into eqn. (50), we generate the total lung-volume data, as illustrated in Fig. 7.

Now our clinical data for this two-compartment model comprises of the pressure data of Fig. 2 and the generated volume data of Fig. 6. For this clinical data, we match the volume solution given by eqn. (50) with the generated volume data, illustrated in Fig. 7, and carry our parameter identification. The computed values of \( R \) and \( C \), listed in the table of Fig. 7, are in close agreement with the initially assumed parametric values of eqn. (51). This lends credibility to our model and to our use of parameter-identification method.

Now for differential diagnosis, we compute the lung-ventilatory indices, as shown in the table in Fig. 7.

7.1.2 Right lung with \( R \) problems

Now, we simulate a lung with an obstructive right lung, as represented by:

\[ R^L = 1.14 \text{ and } R^R = 2.28 \text{ cmH}_2\text{O l}^{-1} \text{ s and } C_L = C_R = 0.11/\text{cmH}_2\text{O}. \]  (52)

As in the case of the stiff right lung, we first generate the lung-volume data for the above values of compliance and resistances. We then match the total lung-volume solution given by eqn. (50) with the generated lung-volume data, and compute the compliance and flow resistance values of the right and left lung. These are tabulated in Fig. 8, and found to have good correspondence with the assumed values of eqn. (52).
Chapter 4 Lung Air-Transfer Performance Analysis [1-4]

4.1 Motivation behind the Project

An outbreak of severe acute respiratory syndrome (SARS) began in Guangdong, China, on November 16, 2002. The first three SARS cases in Singapore were confirmed on March 6, 2003. By May 5, a total of 204 cases, including 27 deaths, had been confirmed. The last case was isolated on May 11, and by July 30, the end of the outbreak, 205 patients had recovered and 33 had died [5].

4.2 Objectives

The primary function of the lung is to (i) oxygenate the blood and thereby provide oxygen to the cells for metabolization purposes, and (ii) to remove the collected $CO_2$ from the pulmonary blood. Herein, we will analyze the compositions of the inspired and expired air per breath, and from there compute the $O_2$ consumption and $CO_2$ production rates. Next, we derive expressions for diffusion coefficients $D_{O_2}$ and $D_{CO_2}$ in terms of the evaluated cardiac-output, $O_2$ and $CO_2$ concentrations in arterial and venous blood, alveolar and blood $O_2$ and $CO_2$ partial-pressures. We then take up a typical case study, and demonstrate the computation of $D_{O_2}$ and $D_{CO_2}$, to represent the lung performance capability to oxygenate the blood.

4.3 Respiratory System

The respiratory system is the system of the body that deals with breathing. When we breathe, the body takes in the oxygen that it needs and removes the carbon dioxide that it doesn't need.

First the body breathes in the air which is sucked through the nose or mouth and down through the trachea (windpipe). The trachea is a pipe shaped by rings of cartilage. It divides into two tubes called bronchi. These carry air into each lung.
Inside the lung, the tubes divide into smaller and smaller tubes called bronchioles. At the end of each of these tubes are small air sacs called alveoli.
Capillaries, which are small blood vessels with thin walls, are wrapped around these alveoli. The walls are so thin and close to each other that the air easily seeps through. In this way, oxygen seeps through into the bloodstream and carbon dioxide, in the bloodstream, seeps through into the alveoli, and is then removed from the body when we breathe out.

4.3.1 Exchange of Carbon Dioxide and Oxygen

The lung is for gas exchange. Its prime function is to allow oxygen to move from the air into the venous blood and carbon dioxide move out. It also metabolises some compounds, filters toxic materials from the circulation, and acts as a reservoir for blood. But its key function is to exchange gas.
4.3.2 Blood-Gas Interface

Oxygen and carbon dioxide move between air and blood by simple diffusion. Fick’s law of diffusion states that the amount of gas which moves across a sheet of tissue is proportional to the area of sheet but inverse proportional to its thickness. The blood-gas barrier is about 0.5µm and has an area of between 50 and 100 m².

The prodigious surface area for diffusion inside the limited cavity is obtained by wrapping the capillaries around an enormous number of alveoli as shown in figure 4-5. There are about 300 million alveoli in the human lung, each about \( \frac{1}{3} \) mm in diameter. If they were spherical, their total surface area would be 85 m², but their volume only 4 litres.

Gas is brought to one side of the blood-gas interface by airways and blood to the other side by blood vessels.
Figure 4.4 Electron micrograph showing a pulmonary capillary (C) in the alveolar wall. The blood-gas barrier is less than 0.5 µm. The large arrow indicates the diffusion path from alveolar gas to the interior of the erythrocyte (EC) and includes the layer of surfactant (not shown), alveolar epithelium (EP), interstitium (IN), capillary endothelium (EN) and plasma. Parts of structural cells called fibroblasts (FB), basement membrane (BM), and a nucleus of an endothelial cell are also seen. [ER Weibel: Respiration Physiology 11:54, 1970.]
Figure 4.5 Section of the lung showing many alveoli and a small bronchiole. The pulmonary capillaries run in the walls of the alveoli (previous figure). The holes in the alveolar walls are the pores of Kohn. [Scanning electron micrograph by JA Nowell and WS Tyler].
Figure 4.6 Cast of the airways of a human lung. The alveolo have been pruned away, but the conducting airways from the trachea to the terminal bronchioles can been seen.
4.3.3 Airways and Air Flow

The airways consists of a series of branching tubes which become narrower, shorter and more numerous as they penetrate deeper into the lung (Figures 4.3 and 4.6). The trachea divides into right and left main bronchi, which in turn divide into lobar, then segmental bronchi. This process continues down to the terminal bronchioles, which are the smallest airways without alveoli. All these bronchi make up the conducting airways. Their function is to lead inspired air to the gas exchanging regions of the lung (Figure 4.7). Since the conducting airways contain no alveoli and therefore they take no part in gas exchange, they constitute the anatomic dead space. Its volume is about 150 ml.

![Diagram of human airways]

**Figure 4.7** Idealization of the human airways according to Weibel. Note that the first 16 generations (Z) make up the conducting airways and the last 7 the respiratory zone (or the transitional and respiratory zone). BR, bronchus; BL, bronchioles; TBL, terminal bronchiole; RBL, respiratory bronchiole; AD, alveolar duct; AS, alveolar sac. [ER Weibel, Morphometry of the Human Lung. Berlin, Spring-Verlag, 1963, p 111].

The terminal bronchioles divide into respiratory bronchioles which have occasional alveoli budding from their walls. Finally, we come to the alveolar ducts completely lined with alveoli. This alveolated region of the lung where the gas exchange occurs is known as the respiratory zone. The portion of the lung distal to a terminal bronchiole forms an anatomical unit called the primary lobule or, better, the acinus. The distance
from the terminal bronchiole to the most distal alveolus is only about 5 mm, but the respiratory zone makes up most of the lung, its volume being about 3000 ml.

During inspiration, the volume of the thoracic cavity increases and air drawn into the lung. The increase in volume is brought about partly by contraction of the diaphragm, which causes it to descend, and partly by the action of the intercostals muscles, which raise the ribs, thus increasing the cross-sectional area of the thorax. Inspired air flows down to about the terminal bronchioles by the bulk flow, like water through a hose. Beyond that point, the combined cross-sectional area of the airways is so enormous because of the large number of branches (Figure 4-8) that the forward velocity of the gas becomes very small. Diffusion of gas within the airways then takes over as the dominant mechanism of ventilation in the respiratory zone. The rate of diffusion of gas molecules within the airways is so rapid, and the distances to be covered are so short, that differences in concentration within the acinus are virtually abolished within a second. However, because the velocity of gas falls rapidly in the region of the terminal bronchioles, inhaled dust frequently settles out there.

The lung is elastic and returns passively to its pre-inspiratory volume during resting breathing.
Figure 4.8 Diagram to show the extremely rapid increase in total cross-sectional area of the airways in the respiratory zone (compare with the previous figure). As a result, the forward velocity of the gas during inspiration becomes very small in the region of the respiratory bronchioles, and gaseous diffusion becomes the chief mechanism of ventilation.

The pressure required to move gas through the airways is very small. During normal inspiration, an air flow rate of 1 litre/sec requires a pressure drop along the airways of less than 2 cm water. Compare a smoker’s pipe which needs a pressure of about 500 cm water for the same flow rate.
Figure 4.9 View of an alveolar wall (in a frog) showing the dense network of capillaries. A small artery (left) and vein (right) can be seen. The individual capillary segments are so short that the blood forms an almost continuous sheet. [JE Maloney and BL Castle, Respiratory Physiology 7:150, 1969].
4.3.4 Blood Vessels and Flow

The pulmonary blood vessels also form a series of branching tubes from the pulmonary artery to the capillaries and back to the pulmonary veins. Initially the arteries, veins, and bronchi run close together, but toward the periphery of the lung, the veins move away to pass between the lobules, whereas the arteries and bronchi travel together down the centers of the lobules. The capillaries form a dense network in the walls of the alveoli (Figure 4.9). The diameter of a capillary segment is about 10 $\mu m$, just large enough for a red blood cell. The lengths of the segments are so short that the dense wall, a vernetwork forms an almost continuous sheet of blood in the alveolar wall, a very efficient arrangement for gas exchange. Alveolar walls are not often seen face on, as in Figure 4.9. The usual microscopic cross-section (Figure 4.10) shows the red blood cells in the capillaries and emphasizes the enormous exposure of blood to alveolar gas, with only the thin blood-gas barrier intervening (compare Figure 4.4).
The pulmonary artery receives the whole output of the right heart, but the resistance of the pulmonary circuit is astonishingly small. A mean pulmonary arterial pressure of only 20 cm water is required for a flow of 6 litres/min. (The same flow through a soda straw need 120 cm water.)

Each red blood cell spends about $\frac{3}{4}$ sec in the capillary network and during this time probably transverses two or three alveoli. So efficient is the anatomy for gas exchange that this brief time is sufficient for virtually complete equilibration of oxygen and carbon dioxide between alveolar gas and capillary blood.

The lung has an additional blood system, the bronchial circulation, which supplies the conducting airways down to about the terminal bronchioles. Most of this blood is carried away from the lung via the pulmonary veins. The flow through the bronchial circulation is a mere fraction of that through the pulmonary circulation, and the lung can function fairly.

4.3.5 Ventilation

![Diagram of a lung showing typical volume and flows. There is a considerable variation around these values. [John B West, Respiratory Physiology, 3rd ed., 1984].](image)

The above figure is a highly simplified diagram of a lung. The various bronchi which make up the conducting airways as shown in Figure 4.6 are now represented by a single tube labeled anatomic dead space. This leads into the gas exchanging region of the lung which is bounded by the blood-gas interface and the pulmonary capillary
blood. With each inspiration, about 500 ml of air enter the lung (tidal volume). Note how small a proportion of the total lung volume is represented by the anatomical dead space. Also note the very small volume of capillary blood, compared with that of alveolar gas (compare Figure 4.10).
4.3.6 Anatomic Dead Space

This is the volume of the conducting airways (Figures 4-6 and 4-7). The normal value is about 150 $ml$, it increases with large inspirations because of the traction exerted on the bronchi by the surrounding lung parenchyma. The dead space also depends on the size and posture of the subject; a rule of thumb is that the volume in milliliters of the seated subject is approximately equal to the body weight in pounds.

4.3.7 Diffusion

Fick’s Law states that the rate of transfer of a gas through a sheet of tissue is proportional to the tissue area and the difference in gas partial pressure between the two sides, and inversely proportional to the tissue thickness.

![Figure 4.12 Diffusion through a tissue sheet. The amount of gas transferred is proportional to the area, a diffusion constant, and the difference in partial pressure, and is inversely proportional to the thickness. The constant is proportional to the gas solubility but inversely proportional to the square root of its molecular weight.](image)

From the above figure, the area of the blood-gas barrier in the lung is enormous (50-100 $m^2$), and the thickness is less than $\frac{1}{2} \mu m$ (refer to Figure 4.4), so the dimensions of the barrier are ideal for diffusion. In addition, the rate of transfer is proportional to a diffusion constant which depends on the properties of the tissue and the particular gas. The constant is proportional to the solubility of the gas and inversely proportional to the square root of the molecular weight. This means that $CO_2$ diffuses about 20 times more rapidly than $O_2$ through tissue sheets since it has a much higher solubility but not a very different molecular weight.
4.3.8 Diffusion and Perfusion Limitations

The figure below shows the time courses as a red blood cell (RBC) moves through the capillary, a process which takes about ¾ sec.

First, let's take a look what happens when the gas is carbon monoxide. When the RBC enters the capillary, carbon monoxide (CO) moves rapidly across the extremely thin blood-gas barrier from the alveolar gas into the cell. As a result, the content of CO in the cell rises. However, because of the tight bond which forms between CO and hemoglobin within the cell, a large amount of CO can be taken up by the cell with almost no increase in partial pressure. Thus, as the cell moves through the capillary, the CO partial pressure in the blood hardly changes so that no appreciable back pressure developed, and the gas continues the move rapidly across the alveolar wall. Therefore, the amount of CO which gets into the blood is limited by the diffusion properties of the blood-gas barrier and not by the amount of blood available. The transfer of CO is diffusion limited.

![Figure 4.13](image)

**Figure 4.13** Uptake of carbon monoxide, nitrous oxide, and O₂ along the pulmonary capillary. Note that the blood partial pressure of nitrous oxide virtually reaches that of alveolar gas very early in the capillary so that the transfer of this gas is perfusion limited. By contrast, the partial pressure of carbon monoxide in the blood is almost unchanged so that its transfer is diffusion limited. O₂ transfer can be perfusion or partly diffusion limited depending on the conditions.
Next let’s take a look at nitrous oxide (N\textsubscript{2}O). When this gas moves across the alveolar wall into the blood, no combination with hemoglobin takes place. As a result the blood has nothing like the avidity for N\textsubscript{2}O that it has for CO and the partial pressure rises rapidly. From the above figure, the partial pressure of N\textsubscript{2}O in the blood has virtually reached that of the alveolar gas by the time the RBC is only 1/10 of the way along the capillary. Thus the amount of this gas taken up by the blood depends entirely on the amount of blood flow and not at all on the diffusion properties of the blood-gas barrier. The transfer of N\textsubscript{2}O is therefore perfusion limited.

Lastly, let’s take a look at what happens when the gas is O\textsubscript{2}. Its time course lies between that of CO and N\textsubscript{2}O. O\textsubscript{2} combines with hemoglobin (unlike N\textsubscript{2}O) but with nothing like the avidity of CO. In other words, the rise in partial pressure when O\textsubscript{2} enters a RBC is much greater than is the case for the same number of molecules of CO. Under typical resting conditions, the capillary \(P_{O_2}\) virtually reaches that of alveolar gas when the RBC is about 1/3 of the way along the capillary. Under these conditions, O\textsubscript{2} transfer is perfusion limited like N\textsubscript{2}O.
Figure 4.14 Oxygen time courses in the pulmonary capillary when diffusion is normal and abnormal (for example, because of thickening of the alveolar membrane). A shows time courses when the alveolar $P_{O_2}$ is normal. B shows slower oxygenation when the alveolar $P_{O_2}$ is abnormally low. Note that in both cases, severe exercise reduces the time available for oxygenation.

However, in some abnormal circumstances (as shown in the above figure) when the diffusion properties of the lung are impaired, for example, because of thickening of the alveolar wall, $P_{O_2}$ does not reach the alveolar value by the end of the capillary, and now there is some diffusion limitation as well.

4.3.9 Carbon Dioxide (CO$_2$) Transfer Along the Pulmonary Capillary

In the section 4.3.9, we have seen that the rate of diffusion of CO$_2$ through tissue is about 20 times faster than that of O$_2$ because of the much higher solubility of CO$_2$. It is possible that a difference between end-capillary blood and alveolar gas can develop if the blood-gas barrier is diseased.
Figure 4.15 Calculated changes in $P_{CO_2}$ along the capillary when the diffusion properties are normal and abnormal (compare the time course of $P_{O_2}$ in Figure 4.14). [PD Wagner and JB West, J Appl Physiol 33:62, 1972].

The above figure shows that the normal time course for CO$_2$ and how it might be affected by thickening of the blood-gas barrier. Note that the $P_{CO_2}$ of the blood as it enters the capillary is about 45mmHg and that the normal $P_{CO_2}$ of alveolar gas is about 40mmHg. It can be seen that the time taken for the blood to reach virtually the same partial pressure as alveolar gas is similar to that for O$_2$ under normal conditions (Figure 4.14), so that there are good reserves of diffusion. However when the diffusing capacity of the membrane is reduced to about $\frac{1}{4}$ of its normal value, a small difference between end-capillary blood and alveolar gas may be seen.
4.4 Author’s work Lung Air Composition Analysis (and $O_2$ consumption and $CO_2$ production rates) [3-4]

The lung functional performance is characterized by (i) its ventilatory capacity, to bring air (and hence $O_2$) into the alveoli, and (ii) its capacity to transfer $O_2$ and $CO_2$ into and from the pulmonary capillary bed. Hence, the $O_2$ and $CO_2$ diffusion coefficients as well as the $O_2$ consumption-rate and the $CO_2$ production rate represent the lung performance indices.

We carry out a mass balance analysis, involving:

(i) compositions of air breathed in and out

(ii) consumption or losses of $O_2$, $CO_2$ and $H_2O$.

The Table 4.1 below provides clinical data on partial pressures and volumes of $N_2$, $O_2$, $CO_2$ and $H_2O$ of atmospheric air breathed in and expired air, of one breath cycle. The monitored breathing rate (BR) = 12 breaths/min, at each breath 500ml of air is inspired and we assume $P_{H2O}$ at 37°C = 47mmHg.

**Table 4.1** Inspired air composition and partial pressures. (i) We first compute the volume of expired air compositions, (ii) their pressures based on percent volume.

<table>
<thead>
<tr>
<th>Respiratory gases</th>
<th>Atmospheric Air</th>
<th>Expired Air</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmHg</td>
<td>ml/%</td>
</tr>
<tr>
<td>$N_2$</td>
<td>597</td>
<td>393.1</td>
</tr>
<tr>
<td>$O_2$</td>
<td>159</td>
<td>104.2</td>
</tr>
<tr>
<td>$CO_2$</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>$H_2O$</td>
<td>3.7</td>
<td>2.5</td>
</tr>
<tr>
<td>Total</td>
<td>760</td>
<td>500</td>
</tr>
</tbody>
</table>

It can be noted that the expired air volume exceeds the inspired air volume for this particular breath cycle. The $H_2O$ loss of 30.1ml (=32.6ml - 2.5ml) contributes to the major portion of this difference.
Note: Water vapor in atmospheric air or inspired air is 0.49% expired air is 6.2%.

In expired air, $393.1 + 80.6 + 19.1 = 492.8\, \text{ml}$
Water vapor in expired air = $47\, \text{mmHg} / 713\, \text{mmHg} \times 492.8 = 32.4$

**4.4.1 Calculation of $O_2$ Consumption-Rate and $CO_2$ Production-Rate**

We now determine the $O_2$ consumption rate and $CO_2$ production rates from the inspired and expired gases

Assuming the patient breathes at 12 times per minute (and 500 $\text{ml}$ of air at each breadth), we have

$O_2$ Consumption Rate $= (\text{Inspired } O_2 - \text{Expired } O_2) \times 12$

$= (104.2-80.6) \times 12$

$= 283.2\, \text{ml/min}$

$CO_2$ Production Rate $= (\text{Expired } CO_2 - \text{Inspired } CO_2) \times 12$

$= (19.1-0.2) \times 12$

$= 226.8\, \text{ml/min}$

The amount of water vapor in the humidified expired air amounts to 6.2% of the expired air (compared to 0.49% of the dry inspired air) corresponding to partial pressure ratio of water vapor in the expired air ($= 47/760$). The volume of the dry expired air = $(525.3-32.6)\, \text{ml} = 492.7\, \text{ml}$.

Now, assume that out of 500 $\text{ml}$ of inspired air, the dead space air volume (not taking part in gas transfer process) is 150 $\text{ml}$ and the alveolar air volume is 350 $\text{ml}$. We next compute the dead space air volume composition.
4.4.2 Dead Space Air Composition

The clinical data of expired air composition is:

\[
\begin{align*}
N_2 &= 393.1 ml \\
O_2 &= 83.36 ml \\
CO_2 &= 16.87 ml \\
H_2O &= 34.15 ml
\end{align*}
\]

Total 527.49 ml

Now, the dead-space air will be made up of (i) dry air portion from the inspired air (assumed to be of amount=141ml), plus (ii) the water vapor taken up by the dry air (estimated to be =9ml) since the expired air portion of 141ml will not have undergone \( O_2 \) and \( CO_2 \) transfer, it’s composition is the same as that of inspired air:

\[
\begin{align*}
N_2 &= 111ml \ (78.55\%), \\
O_2 &= 29.40ml \ (20.84\%), \\
CO_2 &= 0.06ml \ (0.04\%), \\
H_2O &= 0.69ml \ (0.49%).
\end{align*}
\]
When this inspired air (in the dead space) of 141 ml is fully humidified, it will take up a further \( X \) ml of \( H_2O \) vapour, in the ratio of the partial-pressures, as:

\[
\frac{X}{141} = \frac{47}{713} = 0.0659
\]

\[
\therefore X = 0.0659 \times 141 = 9.29 \text{ml of } H_2O \text{ vapour (which is close to our estimate).}
\]

So, by adding 9.29 ml of \( H_2O \) vapour to 0.69 ml of water vapour in the inspired portion of dead-space air volume of 141 ml, the total water vapour in the dead-space air is 9.98 ml. The humified dead-space air composition will be:

\[
\begin{align*}
N_2 & = 111.00 \text{ml} \quad (=73.78\%) \\
O_2 & = 29.40 \text{ml} \quad (=19.55\%) \\
CO_2 & = 0.06 \text{ml} \quad (=0.04\%) \\
H_2O & = 9.98 \text{ml} \quad (=6.63\%) \\
\text{Total} & = 150.44 \text{ml}
\end{align*}
\]

### 4.4.3 Alveolar Air Composition and Partial Pressures

We can now compute the alveolar air composition, by subtracting the dead-space air from expired air. These values are tabulated in column 4 of the below Table.

**Table 4.2** The alveolar air composition.

<table>
<thead>
<tr>
<th></th>
<th>Expired Air (ml)</th>
<th>Dead Space Air (ml)</th>
<th>Alveolar Air (ml)</th>
<th>Alveolar Air Partial Pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( N_2 )</td>
<td>393.1 ml</td>
<td>111.00 ml</td>
<td>282.1 ml</td>
<td>569.41 \text{mmHg}</td>
</tr>
<tr>
<td>( O_2 )</td>
<td>80.53 ml</td>
<td>29.40 ml</td>
<td>51.13 ml</td>
<td>103.21 \text{mmHg}</td>
</tr>
<tr>
<td>( CO_2 )</td>
<td>19.12 ml</td>
<td>0.06 ml</td>
<td>19.06 ml</td>
<td>38.47 \text{mmHg}</td>
</tr>
<tr>
<td>( H_2O )</td>
<td>34.21 ml</td>
<td>9.98 ml</td>
<td>24.23 ml</td>
<td>48.91 \text{mmHg}</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>526.96 ml</td>
<td>150.44 ml</td>
<td>376.52 ml</td>
<td>760 \text{mmHg}</td>
</tr>
</tbody>
</table>

Finally, we compute the partial pressure of \( O_2 \) and \( CO_2 \) (as well as of \( N_2 \) and \( H_2O \)), so that we can determine next the diffusion coefficients of \( O_2 \) and \( CO_2 \) based on the monitoring of arterial and venous blood concentrations. These values are tabulated in column 5 of the above Table.
4.5 Lung Gas-Exchange Model & Parametric Analysis

4.5.1 Expressions for $D_{O_2}$ and $D_{CO_2}$

The gas exchange between the alveolar air and pulmonary capillary blood is represented by the following $O_2$ and $CO_2$ conservation equations (figure 2):

$$Q^{VE}C_{O_2} = Q^{AE}C_{O_2} + V O_2$$  (from the alveolar air to capillary blood)

$$Q^{VE}C_{CO_2} = Q^{AE}C_{CO_2} - V CO_2$$  (from capillary blood to alveoli)

in which $P_{O_2}^{cap} = P_{O_2}^{PRB}$  (O$_2$ concentration of the pre-oxygenated blood)

wherein

(i) $Q^{AB}$ and $Q^{VB}$ are arterial and venous blood flow-rates

$Q^{AB} = Q^{VE}$  (at venous end),  $Q^{VB} = Q^{AE}$  (at arterial end);

(ii) $P_{O_2}^{al}$ and $P_{O_2}^{cap}$ are the alveolar and capillary $O_2$ partial pressures;

(iii) $P_{CO_2}^{al}$ and $P_{CO_2}^{cap}$ are the alveolar and capillary $CO_2$ partial pressures;

(iv) $D_{O_2}$ and $D_{CO_2}$ are the $O_2$ and $CO_2$ diffusion coefficients, defined in the caption of figure 2;

(v) $\Delta P_{O_2}^{av}$ = average of $(P_{O_2}^{al} - P_{O_2}^{cap})$ over the capillary length

$\Delta P_{CO_2}^{av}$ = average of $(P_{CO_2}^{al} - P_{CO_2}^{cap})$ over the capillary length;

(vi) $V O_2$ is the $O_2$ transfer rate from alveolar air to capillary blood (= $O_2$ consumption rate), $V_{CO_2}$ is the $CO_2$ transfer-rate from capillary blood at arterial end to alveolar air.

Now we can equate the arterial and venous blood flow rates, as

$$Q^{AB} = Q^{VB} = (SV)/(EP) = CO / 60$$

SV, EP and CO being the stroke-volume (in cc), ejection-period (in secs) and cardiac-output (in cc or ml per sec) respectively. Hence the above equations can be rewritten as:

283
We define diffusing capacity of gas across the alveolar-capillary membrane as

$$D = \frac{\text{Volume-rate of transfer of gas}}{\text{Average partial pressure difference of the gas}} = \frac{\dot{V}}{\Delta P_{av}}$$

For instance for $O_2$, $D_{O_2} = \frac{\dot{V}_{O_2}}{\Delta P_{av}}$ from alveolar air to blood ($ml/min$)

We will refer to $D_{O_2}$ as diffusion coefficient of $O_2$ ($21ml/min/mmHg$)

For example, $D_{O_2} = \frac{252 ml/min}{12 mmHg} = 21 ml/min/mmHg$

$V_{O_2}$ is the $O_2$ consumption rate, which can either be obtained from inspired and expired compositions or from $Q(O_{2}^{AB} - O_{2}^{A}) = Q(O_{2}^{VE} - O_{2}^{A})$.

From equation (1):

$$Q^{VE}C_{O_2} = Q^{AB}C_{O_2}^{AB} + (\Delta P_{O_2})D_{O_2}$$

$$Q = Q^{AB}C_{O_2}^{AB}$$

$$Q^{VE}C_{O_2} = Q^{AB}C_{O_2}^{AB} + (\Delta P_{O_2})D_{O_2}$$

$$D_{O_2} = \frac{Q_{O_2}(C_{O_2}^{VE} - C_{O_2}^{A})}{(\Delta P_{O_2})} = \frac{Q_{O_2}(C_{O_2}^{AB} - C_{O_2}^{A})}{(\Delta P_{O_2})} = \frac{\dot{V}_{O_2}}{\Delta P_{av}}$$

wherein $\dot{V}_{O_2}$ is the oxygen consumption rate.
From equation (2):

\[ Q^{\text{VE}}_{\text{CO}_2} = Q^{\text{AE}}_{\text{CO}_2} - (\Delta P_{\text{CO}_2}) D_{\text{CO}_2}; \quad P_{\text{CO}_2}^{\text{cap}} = P_{\text{CO}_2}^{\text{TB}} \]

\[ Q^{\text{VE}}_{\text{O}_2} = Q^{\text{AE}}_{\text{O}_2} - (\Delta P_{\text{O}_2}) D_{\text{CO}_2} \]

\[ D_{\text{CO}_2} = \frac{Q(C^{\text{VE}}_{\text{CO}_2} - C^{\text{AE}}_{\text{CO}_2})}{(\Delta P_{\text{CO}_2})} = \frac{V_{\text{CO}_2}^o}{\Delta P_{\text{CO}_2}} \]  \hspace{1cm} (4)

wherein \( V_{\text{CO}_2} \) is the carbon dioxide production rate.

In equations (3) & (4):

(i) \( Q, \, C^{\text{VE}}_{\text{O}_2} \) and \( C^{\text{AE}}_{\text{O}_2} \) can be monitored because

\[ C^{\text{VE}}_{\text{O}_2} \, \& \, C^{\text{VE}}_{\text{CO}_2} = C^{\text{AE}}_{\text{O}_2} \, \& \, C^{\text{AE}}_{\text{CO}_2} \] \hspace{1cm} (i)

(ii) \( D_{\text{O}_2} \) and \( D_{\text{CO}_2} \) represent the lung gas-exchange parameters.

(iii) \( \Delta P_{\text{O}_2} \) and \( \Delta P_{\text{CO}_2} \) need to be determined in terms of \( (P_{\text{O}_2}^{\text{al}} \, \& \, P_{\text{O}_2}^{\text{TB}}) \) and \( (P_{\text{CO}_2}^{\text{al}} \, \& \, P_{\text{CO}_2}^{\text{TB}}) \) respectively, in order to be able to evaluate \( D_{\text{O}_2} \) and \( D_{\text{CO}_2} \).

(iv) \( P_{\text{O}_2}^{\text{al}} \) itself depends on \( V_{\text{O}_2}^o \) and ventilation-rate \( V_o \);

\[ P_{\text{CO}_2}^{\text{al}} \] itself depends on \( V_{\text{CO}_2}^o \) and ventilation-rate \( V_o \).

(v) \( P_{\text{O}_2}^{\text{TB}} \) depends on \( C_{\text{O}_2}^{\text{TB}} \)

\( P_{\text{CO}_2}^{\text{TB}} \) depends on \( C_{\text{CO}_2}^{\text{TB}} \)

Now from equations (3) & (4), if we want to evaluate the diffusion coefficients \( D_{\text{O}_2} \) and \( D_{\text{CO}_2} \), we need to also express \( P_{\text{O}_2}^{\text{al}}, \, P_{\text{O}_2}^{\text{cap}} \) and \( P_{\text{CO}_2}^{\text{al}}, \, P_{\text{CO}_2}^{\text{cap}} \) in terms of monitorable quantities. In this regard,

(i) Alveolar \( P_{\text{O}_2}^{\text{al}} \) can be expressed in terms of \( V \) (the ventilation rate) and \( V^o \) (the \( O_2 \) consumption rate) as Figure 4.18:

\[
P_{\text{O}_2}^{\text{al}} \text{(in mmHg)} = k_1 \left[ -k_2 \left( \frac{V^o}{V_m} \right) \frac{V^o}{V^o} \right] \]

\[
1 - e^{\left( \frac{V}{V_m} \right)} \]  \hspace{1cm} (5)
where \( V_m \) is the maximum ventilation rate and \( V_{O_2}^* \) (the \( O_2 \) consumption rate or absorption rate from the alveoli) = \( Q(C_{O_2}^{AB} - C_{O_2}^{VB}) \). Equation (5) implies that as \( \left( \frac{V}{V_m} \right) \) increases, (the exponential term decreases, and) \( P_{O_2}^{al} \) increases (as in Figure 4.18), and as \( V_{O_2}^* \) increases \( P_{O_2}^{al} \) decreases (as in Figure 4.18).

**Figure 4.18** Effect on alveolar \( P_{O_2} \) of (i) Alveolar ventilation \( (V_{O_2}^*) \), and (ii) rate of Oxygen absorption from alveolar \( P_{O_2} \) or \( O_2 \) consumption rate, \( V_{O_2}^* \) [From Guyton (1971), p. 476]. This relationship is expressed by equation by equation (5).

(ii) Alveolar \( P_{CO_2}^{al} \) can be expressed in terms of \( V \) and \( V_{O_2}^* \) as in Figure 4.19.

\[
P_{CO_2}^{al} \ (\text{in } mmHg) = k_3 e^{-k_d \left[ \left( \frac{V}{V_m} \right) / V_{CO_2}^* \right]} \tag{6}
\]

where \( V_{CO_2}^* \) (the \( CO_2 \) production rate or excretion rate from the blood) = \( Q(C_{CO_2}^{VB} - C_{CO_2}^{AB}) \).
Figure 4.19 Effect on alveolar $P_{CO_2}$ of Alveolar ventilation and rate of Carbon dioxide excretion from the blood or $CO_2$ production rate, $V_{CO_2}$. [From Guyton (1971), p. 476].

This relationship is expressed by equation by equation (6).

This equation implies that as $V/V_m$ increases, $P_{CO_2}^{al}$ decreases; also, as $V_{CO_2}$ increases (the exponential term decreases, and hence) $P_{CO_2}^{al}$ increases, as per figure 4.

(iii) Blood $P_{O_2}$ can be obtained in terms of blood $C_{O_2}$, from the $O_2$ disassociation curve (providing concentrations in arterial or venous blood, as represented in Figure 4.20.) as:

$$C_{O_2} (ml/100ml) = C_{O_2}^m (1 - e^{-k_5 P_{O_2}^m}), \text{ or } C_{O_2}^* = 1 - e^{-k_5 P_{O_2}^*}$$

(7)

where

- $C_{O_2}^m$ and $P_{O_2}^m$ are the maximum values of blood $O_2$ concentration and partial, respectively pressure
- $C_{O_2}^* = C_{O_2} / C_{O_2}^m$
- $P_{O_2}^* = P_{O_2} / P_{O_2}^m$
Figure 4.20 $O_2$ dissociation curves, showing the total oxygen in each 100 ml of normal blood, the portion dissolved in the water of the blood [From Guyton (1971), p. 485]. We will adopt oxygen concentration units to be (ml of $O_2$/100 ml of blood), and hence we will divide the numbers on the y-axis by 100.

(iv) Blood $P_{CO_2}$ can be obtained in terms of $C_{CO_2}$, from the $CO_2$ disassociation curve (providing $CO_2$ concentration in arterial or venous blood, as represented in Figure 4.21) as:

\[
C_{CO_2}^{(ml/100ml)} = C_{CO_2}^m (1 - e^{-k_6 (P_{CO_2}/P_{CO_2}^m)})
\]

or, $C_{CO_2}^* = 1 - e^{-k_6 (P_{CO_2}/P_{CO_2}^m)} = 1 - e^{-k_6 P_{CO_2}^*}$

(8)
Figure 4.21 The carbon dioxide dissociation curve [From Guyton (1971), p. 491]. We will adopt carbon dioxide concentration units to be (ml of CO\textsubscript{2}/100 ml of blood), and hence we will divide the numbers on the y-axis by 100.

4.5.2 Alveolar \( O_2 \) and \( CO_2 \) Partial Pressure Expressions

We will now quantify the earlier mentioned empirical expressions of \( P_{O_2}^{al} \) and \( P_{CO_2}^{al} \) in equations (5) and (6).

(a) Now, let us refer equation (5) for the \( P_{O_2}^{al} \) partial pressure curve (Figure 4.18), represented by the equation:

\[
P_{O_2}^{al} = k_1 \left[ 1 - e^{-k_2 \left( \frac{V \circ}{V_m} / V \circ_{O_2} \right)} \right]
\]

\[
= k_1 \left[ 1 - e^{-k_2 \left( \frac{\circ^*}{V / V_{O_2}} \right)} \right], \text{ where } V = \frac{V}{V_m}
\]  \( (9) \)
wherein \( V \) is the alveolar ventilation rate (in liters/min), \( V_m \) is the maximum ventilation rate (= 50 liters/min) and \( V_{O_2} \) is the \( O_2 \) consumption rate (in liters/min). Herein, the coefficients \( k_1 \) and \( k_2 \) can be determined by having this equation match the Figure 4.18 data. Note, in this equation, when \( V = 0 \), \( P_{O_2}^{al} = 0 \) from the equation, which satisfies the data.

In Figure 3 for \( V_{O_2} = 0.25 \) liters/min, when \( V = \frac{V_{O_2}}{V_m} = 0.5 \), \( P_{O_2}^{al} = 140 \) mmHg. Hence,

\[
140 = k_1 \left[ 1 - e^{-k_2 \left[ \frac{0.5}{0.25} \right]} \right] = k_1 (1 - e^{-2k_2}) \tag{10}
\]

Also, when \( V_{O_2} = 1 \) liter/min \( V = 0.3 \) liter/min, \( P_{O_2}^{al} = 100 \) mmHg. Hence

\[
100 = k_1 \left[ 1 - e^{-k_2 \left[ \frac{0.3}{1} \right]} \right] = k_1 (1 - e^{-0.3k_2}) \tag{11}
\]

From equations (10) and (11), we get:

\[
\frac{140}{100} = \frac{k_1 (1 - e^{-2k_2})}{k_1 (1 - e^{-0.3k_2})} = \frac{1 - e^{-2k_2}}{1 - e^{-0.3k_2}}
\]

\[
\therefore 140 - 140e^{-0.3k_2} = 100 - 100e^{-2k_2}
\]

or, \( 40 = 100e^{-2k_2} + 140e^{-0.3k_2} \), so that \( k_2 = 4.18 \) min/l

Upon substituting \( k_2 = 4.18 \) min/l into equation (10) we obtain:

\[
140 = k_1 (1 - e^{-(2\times4.18)}) \text{, so that } k_1 \approx 140 \text{ mmHg}
\tag{13}
\]

Hence, the \( P_{O_2}^{al} \) curve can be represented by:
\[ P_{O_2}^{al} (\text{mmHg}) = 140 \left[ 1 - e^{-4.18 \left[ \frac{V^*}{V_O} \right]} \right], \quad (14) \]

wherein \( V_O = Q \left( C^{AB}_{O_2} - C^{VB}_{O_2} \right) \) and \( V = V/50l/min \)

(b) Now, let us look at the \( P_{CO_2}^{al} \) expression:

\[
P_{CO_2}^{al} = k_3 e^{-k_4 \left[ \frac{V}{V_m} \right] / V_{CO_2}} = k_3 e^{-k_4 \left[ \frac{V^*}{V_{CO_2}} \right]} \]

We note from Figure 4.19 that for \( V_{CO_2} = 0.2/l/min \) and \( V_m = 0.2 \), \( P_{CO_2}^{al} = 12 \). Hence, from the above equation, we get:

\[ 12 = k_3 e^{-k_4} \quad (15) \]

Also, for \( V_{CO_2} = 0.8/l/min \) and \( V_m = 0.2 \), \( P_{CO_2}^{al} = 62 \text{mmHg}. \) Hence

\[ 62 = k_3 e^{-k_4 \left[ \frac{0.20}{0.80} \right]} = k_3 e^{-k_4/4} \quad (16) \]

From equations (15) and (16), we get:

\[
\frac{12}{62} = e^{-k_4} = e^{-\frac{3}{4}k_4} \quad (17)
\]

\[
\ln \left( \frac{12}{62} \right) = -\frac{3}{4}k_4, \quad \text{so that} \quad k_4 = 2.19
\]

Substituting \( k_4 = 2.19 \) into equation (16), we obtain:

\[ 62 = k_3 e^{-2.19 \frac{4}{4}}, \quad \therefore k_3 = 107.18 \quad (18) \]

Hence, the \( P_{CO_2}^{al} \) curve can be represented as
\[ P_{CO_2}^{al} (mmHg) = 107.18 e^{-2.19 \left( \frac{V^*}{V_{CO_2}} \right)} \]  
\[ (19) \]

wherein \( V^* = \frac{V}{50l/min} \) and \( V_{CO_2} = Q(C^{VB}_{CO_2} - C^{AB}_{CO_2}) \)

### 4.5.3 Arterial and Venous \( O_2 \) and \( CO_2 \) Partial Pressure Expressions

We will now quantify the previous expressions of \( P_{O_2}^{AB} \) and \( P_{CO_2}^{VB} \) in terms of \( C_{O_2}^{AB} \) and \( C_{CO_2}^{VB} \), as given by equations (7) and (8).

(a) From the \( O_2 \) disassociation curve in Figure 4.20, we had put down:

Blood \( C_{O_2} = C_{O_2}^m \left[ 1 - e^{-k_5 \frac{P_{O_2}}{P_{O_2}^m}} \right] \)

or, \( C_{O_2}^* = 1 - e^{-k_5 P_{O_2}^*} \) \[ (20) \]

where \( C_{O_2} = \frac{C_{O_2}^*}{C_{O_2}^m} \) and \( P_{O_2}^* = \frac{P_{O_2}}{P_{O_2}^m} \)

From Figure 4.20, at \( P_{O_2}^* = \frac{40mmHg}{140mmHg} = 0.29 \) (for normal venous blood), and

\[ C_{O_2}^* = \frac{15}{20} = 0.75 \]

Hence from equation (20):

\[ 0.75 = 1 - e^{-0.29 k_5} \]

\[ \therefore k_5 = 4.78 \] \[ (21) \]

Also, for \( P_{O_2}^* = \frac{95mmHg}{140mmHg} = 0.68 \) (for normal arterial blood), and

\[ C_{O_2}^* = \frac{0.19}{0.20} = 0.95 \]
Hence from (20):

\[0.95 = 1 - e^{-0.68k_5}, \text{ or } k_5 = 4.4\] (22)

So we take the average value of \(k_5\):

\[\therefore k_5 = \frac{(4.78+4.4)}{2} = 4.59\] (23)

Then the \(O_2\) disassociation curve is given by:

\[C_{O_2} = C_{O_2}^B = 0.2 \left[ 1 - e^{-4.59\left[\frac{P_{O_2}}{140}\right]} \right],\] (24)

Hence from the above equation, the partial pressure of \(O_2\) in blood \((p_{O_2}^B)\) is given by:

\[p_{O_2}^B = \frac{140}{4.59} \ln \left[ \frac{0.2}{0.2 - C_{O_2}^B} \right] = 30.5 \ln \left[ \frac{0.2}{0.2 - C_{O_2}^B} \right] \] (25)

(b) Finally, we look at \(CO_2\) disassociation curve (in Figure 4.21), expressed as:

\[C_{CO_2} = C_{CO_2}^\text{max} \left(1 - e^{-k_6P_{CO_2}^*}\right)\] (26)

or, \(C_{CO_2}^* = 1 - e^{-k_6P_{CO_2}^\text{max}} = 1 - e^{-k_6P_{CO_2}}\)

Based on Figure 4.21, when \(P_{CO_2}^* = \frac{20mmHg}{140mmHg} = 0.14\),

\[C_{CO_2} = \frac{0.38}{0.80} = 0.475\] so that

\[0.475 = 1 - e^{-0.14k_6}, \text{ } k_6 = 4.60\] (27)

Also, when \(P_{CO_2}^* = \frac{70mmHg}{140mmHg} = 0.5\), \(C_{CO_2}^* = \frac{0.60}{0.80} = 0.75\), so that
\[ 0.75 = 1 - e^{-0.5k_6}, \quad k_6 = 2.77 \]  

(29)

So we take the average value of \( k_6 \):

\[ k_6 = \frac{(4.60 + 2.77)}{2} = 3.69 \]  

(30)

Then, in \( CO_2 \) disassociation curve, the \( CO_2 \) concentration is given (from equations 26-30) by:

\[ C_{CO_2} = C_{CO_2}^B = 0.8 \left[ 1 - e^{-3.69 \left( \frac{P_{CO_2}}{140} \right)} \right], \]  

(31)

so that partial pressure of \( CO_2 \) in blood is \( (P_{CO_2}^B) \) is given by

\[ P_{CO_2}^B (mmHg) = 37.94 \ln \left[ \frac{0.8}{0.8 - C_{CO_2}^B} \right] \]  

(32)
4.5.4 Determining $\Delta P_{av}^{O_2}$ and $\Delta P_{av}^{CO_2}$

In order to determine $D_O$ and $D_{CO_2}$, we also need to determine $\Delta P_{av}^{O_2}$ and $\Delta P_{av}^{CO_2}$ in equations (3) and (4) respectively. Figure 4.21 illustrates the variation of $\Delta P^{O_2}$ ($= P_{O_2}^{pO_2} - P_{O_2}^{cap}$) along the length ($l$) of the capillary bed.

Let, $l^* = l/l_m$

Now we can express $\Delta P^{O_2}$ as a function of $l^*$, as follow:

$$\Delta P^{O_2} = \Delta P_{max}^{O_2} f_{O_2}(l^*)$$

(36)

where $f_{O_2}(l^*)$ is illustrated in Figure 4.22.

Then

$$\Delta P_{av}^{O_2} = \Delta P_{max}^{O_2} \left( \frac{1}{l_m} \int_{0}^{l^*} f_{O_2}^*(l^*) dl^* \right) = \Delta P_{max}^{O_2} \left( F_{O_2} \right)$$

(37)

Based on data [3], since $\Delta P_{av}^{O_2} = 12 mmHg$ for $\Delta P_{max}^{O_2} = 65 mmHg$, we have $F_{O_2} = 0.185$. We can hence put down:

$$\Delta P_{av}^{O_2}(mmHg) = 0.185 \Delta P_{max}^{O_2} = 0.185 \left( P_{O_2}^{pO_2} - P_{V}^{O_2} \right)$$

(38)
**Figure 4.22** Uptake of oxygen by the pulmonary capillary blood. At arterial end, arrows unequal as concentration of O\(_2\) goes into capillaries. At venous end, arrows equalized. (The curve in this figure was constructed from data in Mihorn and Pulley: Biophys. J., 8:337, 1968). [From Guyton (1971), p. 434].

We can similarly determine the average value of \(\Delta P_{av}^{CO_2}\) from Figure 4.23 as:

Let \(l^* = l/l_m\)

Then, we can represent figure 8 as:

\[
\Delta P_{CO_2} = \Delta P_{CO_2}^{max} f_{CO_2}(l^*)
\]  
(39)

Then,

\[
\Delta P_{CO_2}^{av} = \Delta P_{CO_2}^{max} \left( \int_0^{l^*} f_{CO_2}(l^*) dl^* \right) = \Delta P_{CO_2}^{max} \left( F_{CO_2} \right)
\]  
(40)

Based on data [3], since \(\Delta P_{av}^{CO_2} = 0.5mmHg\) for \(\Delta P_{max}^{CO_2} = 5mmHg\), we have \(F_{CO_2} = 0.1\).

We can now put down:
\[ \Delta P_{av}^{CO_2} (mmHg) = 0.1 \Delta P_{max}^{O_2} = 0.1 \left( p^{VB}_{CO_2} - p^{al}_{CO_2} \right) \] (41)

**Figure 4.23** Diffusion of carbon dioxide from the pulmonary blood into the alveolus. (The curve in this figure was constructed from data in Mihorn and Pulley: Biophys. J., 8:337, 1968). [Modified from Guyton (1971), p. 435]
4.5.5 Sequential procedure to compute $p_{O_2}$ and $p_{CO_2}$

$$D_{O_2} = \frac{\text{Total O}_2 \text{ consumed}}{\Delta P_{av}^{O_2}} = \frac{V^o_{O_2}}{\Delta P_{av}^{O_2}} = \frac{Q \left( C_{O_2}^{AB} - C_{O_2}^{V_B} \right)}{0.185 \left( P_{O_2}^{al} - P_{O_2}^{V_B} \right)}$$

$$D_{CO_2} = \frac{\text{Total CO}_2 \text{ produced}}{\Delta P_{av}^{CO_2}} = \frac{V^o_{CO_2}}{\Delta P_{av}^{CO_2}} = \frac{Q \left( C_{CO_2}^{VB} - C_{CO_2}^{AB} \right)}{0.1 \left( P_{CO_2}^{VB} - P_{CO_2}^{al} \right)}$$

Note that in the denominators, we need to know $V^o_{O_2}(t)$ and $V^o_{CO_2}(t)$ for $p_{O_2}^{al}$ and $p_{CO_2}^{al}$ respectively.

(1) We first monitor: $V(t), V(t)$, SV(stroke volume), EP(Cardiac ejection period), $C_{O_2}^{VB}, C_{O_2}^{AB}, C_{CO_2}^{VB}$ & $C_{CO_2}^{AB}$ (O$_2$ and CO$_2$ concentrations in pre-oxygenated and post-oxygenated blood).

(2) We substitute the values of $C_{O_2}^{AB}$ ($=C_{O_2}^{VE}$) and $C_{O_2}^{VB}$ ($=C_{O_2}^{AE}$) into equation (3), and the values of $C_{CO_2}^{AB}$ ($=C_{CO_2}^{VE}$) and $C_{CO_2}^{VB}$ ($=C_{CO_2}^{AE}$) into equation (4).

(3) We next determine:

$Q$= SV/ejection period,

$V^o_{O_2}(t) = Q \left( C_{O_2}^{AB} - C_{O_2}^{V_B} \right)$, the O$_2$ consumption rate

$V^o_{CO_2}(t) = Q \left( C_{CO_2}^{VB} - C_{CO_2}^{AB} \right)$, the CO$_2$ production rate

Using the monitored values of $C_{O_2}^{VB}, C_{O_2}^{AB}, C_{CO_2}^{VB}$ & $C_{CO_2}^{AB}$ in the above equations.

(4) We then substitute the expressions for $V^o_{O_2}(t)$ and $V^o_{CO_2}(t)$ as well as of $V^* = V/50$ into the equations for $p_{O_2}^{al}$ (equation (14)) and $p_{CO_2}^{al}$ (equation (19)), to obtain $p_{O_2}^{al}$ and $p_{CO_2}^{al}$.
(5) We substitute the monitored values of $C_{O_2}^{VB} (= C_{O_2}^{AE})$ and $C_{CO_2}^{VB} (= C_{CO_2}^{AE})$ as well as $V^* = V/50$ into equations (25) & (32), to obtain the values of $P_{O_2}^{VB}$ (or $P_{O_2}^{AE}$) and $P_{CO_2}^{VB}$ (or $P_{CO_2}^{AE}$).

(6) We now evaluate $\Delta P_{O_2}$ in equation (38), by utilizing values of $p_{O_2}^{al}$ in step (4) and $P_{O_2}^{VB}$ in step (5).

We likewise evaluate $\Delta P_{CO_2}$ in equation (38), by utilizing values of $p_{CO_2}^{al}$ in step (4) and $P_{CO_2}$ in step (5).

(7) Now, in order to determine the values of the lung gas-exchange parameters (or indices) $D_{O_2}$ and $D_{CO_2}$, we substitute into equations (42) and (43) for (i) $V_{O_2}(t)$ and $V_{CO_2}(t)$ from step (3) and for (ii) $\Delta P_{O_2}$ and $\Delta P_{CO_2}$ from step (6).
4.6. Case Studies

(A) We monitor the partial pressures blood concentrations of $O_2$ and $CO_2$ as:

\[
C_O^{AE} = C_O^{JE} = 0.13, \quad C_O^{AB} = C_C^{AE} = 0.18, \quad C_C^{AB} = C_C^{JE} = 0.525, \\
C_C^{VE} = C_C^{AB} = 0.485; \text{ Alveolar ventilation rate (} V^o) = 5\text{litres/min, Blood flow rate in the}
\]

pulmonary vascular bed (Q) = 5 litres/min

From equation (26), we obtain:

\[
P_O^{VB} = 30.5 \ln \left[ \frac{0.2}{0.2 - C_O^{VB}} \right] = 30.5 \ln \left[ \frac{0.2}{0.2 - 0.13} \right]
\]

\[
= 32.02 \text{mmHg} \quad (44)
\]

From equation (32), we obtain:

\[
P_O^{VB} = 37.94 \ln \left[ \frac{0.8}{0.8 - C_C^{VB}} \right] = 37.94 \ln \left[ \frac{0.8}{0.8 - 0.525} \right]
\]

\[
= 40.51 \text{mmHg} \quad (45)
\]

We now also monitor $Q=5$ Litres/min and $V^o = 5l/min$, so that $V = 5/50 = 0.1 \quad (46)$

Then from equation (34):

\[
V_O^o(t) = Q \left( C_O^{AB} - C_O^{JE} \right), \text{ so that from the above data,}
\]

\[
V_O^o(t) = 5000 \times 0.05 = 250 \text{ ml of } O_2/\text{min consumption rate} \quad (47)
\]

From equation (35):

\[
V_{CO_2}^o(t) = Q \left( C_{CO_2}^{AB} - C_{CO_2}^{JE} \right) = 5000(0.04)
\]
Now, from equation (14):

For $V^* = 0.1$ (equation 46) and $V_{O_2} = 0.25l$ (equation 47), we obtain $P_{O_2}^{al}$:

$$P_{O_2}^{al} = 140 \left[ 1 - e^{-4.18 \frac{V^*}{V_{O_2}}} \right]$$

$$= 140 \left[ 1 - e^{-4.18 \left( \frac{0.1}{0.25} \right)} \right] = 113.7 \text{mmHg}$$

From equation (19), for $V = 0.1$ (equation (46)) and $V_{CO_2} = 0.20l$ (equation 48), we obtain:

$$P_{CO_2}^{al} = 107.18e^{-2.19 \frac{V^*}{V_{CO_2}}} = 107.18e^{-2.19 \left( \frac{0.1}{0.2} \right)}$$

$$= 35.86 \text{mmHg}$$

Now, we can evaluate the diffusion coefficients:

From equations (42, 44, 47, 49):

$$D_{O_2} = \frac{Q(C_{O_2}^{AB} - C_{O_2}^{VB})}{\Delta P_{O_2}^{av}} = \frac{Q(C_{O_2}^{AB} - C_{O_2}^{VB})}{\Delta P_{O_2}^{max} \left( F_{O_2} \right)} = \frac{V_{O_2}^*}{0.185 \left( p_{O_2}^{al} - p_{O_2}^{VB} \right) \text{mmHg}}$$

$$= \frac{5000(0.18 - 0.13)}{(113.7 - 31.2) \times 0.18} = 16.84 \text{ml}O_2 / \text{min/mmHg}$$

From equations (43, 48, 45, 50):
\[ D_{CO_2} = \frac{Q(C^{VB}_{CO_2} - C^{AB}_{CO_2})}{\Delta P_{\text{av}}} = \frac{V^{\circ}_{CO_2} \text{(in ml/min)}}{0.1(p^{VB}_{O_2} - p^{al}_{O_2})_{\text{mmHg}}} \]

\[ = \frac{5000(0.04)}{(40.51 - 35.86) \times 0.1} = 430.11 \text{mlCO}_2 / \text{min/ mmHg} \]  

(52)
(B) Alternately, we derive data from:

(i) the inspired and expired air data analysis (such as that carried out in section 2.1-2.3); to compute:

\[
O_2 \text{ consumption rate } = 283.2 \text{ml/min},
\]
\[
CO_2 \text{ production rate } = 226.8 \text{ml/min},
\]
\[
P_{O_2}^{ai} = 103.03 \text{mmHg} \text{ and } P_{CO_2}^{ai} = 38.41 \text{mmHg} \tag{53}
\]

and (ii) venous blood gas analysis:

\[
C_{O_2}^{VB} = 0.13, \quad C_{CO_2}^{VB} = 0.548
\]

Then, as per equation (26), \( P_{O_2}^{VB} = 31.2 \text{mmHg} \tag{54} \), corresponding to \( C_{O_2}^{VB} = 0.13 \).

For \( C_{O_2}^{VB} = 0.617 \), as per equation (32):

\[
P_{CO_2}^{VB} = 37.94 \ln \left[ \frac{0.8}{0.8 - C_{CO_2}^{VB}} \right] = 37.94 \ln \left[ \frac{0.8}{0.8 - 0.548} \right]
\]
\[
= 43.84 \text{mmHg} \tag{55}
\]

We obtain, from air composition analysis, that \( O_2 \) consumption rate
\[
V_{O_2}^o (t) = 283.3 \text{ml/min} \tag{56}
\]
and \( CO_2 \) production rate \( V_{CO_2}^o (t) = 226.8 \text{ml/min} \tag{57} \)

Hence, from equations (55, 42 & 55) with the calculated value of \( P_{O_2}^{ai} \) (equation 53) and of \( P_{O_2}^{VV} \) (equation (54)), we obtain:
\[
D_{O_2} = \frac{V_{O_2}}{\Delta P_{O_2}^{av}}
\]

\[
= \frac{283.2}{(103.03 - 31.2) \times 0.18} = 21.90 \text{mlO}_2 / \text{min/mmHg} \quad (58)
\]

Likewise, from equations (43) & (56) along with the calculated values of \(P_{CO_2}^{in}(\text{equation (53)})\) and \(P_{CO_2}^{av}(\text{equation (57)})\), we obtain

\[
D_{CO_2} = \frac{V_{CO_2}}{\Delta P_{CO_2}^{av}}
\]

\[
= \frac{226.8}{(43.84 - 38.41) \times 0.1} = 417.68 \text{mlCO}_2 / \text{min/mmHg} \quad (59)
\]

The advantage of this method (B) over (A) is that it does not require monitoring the cardiac output, and is hence simpler to implement clinically.
4.7 Non-Dimensional Physiological Index

\[ NDPI = \frac{D_{CO_2}}{D_{O_2}} \times \frac{\text{O}_2 \text{ consumption rate}}{\text{CO}_2 \text{ production rate}} \]

Checking dimensions:

\[ NDPI = \frac{D_{CO_2}}{D_{O_2}} \times \frac{\text{O}_2 \text{ consumption rate}}{\text{CO}_2 \text{ production rate}} = \frac{\text{mlCO}_2/\text{min/mmHg}}{\text{mlO}_2/\text{min/mmHg}} \times \frac{\text{mlO}_2/\text{min}}{\text{mlCO}_2/\text{min}} \]

Example:

\[ NDPI = \frac{417.68 \text{mlCO}_2/\text{min/mmHg}}{21.90 \text{mlO}_2/\text{min/mmHg}} \times \frac{283.2 \text{ml/min}}{226.8 \text{ml/min}} = 23.8 \]

4.8 Conclusion

We derive expressions for diffusion coefficients \( D_{O_2} \) and \( D_{CO_2} \), in terms of the evaluated cardiac-output \( CO \), \( O_2 \) and \( CO_2 \) concentrations in arterial and venous blood as well as alveolar and blood \( O_2 \) and \( CO_2 \) partial-pressures. The coefficients \( D_{O_2} \) and \( D_{CO_2} \) represent the lung capability to oxygenate the blood. We can then also determine the cardiac output, from knowing the concentrations of oxygen and carbon dioxide in the arterial and venous bloods. The derived information of \( D_{O_2} \) and \( D_{CO_2} \) as well as of \( O_2 \) and \( CO_2 \) metabolic rates can be of considerable use (including for SARS assessment). Finally, the derived NDI can be used to assist clinicians in classifying the type of pulmonary diseases and concentrate the precious medical resources on the diseased patients.
Reference On Lung Air Performance Analysis


2. Loh Kah Meng, Dhanjoo N. Ghista and Heiko Rudolph, *Determination of O₂ and CO₂ Metabolic-Rates and Lung Diffusion Coefficients, based on the Data of Inspired and Expired Air Compositions*, Annals, Academy of Medicine, Singapore.


Chapter 5 Modeling of Renal Obstructions

5.1 Purpose of Renal Scan

A renal scan is a simple way to evaluate the split renal function. Split renal function is the relative function of each of the kidneys. The scan can show that one of the kidneys is contributing 60% and the other is contributing 40% to the overall renal function.

5.2 Evaluation of Renal Function by Radionuclide Methods

Radiopharmaceuticals are used in nephrology and urology to evaluate renal function and morphology. The three main categories are:

(a) those excreted by tubular secretion
(b) those excreted by glomerular filtration
(c) those bound in the renal tubules for a sufficiently long time to permit cortical anatomical imaging

5.2.1 Radionuclide methods used in nephrourology

Renal scintigraphy offers a rapid, noninvasive means of evaluating suspected urinary tract disorders. It provides sensitive indices of relative renal blood flow, glomerular filtration, tubular function, and urinary excretion. We can use different radiopharmaceuticals a also different method to collect data. From this point of view it is very important to clearly know the clinician diagnostic question. This knowledge makes possible to choose proper radiopharmaceutical and imaging method to answer this question. On the other hand we must take in mind that not all renal scans are diagnostic.

5.2.1.1 Radiopharmaceuticals

(a) 99mTc DTPA: It has a clearance comparable to insulin and may be used to measure glomerular filtration rate.
(b) **123I or 131I hippurate:** Orthoiodohippurate is cleared similarly to paraaminohippuric acid and provides a measure of effective renal plasma flow and tubular function. Approximately 60 to 80% of OIH entering the kidneys is extracted with each pass. A small percentage is cleared by glomerular filtration while the remainder is removed by the tubules. In normal conditions, the rate of OIH clearance by the kidneys is dependent on renal blood flow. In certain disease states, the extraction fraction may fall and OIH clearance is no longer a measure of renal plasma flow.

(c) **99mTc DMSA:** It binds to the cortical tubules and is considered to represent functioning tubular mass. 99mTc DMSA reaches the tubules via the glomerular filtrate as well as tubular extraction from the peritubular capillaries. About 50% of the injected dose accumulates in the cortex within 1 hour of injection and remains in the kidneys for 24 hours.

(d) **99mTc MAG3:** It has similar properties as OIH does. The clearance of 99mTc MAG3 can be used as an independent measure of renal function. The clearance of 99mTc MAG3 can be calculated based on the dose injected and a single sample of plasma obtained 43 minutes postinjection. The image quality of 99mTc MAG3 is superior to that obtained with 99mTc DTPA.

(e) **51Cr-EDTA:** It is excreted by means of glomerular filtration and so it is used for in vitro measurement of glomerular filtration rate. This method is supposed to be the most accurate.

### 5.3 Diagnostic methods: In vivo – non-imaging methods

#### 5.3.1 GFR and ERPF measurement

They are not widely used. They require several plasma samples and their measurements. They use several mathematical models to calculate particular physiologic parameters. They can assess only global parameters.
5.3.2 Radionuclide nephrography

They are still used by some departments. They use scintillation probe to measure radioactivity over both kidneys and sometimes also blood clearance. They are very simple and are used namely in patient follow-up. They make possible evaluation of both kidneys separately.

5.3.3 Imaging methods

They are most often used methods for kidney and urinary tract evaluation. They can be divided into two types - static and dynamic imaging.

5.3.4 Static imaging

Renal images are usually obtained 2 to 3 hours following intravenous injection of 99mTc DMSA. Since rapid loss of tracer does not occur, several views of the kidneys can be obtained, including SPECT imaging. The static renal images obtained provide good definition of the cortical outline and, in addition, show the relative distribution of functional tissue. The ratio of tracer uptake between kidneys provides a measure of divided renal function.

5.3.5 Dynamic imaging

Dynamic imaging is performed most often with 99mTc DTPA or 99mTc MAG3. In contrast to DMSA the tracers are rapidly excreted, and thus rapid sequential renal imaging must be performed. The images that are obtained provide information relating to renal vascularity, renal function and excretion. Following an intravenous bolus of these tracers an image obtained for the first 30 seconds provides a so called vascular image, with the major blood vessels and perfusion to both kidneys, liver and spleen being visualized. The amount of activity at each site reflects the relative vascularity. Renal function is assessed at 2 minutes after injection, when there is good renal visualization and an image show the relative distribution of function between the kidneys. Thereafter, cortical activity rapidly diminishes as the tracer is excreted by glomerular filtration or tubular secretion. By 5 minutes activity is normally seen in the collecting systems and serial images are obtained up to 20 to 30 minutes which show progressive excretion of tracer. If there is any suggestion of obstruction, it is important to mobilize the patient and obtain a subsequent image to ensure that there is no functional hold-up caused by patient positioning. If the question of obstruction has
not been resolved, the study will need to be extended and further images obtained following diuretic administration.

### 5.4 Patient positioning

Some clinicians image the patient in a seated or prone position, but most image the patient supine with the camera positioned beneath the kidneys. In the supine position the kidneys are most likely to be equidistant from the camera, and differences in uptake will represent differences in relative function rather than differences in attenuation. Imaging the patient in an upright or seated position may interfere with measurements of relative function. Occasionally, patients will be imaged in the upright or seated position to facilitate drainage of the urine from the renal pelvis when the clinical question is obstruction.

### 5.5 The renogram curve

The renogram curve is a time-activity curve describing the transit of any tracer through the kidney. The curve is obtained by placing a computer-assessed region of interest over the whole kidney or the cortex, obtaining the counts in the renal region of interest (ROI) for each period of data acquisition, and plotting these counts as a function of time. The renogram curve is often divided into the period of tracer appearance, tracer extraction and tracer elimination denoted as phase 1, 2 and 3 respectively. Tracer appearance describes the period of blood flow beneath the detector, tracer extraction is proportional to renal plasma flow or glomerular filtration rate according to used tracer. The curve peaks when tracer exits from the kidney at the same rate it is entering the kidney.

The kidney is limited in the number of ways it can handle a tracer in response to disease; it may accumulate less of the tracer, accumulate it at a slower rate, or eliminate it at a slower rate. Tracer kinetics can be altered by disease as well as by the level of hydration or dehydration. Proper interpretation of the renogram curve requires the clinician to understand what the curve implies in terms of renal function and then to relate that functional information to potential disease processes. Nowadays mathematical function called deconvolution is also used for renogram curve
evaluation. It can better detect renal artery stenosis and distinguish between obstruction and nonobstructed pelvic dilation and detect transplant rejection.

5.6 Clinical applications

5.6.1 Renal function:

Radionuclide renal imaging with quantitation provides the only non-invasive accurate method of measuring the contribution of an individual kidney to overall renal function. In addition, the technique can be used to assess the regional distribution of function within an individual kidney.

Main clinical situation for renal function evaluation:
(a) Renal function in urinary tract infection
(b) Renal tubular dysfunction
(c) Renal function with calculi
(d) Renal function after renal stone removal

It is important to specify the parameter being measure (GFR, ERPF, DMSA uptake) rather than using the more general term function.

5.6.1.1 Obstruction

Hydronephrosis, the dilatation of the renal pelvis and collection system, is often due to obstruction. Intravenous urography, CT and ultrasound can imply the presence of obstruction based on pelvic or ureteral dilatation. If obstruction is present, intervention is usually indicated. It is well recognized, however, that the ureters and renal pelvices may be dilated in patients who have no obstruction to urine flow; dilatation can occur in those with reflux, congenital anomalies, previous obstruction, and prior urinary tract surgery.

The diuretic-augmented renogram is used to distinguish between them. It can also be used to determine if surgery has been successful in relieving a known obstruction.

Main clinical situation for renal obstruction evaluation:
(a) Measurement of renal function in known obstruction
(b) Assessment of equivocal obstruction after IVU or ultrasound
(c) Baseline during a period of observation
(d) Preoperative evaluation
(e) Postoperative comparison

5.6.1.2 Reflux nephropathy

Radionuclide studies are routinely used in the management of vesicoureteral reflux and can be used to help predict which patients will have spontaneous resolution of their reflux. There are two radionuclide techniques for reflux detection. Indirect method means intravenous administration of tracer. When the tracer reaches the bladder, patient is asked to void. The kidneys, ureters, and bladder are monitored by use of a gamma camera and the diagnosis of reflux is based on a significant increase in activity in the upper urinary tract during or after voiding. This indirect method is simple, but has several limitations. The second technique is direct cystography. It serves as an important role in the management of patients with reflux or suspected reflux. Bladder catheterization is needed. The bladder volume at which reflux occurs should be noted and may be a useful prognostic factor.

Main clinical situation for reflux evaluation:
   (a) Determination of presence or absence of renal scars
   (b) Measurement of individual kidney function
   (c) Identification of presence or absence of reflux

5.6.1.3 Bacterial infection

Clinical signs of the bacterial of infection like fever, leukocytosis, bacteriuria are not able to distinguish between upper and lower urinary tract infection, but this decision is very important. For this purpose, especially in neonates and infants, static renal scintigraphy using 99mTc DMSA is routinely used. It can detect focal abnormalities of tubular function before distortion of the normal anatomy occurs.

5.6.1.4 Trauma

Scintigraphy is both sensitive and specific for detecting traumatic renal injuries. It can rapidly assess perfusion to both kidneys; it has also possibility of detecting active
intraperitoneal or retroperitoneal hemorrhage. Also excretory function can be evaluated in a few minutes.

5.6.1.5 Renal failure

We can classify renal failure from the point of view of scintigraphic findings to several categories - obstruction, pre-renal (haemorrhage, hypotension, diarrhoea), acute tubular necrosis, parenchymal disease (glomerulonephritis), vascular cause and chronic renal failure.

Main scintigraphic features are:

(a) In obstruction, dilated calyces can be seen.
(b) In pre-renal failure, we can see normal blood flow and good uptake, but delayed intrarenal transit and minimal excretion.
(c) In acute tubular necrosis, we can see almost normal blood flow, but absent or minimal uptake and no excretion.
(d) In parenchymal disease, minimal blood flow, poor uptake and poor or absent excretion can be seen.
(e) In vascular disorders the findings are almost the same.
(f) In chronic renal failure, small kidneys, poor blood flow and little or no uptake and excretion can be seen.

5.6.1.6 Space-occupying lesions

Radionuclide scanning has a limited use in investigating renal masses because other investigations provide the information necessary for the diagnosis and management of these patients. Common lesions:

(a) Tumour
(b) Renal cysts
(c) Renal calculus
(d) Congenital and ectopic abnormalities
(e) Cystic disease
(f) Horseshoe kidney
(g) Crossed renal ectopia
(h) Pelvic kidney
5.6.1.7 Vascular disorders and hypertension

A functional agent is often used to evaluate patients with suspected renovascular hypertension. For this reason mostly the Captopril-Augmented renography is used. It often consists of a baseline scan followed at a later time by oral administration of 25 to 50 mg of captopril and a repeat renogram 1 to 2 hours after the captopril dose. The study is positive if there is a major change in relative uptake or in the washout phase of the renogram curve.

Main clinical situation for this evaluation:

(a) Hypertension due to renal artery stenosis
(b) Renal infarction
(c) Before surgery - angioplasty

5.6.1.8 Renal transplant

Technical problems that require prompt intervention include obstruction of the ureter, leakage at the ureteral anastomosis and renal artery of renal vein stenosis or occlusion. Later problems include renal artery stenosis, cyclosporin toxicity and ureteral stricture. When the graft fails to function normally, the clinician must distinguish between these various possibilities.

Acute renal vessel occlusion, poor parenchymal function, renal infarction, ureteral obstruction and extravasation can be usually detected by renal scintigraphy. Serial scan obtained during the first 1 to 2 weeks post-transplantation are useful in monitoring recovery from transplantation.

Acute rejection is characterized by decreased blood flow, decreased uptake, prolonged intrarenal transit time, decreased excretion and increased renal size.
5.6.2 Scrotal imaging

It makes possible to distinguish between torsion and epididymitis. It enables surgeons to avoid unnecessary surgery. The patient is placed under the gamma camera supine, bolus of 99mTc pertechnetate is injected intravenously and a radionuclide angiogram is obtained. The static images are acquired several minutes thereafter. An area of decreased perfusion corresponding to the involved testis indicated a high probability of torsion. Normally perfused or hypervascular testis can exclude surgery.

5.7 RENOGRAPHY

A renogram is simply a time-activity curve that provides a graphic representation of the uptake and excretion of a radiopharmaceutical by the kidneys. Information is displayed from the time of injection to about 20 to 30 minutes after injection. The classic renogram curve is obtained using agents that are eliminated by tubular secretion, $^{99mTc}$-MAG3 and, less commonly, $^{131I}$-hippurate. Fortunately, the shapes of the renogram curves and the associated data using either agent are essentially identical. Technetium 99m-MAG3 is the radiopharmaceutical of choice because it allows the simultaneous acquisition of high-quality renal images. Renogram curves are generated by placing a region of interest around each kidney, usually the entire kidney, but occasionally just around the renal cortex if a considerable amount of collecting system activity is present. Background subtraction regions of interest are selected just inferior to each kidney (Figure 5.1). An aortic region of interest may be used to assess the discreteness of the injected bolus as well as relative renal perfusion.

The normal computer-generated renogram curve employing a tubular radiopharmaceutical consists of three phases (Figure 5.2). Initial renal perfusion, or the vascular transit phase, lasts about 30 to 60 seconds and represents the initial arrival of the radiopharmaceutical in each kidney. Reconstruction of the first 30 to 60 seconds of the curve using different axes may be performed to assess more carefully the renal perfusion phase. Generally, renal peak activity during the perfusion phase equals or exceeds that of the aorta and should be reasonably symmetric between the two kidneys. The second phase is the cortical or tubular concentration phase of initial parenchyma transit. This phase occurs during minutes 1 through 5 and contains the peak of the curve. The initial uptake slope closely correlates with ERPF values. The third phase is the clearance or excretion phase, which represents the downslope of the
curve and is produced by excretion of the radiopharmaceutical from the kidney and clearance from the collecting system.

**Figure 5.1** Typical regions of interest for computer analysis. Outlined regions of interest are drawn over the aorta, the kidneys, and the bladder. Areas of background activity (Bkd) are also drawn. Time-activity curves are then generated for each of these after appropriate background subtraction has been made [64].
Figure 5.2 Typical renogram curves. (A) A schematic drawing demonstrates the conceptual portions of the time-activity curve within the kidney. (B) An actual renogram shows symmetric activity between right and left kidney, rapid dropoff after the peak, and a long tail extending to the right. The curve also shows increasing activity within the bladder after about 4 minutes [64].

Overall, the renogram curves for each kidney should be reasonably symmetric, although slight asymmetries are not unusual. The shapes of curves should also be inspected individually for alterations in the normal configuration. Semiquantitative indices derived from the curves may be helpful in this respect. Data commonly derived from the $^{99m}$Tc-MAG3 and radioiodinated iodohippurate sodium renograms include the following:

(a) *Time to peak activity.* Normal is about 3 to 5 minutes.
(b) Relative renal uptake ratios at 2 to 3 minutes. This is an index of relative renal function. Activity in each kidney should be equal, ideally 50%. A value of 40% or less in one kidney should be considered abnormal.

(c) Half-time excretion is the time for half of the peak activity to be cleared from the kidney. Normal is about 7 to 10 minutes.

(d) Differential cortical retention at 15 minutes. The percentage of retained activity about 15 minutes after injection in each kidney should be relatively equal. Differences of 20% or more should be considered abnormal.

(e) The 20-minute maximal count ratio. This is the activity measured in each kidney at 20 minutes expressed as a percentage of peak curve activity. As renal function deteriorates, delayed transit of the radiopharmaceutical in the kidney results in an abnormal renogram curve, which can be quantitated using this index. In the absence of pelvic calyceal retention, a normal 20-minute maximal cortical ratio for $^{99m}$Tc-MAG3 or $^{131}$I-hippurate is less than 0.3.

Patients should be well hydrated when renography is performed because in the presence of dehydration, an abnormal renogram curve demonstrating delayed peak activity, delayed radiopharmaceutical clearance, or an elevation of the excretion slope may result.

5.7.1 QUANTITATION OF RENAL FUNCTION

Quantitative assessment of renal function using radionuclide techniques is an important part of nuclear nephrology. Because up to half of renal function, including Glomerular Filtration Rate (GFR), may be lost before serum creatinine levels become abnormal, direct measurement of GFR and ERPF (Effective Renal Plasma Flow) using radiopharmaceuticals plays an important role in the assessment of renal function.

The classic measures of renal function involve the ability of the kidneys to clear certain substances from the plasma. These so-called clearances are expressed as volume of plasma cleared of a particular substance per minute ($mL/min$) as the plasma passes through the kidneys. The significance of the clearance depends on the substance employed. The clearance of inulin, which is entirely filtered, defines the GFR; and the clearance of para-aminohippurate (PAH), which is both filtered and secreted by the tubules, defines renal plasma flow. The radiopharmaceutical analogs for calculation of these clearances are the totally filtered $^{99m}$Tc-DTPA for inulin clearance and GFR.
estimation, and $^{131}$I OTH and $^{99}$mTc MAG3, which are primarily secreted by the tubules, with some filtration, for PAH clearance and ERPF. The latter index is termed effective because the radiopharmaceuticals used closely estimate but do not equal the PAH clearance.

Two dominant radionuclide methods of determining GFR and ERPF are employed:

(a) Plasma sample-based clearances, which are more tedious but more accurate; and
(b) Camera-based clearances, which do not require sampling of plasma or urine.

5.7.1.1 Plasma Sample-Based Clearances

These measurements are generally obtained by determining the plasma levels of the injected radiopharmaceutical at a specified time, although some techniques require urine collection as well. For tubular agents such as $^{131}$I-OTH and $^{99}$mTc-MAG3, effective renal plasma flow can be estimated by a single, timed blood sample obtained about 45 minutes after injection. Because the glomerular agent $^{99}$Tc DTPA is cleared more slowly than tubular agents, plasma samples are obtained 60 and 180 minutes after injection. The amount of activity remaining in the blood at these times is a measurement of activity not yet cleared by the renal mechanism and therefore is indirectly a measure of activity already cleared. These techniques require meticulous attention to detail and must employ personnel expertly trained in in vitro techniques. When performed correctly, GFR and ERPF measurements are theoretically more accurate than those based on camera measurements.

5.7.1.2 Camera-Based Clearances

State-of-the-art gamma cameras and computers have allowed the development of methods for estimating GFR and ERPF without collecting blood or urine samples. Commonly, calculations are made using counts acquired from the syringe containing the radiopharmaceutical before injection and subsequent counts over the kidneys after injection. Commercially available software for camera-based clearances simplifies corrections for patient and acquisition variables and provides reasonably accurate computer-derived clearance values. Although camera-based clearances are not as accurate as those based on plasma samples, they are highly reproducible and sufficiently reliable to be employed in clinical practice.
5.8 SCINTIGRAPHIC PROCEDURE

5.8.1 Patient positioning

Renography is performed on patients in either supine or sitting position. When supine, the patient is less likely to move and the difference in kidney depth is minimized. Moreover, the risk of fainting is negligible [1, 3, 5, 9]. However, patients with a severely dilated upper urinary tract will show disability of ureteric peristalsis to transport urine from the renal pelvis to the bladder, resulting in impaired emptying of the renal pelvis in supine position. Therefore, in many centers diuresis renography is performed in sitting position, so that gravity facilitates optimal drainage of the collecting system [5, 10]. Alternatively, if diuresis renography is performed in supine position, postvoid images should be obtained at the conclusion of the study at all times." Another advantage of the sitting position is the induction of position-dependent urinary tract obstruction, which can be observed in severe nephroptosis (Figure 5.3). This condition, however, is very rare.
Figure 5.3 Position-dependent urinary tract obstruction. A 33-year-old female with low back pain. (A) On the diuresis renogram (F-15 protocol) performed in a supine position, the time to peak of the right kidney is slightly longer than that of the left, while the excretion phase of both curves follows a symmetrical course. (B) The study performed in sitting position (F-15 protocol), however, demonstrated a right-sided obstruction. Several minutes after turning into supine position, prompt excretion took place. (C) The images obtained during study (B). In the second minute both kidneys are visualized with the same intensity. The right kidney is somewhat larger than the left and shows less radioactivity in the medial part because of the enlarged renal pelvis. Obvious retention in the right kidney, mainly in the renal cortex, was observed at the 20th minute during the study in the sitting position. Three minutes after turning into supine position, the renal pelvis is filled with radioactivity and there is excretion in the ureters [65].
5.8.2 Data acquisition in standard renography

In patients with native kidneys, imaging should be performed posteriorly. If the Patlak-Rutland method of deconvolution analysis is applied, the heart should be included within the field of view of the camera. In renal transplant patients the detector should be placed anteriorly. With $^{99m}$Tc-labeled compounds, a LEAP collimator is suitable. The LEAP collimator is also suitable for $^{123}$I-OIH, but a special collimator for the 159 keV energy will reduce scattering, resulting in better images. In the literature the duration of the study varies between 20 and 40 min [?, ?, 8, 10], a study length of 20 min is usually sufficient, as it is for diuresis renography if frusemide is administered before renography [11, 13-15].

RPI should only be performed when indicated. When not performing RPI, digital data acquisition of the whole study can be accomplished in a frame mode with constant frame time. In literature, the frame time used for this purpose varies between 10 and 30s. Using a large field-of-view camera, matrices of 128 x128 are recommended [?, 2, 102, 5, 10, 12]. In infants, Conway recommends zoom mode for easy ROI assignment.

5.8.3 Sequential and delayed images

Most centers perform 3-5 min sequential images during renography. In our experience it is essential to make 1 min images in the first 10 min of the study. The appearance in the renal pelvis or ureter can be determined on these images, which is essential for a correct interpretation of the study [11, 13, 15]. For an easier identification of the start of tracer excretion into the renal pelvis, contrast enhancement is obtained by truncating the file of 1 min images with a number corresponding to 1.25 times the maximum count within the third minute frame (Figure 5.7).

In children it is fairly easy to include kidneys, ureters and bladder simultaneously in the field of view of a large-field gamma camera. However, in adults this is often impossible. To achieve this, we routinely perform a scintigram including the bladder at the end of the study. If there is significant retention of activity in the upper tract, a post-micturition image should be obtained [4, 16]. As advocated by Rossleigh et al [17], babies and sedated children are kept in an upright position for 10-15 min before acquiring an image. A dilated non-obstructive system can thereby be differentiated from an obstructive system. In cases of severe obstruction in which excretion is
seriously impeded, a delayed image may help to localize the abnormality [8, 13-14]. Urine leakage, in which tracer excretion starts on time, can also be diagnosed on the late image.

5.9 PROCESSING AND ANALYSIS OF THE STUDY

5.9.1 Relative renal function

The relative renal function or left-to-right ratio is important for the management of patients with renal disease, in particular those with unilateral renal pathology. Care should be exercised in interpreting changes of relative function in patients with bilateral disease. Any of the already mentioned radiopharmaceuticals can provide this information. Reproducibility of the results is the most important aspect from the clinical point of view, since it allows a longitudinal study in patients to see whether there is a significant change in renal function [?, 5, 6, 8, 9, 10, 83, 19].

The measurement is frequently assessed in the follow-up on children with unilateral pathology of the upper urinary tract. It is also important for the interpretation of renography after ACE inhibition, in particular if DTPA is used. In unilateral renal artery stenosis the relative uptake of the affected kidney is almost always decreased and will show a further deterioration after ACE inhibition [102, 20-22].

Initially the consensus report only recommended the application of the integral method owing to its simplicity, reproducibility and accuracy; however, in the latest report the Rutland-Patlak method is also recommended. As recommended by the consensus report, relative uptake should be measured between 1 and 2 or 2.5 min after injection. Both time points have been chosen after the consideration that the first point should not be chosen too early for it would be reflecting arterial flow and the last point should be selected before significant escape of tracer out of the renal ROIs [3, 23-24].

In a recent study reproducibility and accuracy of the abovementioned two methods and the normalized slope method were compared with DMSA uptake. Reproducibility was excellent for the integral and the Rutland-Patlak methods. For the normalized slope method, however, differences between successive tests were as great as 10%.
Also, the accuracy of the integral and Rutland-Patlak methods was comparable, whereas the normalized slope method was less accurate.

The Rutland-Patlak method, in which double background correction is applied, has mainly been developed to estimate single kidney GFR from DTPA studies. For DTPA renal extraction is about 20%, resulting in high background counts which represent 50-80% of non-corrected kidney counts. Although this method is robust and accurate, its implementation in commercial software is still limited [3].

5.9.2 ROI assignment

Reproducibility and accuracy of measurement depend on the size of kidney ROI and the placing of background ROI (BG ROI). To overcome interobserver variability in drawing the ROIs, effort was made to standardize the ROI assignment and to develop a computer program for automated ROI selection for both kidneys and BG. Indeed, employing such a program, Der Kinderen et al [25] obtained a high degree of reproducibility of the left-to-right ratio using $^{131}$I-OIH (which already has low BG activity). A high degree of accuracy was also obtained by Granerus & Moonen [26] in their DTPA study in which the kidney ROIs were drawn manually and the BG ROI of each kidney was automatically determined by the computer. A similar software program was applied by Taylor et al [31] for processing their MAG3 data. Recently several methods for automated ROI assignment have been published [18, 27-30].

Although the choice of ROI method is important for camera based clearance measurements, especially in terms of reproducibility and accuracy, for relative renal function these different ROI methods probably perform equally well, at least as long as renal function is not severely decreased [3].

5.9.3 Background correction

Renal BG consists of extrarenal and intrarenal components. The extrarenal components are often called interstitial, but actually include an intra- and an extravascular part. Within the first minutes after injection, activity in the intravascular part is rapidly falling, while extravascular (interstitial) activity is slowly increasing. Depending on the placement of the extrarenal BG ROI, several vascular structures (liver, spleen, abdominal vessels) are included. The extrarenal BG curve is an integral of the two components within the ROI and will show a plateau or decrease with time [28, 27-30].
If only one BG ROI is used, a suprarenal BG ROI including large areas of liver and spleen will overestimate the intravascular intrarenal component and underestimate the extrarenal/interstitial part, resulting in underestimation of kidney uptake. Conversely, a BG ROI below the kidney is presumed to correctly present the extrarenal/interstitial part but underestimates the intravascular intrarenal component. This will result in overestimation of renal uptake [23, 31].

In conclusion, to measure the true renal uptake, data obtained during renography must be corrected for radioactivity in extrarenal tissue and intravascular activity within the kidney. However, the complicated double background correction method is only necessary in estimation of camera-based renal clearance. To measure left-to-right ratio the consensus reports recommended a simple ring, elliptical or perirenal BG ROI, because such a BG ROI which incorporates a bit of liver or spleen is representative of intravascular radioactivity [1, 3, 86, 31]. The accuracy of perirenal BG was demonstrated by obtaining the zero function at a nephrectomized site in studies using DTPA$^{30k}$ and MAG$_3$ [23]. To avoid side-scattering, the BG ROI should be slightly separated from the kidney ROI. Before subtracting, the BG ROI counts should be area-normalized to the kidney ROI [3].

In azotemic patients, due to elevated background activity and low renal concentration of radiotracer, measurement of relative renal function on the renographic data between 1-2 min can be misleading. In such patients with delayed excretion, more accurate assessment of relative function can be achieved using delayed images before excretion of tracer occurs [32].

5.9.4 Renal depth correction

Determination of renal depth for correction of attenuation by tissue between the kidney and the camera is only mandatory if camera based renal clearance is to be measured. For estimation of the left to-right ratio, this correction is not necessary as in the majority the difference in renal depth between the left and right kidney is less than 2 cm.

Among 150 adults studied by Gruenewald et al [33] in the seated position using ultrasound, 66% showed a depth difference of less than 1 cm, in 21% the difference was between 1 and 2 cm and in the remaining 13% the difference was greater than 2 cm. Taylor et al [34], who investigated the patients in supine position using CT scan,
observed in only three of the 201 adults a difference of more than 2 cm. These studies were in accordance with previous studies using renal scintigraphy obtained in lateral view [35-37]. Large differences of up to 7 cm were only found in patients with lumbar kyphoscoliosis or with an ectopic kidney. In these patients correction of renal depth is necessary. This can be achieved by performing a lateral projection scan, ultrasound or by calculating the geometric mean from DMSA study or during scintirenography with a dual-headed camera [5, 36-39].

Effective attenuation of $^{99m}$Tc measured using a renal phantom in a waterbath was approximately 0.14 cm$^{-1}$. Thus, if a $^{99m}$Tc-labeled compound is used, a difference in depth of 1 cm will change a true left-to-right ratio of 50:50 to approximately 53:47; a difference of 2 cm will change the ratio to 57:43. Therefore, if depth correction is not applied, a range between 43% and 57% should be regarded as normal [32, 38].

5.9.5 Excretory function

To characterize the pattern of the renographic curve and for objective comparison between studies performed successively, numerical parameters were introduced early in the 1960s; before this, examination was performed with a gamma camera. Figure 5.2 shows the most popular parameters derived from a renogram to evaluate the excretory function: the time to peak ($T_p$), the $t_{1/2}$, and the residual cortical activity [40-42]. The residual cortical activity is the ratio of counts at 20 min and peak counts, and is a recommended parameter for evaluation studies after ACE inhibition [102, 21]. Table 108.2 shows normal values obtained with MAG3 in normal volunteers aged between 23 and 72 years [41]. Gault et al [44] have demonstrated that the $t_{1/2}$, obtained from an OTH study correlates with serum creatinine. This correlation was also observed in MAG3 renograms [95]. Thus, the $t_{1/2}$, is not a pure reflection of excretory function, but depends on renal clearance as well.

As mentioned earlier in this chapter, the $T_p$ and the decrease in the third phase depend on the transit time of the initial bolus and the further transport of urine leaving the collecting system. The background-corrected renogram obtained with the gamma camera, in which kidney ROIs include the renal pelvis (the so-called "whole kidney curve"), reflects the radioactivity within the renal parenchyma and pelvicalyceal system. If there is no pooling of tracer in the renal pelvis, $T_p$ equals the transit time. To exclude tracer in the renal pelvis, parameters can be determined on cortical renograms using parenchyma) ROIs that exclude any activity in the calyces or pelvis.
Cortical renograms are especially important in patients with dilated pelvicaliceal systems (see Figure 5.5). The parenchyma ROIs can be drawn either manually or automatically using factor analysis [30, 45]. Generating both whole-kidney curves and cortical curves is recommended [102, 9].

Figure 5.4 A typical renogram curve. Parameters frequently used for evaluation of the excretory function are time to peak (a), time to half peak (b) and the residual cortical activity (d/c) [65].
Figure 5.5 Scintirenography in dilated non-obstructive left renal and ureter. (A) Sequential images (0-8 minutes) obtained during diuresis renography (F-15 protocol) from a 7-year girl with severely dilated left renal pelvis and ureter due to reflex. Reimplantation of the left ureter performed 6 years before. In the 2nd min the dilated left renal pelvis is visualized as photon-deficient area. Excretion in both renal pelvis and ureters is clearly visualized in the 4th min. The dilated renal pelvis is immediately fully filled with tracer. (B) Retention in left renal pelvis and ureter diminished clearly after micturition. (C) Whole kidney-curve of the left-kidney (L) shows an obstructive pattern. (D) The cortical curve nevertheless demonstrates a normal time to peak followed by a sharp decline. For easier recognition of whether the decline is symmetrical or not, the curves of the left and right kidney are plotted with the same peak curve [65].
Table 5.1 MAG3 renogram parameters (mean ± SD) obtained in healthy Volunteer (Adapted from [76]).

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Left</th>
<th>Right</th>
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<tbody>
<tr>
<td>Percent of total clearance</td>
<td>36</td>
<td>49.4 ± 3.9</td>
<td>50.6 ± 3.9</td>
</tr>
<tr>
<td>Peak Time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal ROI (min)*</td>
<td>36</td>
<td>3.3 ± 2.0</td>
<td>3.8 ± 2.3</td>
</tr>
<tr>
<td>Cortical ROI (min)</td>
<td>23</td>
<td>2.5 ± 0.2</td>
<td>2.5 ± 0.4</td>
</tr>
<tr>
<td>Half-time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal ROI (min)</td>
<td>36</td>
<td>5.5 ± 1.6</td>
<td>6.4 ± 3.5</td>
</tr>
<tr>
<td>Cortical ROI (min)</td>
<td>23</td>
<td>5.0 ± 1.5</td>
<td>5.5 ± 2.0</td>
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</tbody>
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*Difference between these two results is statistically significant ($P < 0.05$).

Tubular transit parameters have been considered useful but have not been addressed in the consensus report for two main reasons. First, tubular flow rate is not a specific function but rather a composite parameter depending on multiple factors (input function, extracellular volume, salt intake, hydration status, downstream pressure in the pelvicalyceal system). Second, the real value of mean parenchymal transit time has not been properly evaluated due to the absence of a standardized protocol for deconvolution analysis [3, 46-49].

Although to date in most publications interpretation is still based mainly on the pattern of the curves or the changes of numerical parameters, in our opinion evaluation of the sequential and delayed images obtained during renography is an important part of interpreting the study. In a normal study (Figure 5.7) there is a practically symmetrical appearance of the kidneys. In the second minute there is a good delineation of the renal cortex. Appearance of activity in the collecting system and renal pelves begins in the third or fourth minute. Shortly thereafter the activity will reach the ureter and the bladder. If diuresis is voluminous, e.g. after frusemide administration, radioactivity in the renal pelves and ureter may be only vaguely visible.

The abnormal third phase of the whole-kidney curve in patients with dilated non-obstructive pelvicaliceal systems is a well-known phenomenon and has led to the introduction of diuresis renography. However, despite stimulation of diuresis by frusemide the whole-kidney curve can be misleading (see Figure 5.5). Differentiation between obstructive and non-obstructive cases can then be done by reviewing the 1-
min images. In case of obstruction the dilated pelvicaliceal system is filled with tracer slowly, whereas a nonobstructive system is filled on time (Figure 5.6). As shown in this figure, the left kidney, with only moderate partial obstruction, also shows a delayed filling of the renal pelvis. The interobserver reproducibility of the interpretation by the images is acceptable [50].

For the interpretation of studies obtained in renal transplant patients several excretion parameters are applied. In practice, two parameters are applied: the tubular transit index and bladder appearance time [14, 51]. Normally the bladder appearance time ranges between 120 and 180 s. These values are nearly identical to those of the renal transit time calculated from other techniques. In patients with stable renal function both parameters are not correlated with serum creatinine levels. The bladder appearance time, which is determined during frusemide-stimulated diuresis, is obviously prolonged in various parenchyma) diseases and also in partial urinary tract obstruction [67]. In partial obstruction, a prolonged bladder appearance time is observed before the onset of renal function deterioration; in these cases GFR may remain normal for a long period due to the balancing influence of intrarenal vasoactive substances [52-54].

To date, there is little agreement as to what differentiates mild from moderate or severe partial obstruction. It has not been proven that the more complex parameters in the analysis of transit time impairment improve on the information already provided by simple parameters. Techniques which assess drainage relative to kidney uptake function, such as renal output efficiency [55], pelvic excretion efficiency [56], and normalized residual activity [57], require further investigation [4].
Figure 5.6  Scintirenography in moderate and severe PUJ-stenosis; a 20-month-old girl with bilateral stenosis. On ultrasonography the renal length is 7.2 cm on the left and 8.6 cm on the right. The volume of the left renal pelvis is 7ml, on the right it is 16 ml. Cortical thickness is 6 mm on the left, 3-4 mm on the right (data not shown). After pyeloplasty on the right side the kidney has become smaller, although the renal pelvis is still dilated and has a volume of 6.5ml. Serum creatinine was normal (29mmol/L) and remained unchanged after surgery. (A) Sequential images (0-8 min) obtained during diuresis renography (F-15). Zoom 1.6. (B) Images at the end of the study and postmicturition image of study (A) [65].
Figure 5.6 (C) Whole-kidney renograms of study (A). (D) Images obtained after right-sided pyeloplasty. (E) Images at the end of the study and postmicturition image of study (D). The whole-kidney curves in (C) and (F) are plotted with the same peak height [65].
Figure 5.6 (F) Whole kidney renograms of study (D). In the 2nd and 3rd min the dilated renal pelvis on both sides are visualized as photo-deficient area. L/R ratio: 55:45. The left renal pelvis, with moderate partial obstruction, is fully filled in the 9th min (see A), the curve of the left kidney (L) shows a decrease around that time (see C). The right kidney, with severe obstruction, shows slower filling of the renal pelvis. The right renal pelvis is fully filled only after keeping the child on an upright position (see B). The right renal curve (R) shows an accumulation curve (see C). After pyeloplasty the right renal pelvis is promptly filled with tracer (see D), whereas the left renal pelvis will show slow filling as in the previous study. The whole right kidney renogram (R) reaches a maximum around the 5th min followed by a photo-deficient area seen in the 2nd min is disappearing. It is fully filled with tracer by the 6th min, at which time the right renal curve (R) reaches a plateau. Although the whole-kidney curve is still abnormal, the images clearly demonstrate a normalization of excretory function. The left kidney (L) with moderate partial obstruction shows a pattern identical to the previous study. The L/R ratio is unchanged [65].
Figure 5.7 A normal standard scintirenography. (A) Sequential images obtained in the first 8 min in an adult without renal pathology. Study performed with Prism 2000 XP (Picker) equipped with high-resolution collimator, matrix 128 x 128. Injected dose was 74 MBq $^{99m}$Tc-MAG$_3$. Maximum count in the 3rd min was 123; thus the file of 1-min images was truncated with 153. There is a symmetrical appearance of both kidneys. The start of excretion in both renal pelvis (4th min) is visualized clearly. Thereafter the upper part of the ureters can be identified easily. (B) An image at the end of the study and postmicturition image including the bladder. (C) Whole-kidney renal curves; R=Right kidney. (D) Cortical curves show shorter times to peak and steeper decline than the whole-kidney curves. For easier recognition of whether the decline is symmetrical or not, the curves of the left and right kidneys are plotted with the same peak height [65].
5.10 RENAL CORTICAL SCINTIGRAPHY

CLINICAL INDICATIONS

To date the most important indication for performing renal cortical scintigraphy (RCS) is the detection of scarring related to upper urinary tract infection. This modality is also sensitive to detect lesions due to acute pyelonephritis. Similar lesions can be found in renal abscess, cyst, duplex kidney; hydronephrosis and the combination of ultrasound and RCS allows better differentiation between these. Occasionally this method is applied in searching ectopic kidneys and imaging functional renal parenchyma in horseshoe, multicystic, duplex and dyplastic kidneys [101, 17, 10, 91-102].

Figure 5.8 (A) Six consecutive reoriented sagittal sections and (B) three-dimensional display showing a linear area of absent tracer uptake from the left renal hilum into the parenchyma, with an interruption of the rim of cortical uptake. This interruption of the rim of renal cortical uptake was best seen on the reoriented sagittal display and on the threedimensional surface shade display. (Reproduced with permission from de Sadeleer et al [59])
Figure 5.9 (A) Non-reoriented corona) slices and (B) reoriented corona) tomographic section. Cortical rim at the right upper pole with decreased uptake compared to the lower pole. Quantitative evaluation of the maximal upper and lower pole activity revealed differences between the two poles as high as 35%. These hypoactive upper poles were also clearly seen on the three-dimensional surface shade images (data not shown). (Reproduced with permission from de Sadeleer et al [166]).

(a) An interruption of the normal cortical contour between two prominent columns of Bertin (Figure 5.10);

(b) A cortical defect due to the interrenuncular septum described by Rossleigh, which less frequently seen in children under the age of [17, 167, 170] (Figure 5.8);

(c) Hypoactive upper poles (Figure 5.9), probably caused by attenuation from the liver or the spleen [171, 172].
Figure 5.10 (A) Normal planar views (posterior, posterior with magnification, right posterior oblique, left posterior oblique). (B) Two consecutive non-reoriented coronal slices; the left kidney is on the right side of the image. (C) Reoriented coronal topographic section; (D) three-dimensional display. A definite focal defect is demonstrated on the posterosuperior side of the left kidney on the different displays of the SPECT study. It can best be identified on the coronal slices without reorientation, but also on the three reoriented images and even on the three-dimensional surface shade display [59].
5.11 Literature Review on Measurement of Glomerular Filtration Rates (GFRs)

The introduction of radionuclides and their use in monitoring renal function has made serial measurements of Glomerular Filtration Rates (GFRs) and Effective Renal Plasma Flow (ERPF) less time consuming and less demanding to both the patient and the technologist. GFR is the clearance rate of a substance that is excreted from the body by glomerular filtration and is not secreted or reabsorbed by the tubules. Ideally, this substance is not protein bound, does not enter RBCs, and is not changed in the process (44). Assuming the substance is cleared solely by glomerular filtration, this rate can be inferred by observing the rate of disappearance of the substance from the blood, the rate of appearance of the substance in the urine, or the amount of uptake of the substance in the kidneys. The methods in the nuclear medicine department capitalize on either measuring the activity in the urine, in the blood, or, by using the gamma camera, in the kidneys. Although gamma-camera or external probe techniques provide differential function and avoid urine and blood sampling, correction for attenuation by overlying liver and spleen must be addressed [68].

Classically, GFR is the urinary clearance of inulin after a steady state is achieved by a continuous intravenous infusion. GFR is then calculated according to the following formula.

\[
\text{Clearance} = \frac{U \cdot V}{P}
\]

where \( U \) : urine inulin concentration in \( \text{mg/ml} \); 
\( V \) : urinary flow rate in \( \text{ml/min} \); and 
\( P \) : plasma inulin concentration in \( \text{mg/ml} \).

This method requires both continuous infusion and urine sampling [67].

To measure GFR an agent must be excreted entirely by glomerular filtration and not be protein bound. The prototype is inulin. The clearance of 5'CN ethylenediaminetetraacetic acid (EDTA) is equivalent to inulin and has been reported to be the most accurate radio-labeled measure of GFR [69]. \(^{131}\text{I}\)-labeled iothalamate has been used instead of \(^{51}\text{Cr}\)-EDTA in the but has the disadvantage of high radiation doses. More recently, \(^{99m}\text{Tc}\)-DTPA has been employed to measure GFR. Because the clearance of \(^{99m}\text{Tc}\)-DTPA is 5% less than that of inulin, \(^{99m}\text{Tc}\)-DTPA underestimates
the true GFR [70]. This is acceptable clinically because creatinine clearance has an error of 10% to 15%. The low radiation dose, low expense, and opportunity for renal imaging make $^{99m}$Tc-DTPA the agent of choice for the measurement of GFR [48].

The inconvenience of urine collection can be circumvented when the renal clearance can be extrapolated to infinite time. This can be accomplished only when the agent is excreted solely by glomerular filtration, the renal function is not too low, and the patient is not too edematous. When these criteria are met, the plasma clearance can be estimated from one or two plasma samples and the complete clearance curve need not be obtained. This avoids the obvious pitfall of urine collection errors and the need for multiple blood samples. In some instances, blood samples are avoided by using the gamma-camera detectors. The gamma-camera techniques do not require urine or blood samples and are faster than creatinine clearance. An additional advantage to the gamma-camera technique over the standard plasma methods is that differential function can be calculated [69].

The two methods of radionuclide administration for GFR measurements are continuous infusion and single bolus injection. Clinically, the single injection technique has been routinely used. The principle of the continuous infusion method is that once equilibrium is established, the rate of disappearance of the tracer via glomerular filtration is equivalent to the rate of infusion. The rate of infusion can then be substituted for $UV$ in the clearance equation. One potential source of error in the continuous infusion method is the buildup of $^{99m}$Tc-DTPA metabolites that are cleared at a slower rate than $^{99m}$Tc-DTPA. This may artificially overestimate the plasma concentration of tracer and therefore underestimate clearance [67].

The most convenient, least demanding method of measuring GFR is by measuring the plasma clearance after single bolus injection. Clearance can be calculated according to injected dose

$$\text{clearance} = \frac{\text{injected dose}}{\text{area under plasma concentration curve}} = \frac{D}{\int P(t) \, dt}$$

The most accurate model of excretion of a GFR tracer is a dual-compartment model that follows a biexponential curve. The initial phase of the curve is rapid and represents the redistribution of tracer into the extracellular space. The second portion
of the curve is much slower and represents elimination of the tracer by glomerular filtration once distribution in the extracellular space is complete (Figure 5.11).

Figure 5.11 The dual-compartment elimination curve of a glomerular filtration rate agent. 1 represents the rapid distribution into the extracellular or intravascular space. 2 represents the elimination of the tracer via glomerular filtration. [66].

The area under the plasma concentration curve is the sum of these two components.

\[ P(t) = Ae^{-at} + Be^{-2at} \]

To accurately represent activity in the two compartments, a complete plasma clearance curve must be obtained. This requires blood samples from 5 minutes up to 5 hours. If plasma samples are obtained before distribution in the extracellular fluid, the area under the curve will be underestimated and the clearance subsequently overestimated [67].

A simplified method of measuring GFR by the single injection technique is to obtain plasma samples 2, 3, and 4 hours after injection. At this time, equilibration with the extracellular fluid (ECF) will be complete. By using this method, often referred to as
the slope intercept method, the initial fast component of the plasma concentration curve will be disregarded and will, therefore, provide GFR values greater than the true GFR. The amount of this error is greatly reduced in patients with poor renal function [69].

Waller et al. [72] used a reference GFR by obtaining half hour blood samples and corrected the GFR for the single compartment model and for body surface area. This group found the closest correlation to the reference GFR when two blood samples at 2 hours and 4 hours were obtained. The standard error of GFR estimate was 2.8 mL/minute. The least accurate measure was the external detector method where the standard error was greater than 10 mL/minute.

There has been an alternate method of GFR measurement reported that accounts for the volume of distribution. GFR can be calculated from the product of the rate constant of the exponential clearance and the volume of distribution of activity. The volume of distribution of activity is calculated from the estimated activity per unit volume assuming dilution had occurred instantaneously. A correction factor is applied to account for the activity already cleared by the kidneys during the distribution phase. Without this factor, the volume of distribution would be overestimated [72]. Fawdry and Gruenewald [73] studied 800 GFR studies obtained by the standard two-sample slope intercept method and compared these to a 3-hour volume of distribution method. They found that the accuracy of the volume of distribution method was greatest when the GFR was between 60 to 100 mL/minute.

Mulligan et al. [74] examined several methods of measuring GFR with $^{99m}$Tc-DTPA. As stated previously, GFR can be calculated from the activity in single or multiple blood samples, from the accumulation of radioactivity in the urine, or from counts obtained solely from the gamma-camera. Mulligan et al. found that the two plasma sample technique of Russell and the urinary sample technique developed by Jackson were the most accurate methods over a large range of renal function. The Russell method involves obtaining blood samples at either 30 and 180 minutes or at 60 and 180 minutes and applying this data to the linear dual-compartment model of Sapirstein that follows:

$$ GFR = \frac{Q_0}{\int Pdt} = \frac{Q_0}{C_1 + C_2} $$
where \( Q_0 \) : the injected dose;
\[
\int_0^\infty P dt \quad \text{dual-exponential integration of six-point plasma disappearance curve by curve stripping;}
\]
\( C1_0, C2_0 \) : the value of the monoexponential compartment curves of the dual-exponential disappearance curve at time 0, and
\( \lambda_1, \lambda_2 \) : rate constants of the two monoexponential compartment curves.

For the 30- and 180-minute Russell [11] sample method, the GFR was calculated thus
\[
GFR = \left[Q_0 \ln\left(\frac{P_{30}}{P_{180}}\right) \times e^{\frac{30\ln P_{30} - 180\ln P_{180}}{150}}\right]^{0.979}
\]
where \( Q_0 \) : the injected dose and
\( P_{30}, P_{180} \) are the activities of plasma samples drawn at 30- and 180-minute.

In the Jackson urinary method, the GFR is calculated from the terminal slope of a plasma disappearance curve. The initial portion of this curve was obtained by externally measuring the blood pool activity in the heart and extrapolating this data to the postvoid bladder image. The total urinary activity was corrected for unexcreted residual bladder activity and the GFR calculated thus.
\[
GFR \approx \frac{TUA}{\int_0^T P dt} = \frac{TUA}{P(t)}
\]
where \( TUA \) : the total urinary activity corrected for residual volume;
\[
\int_0^T P dt \quad \text{portion of} \quad \int_0^\infty P dt \quad \text{from 0 to} \quad T;
\]
\( T \) : the time of postvoid bladder image; and
\( \bar{P}(t) \) : mean plasma activity.

This method was found to be as accurate as the two-sample plasma method discussed earlier. However, as stated previously, urinary methods are inconvenient and prone to collection errors [74].
More recently, the optimal sample time following a single injection was evaluated for GFR measurements assuming the two-compartment model. Russell found that for the most accurate values, sample times must begin by 10 minutes and continue for at least 240 minutes. Although he felt that the long time interval evaluated was more important than the number of samples," & blood samples were recommended. The duration of sampling needed to be at least 3 hours because the slow component of excretion accounted for most of the clearance. The accuracy obtained by these methods, although essential in research, is seldom required clinically [75].

The gamma-camera method of GFR and ERPF measurements is seldom used for global measurements and is discussed more extensively in regard to differential measurements. However, it is discussed briefly here. Chachati et al. [76] reviewed Gates' technique of global and differential GFR measurements following injection of $^{99m}$Tc-DTPA. Using a scintillation camera, the fraction of the injected dose in the kidneys was determined 1 to 3 minutes after injection and compared with the GFR obtained by simultaneous infusion of inulin. The renal function of the study group varied from normal to anuric and included nine patients with either one kidney or a nephrostomy tube. The GFR was calculated according to Gates' [77] equation.

$%\text{Uptake} = \frac{\text{kidney count-background}}{\text{injected dose}} \times e^{-\mu y} \times 100$

where $y =$ the renal depth and $\mu$ is the attenuation coefficient for $^{99m}$Tc.

This group found a good correlation between Gates' method of GFR measurements and inulin clearance in global measurements ($r = 0.86, n = 24, p < 0.001$) and in the unilateral group ($r = 0.91, n = 9, p < 0.001$). Subsequent investigators, however, have demonstrated a poor correlation between the gamma-camera method of Gates and a complete plasma dual-compartment reference method [74].

There have been reports of impurities in the commercial preparations of $^{99m}$Tc-DTPA that have resulted in GFR errors. This has been attributed to protein binding. Ultrafiltration before use has diminished the amount of impurities and thus the error in GFR [78].
The spectrum of accuracy varies widely based on the method chosen to calculate GFR. The complete plasma clearance curve is the most accurate but requires multiple blood samples. The two-plasma blood sample is only slightly more accurate than the one-plasma sample method, whereas the gamma-camera techniques are less accurate than all of the plasma methods. However, the gamma-camera technique has been shown to be more accurate than creatinine clearance and, furthermore, does not require either plasma or urine samples.

5.11.1 Effective Renal Plasma Flow (ERPF)

ERPF is another parameter of renal function. As inulin clearance is the gold standard in glomerular filtration, para-aminohippurate (PAH) is the gold standard for ERPF measurements. Although the measurements of PAH clearance are very accurate, this method requires constant infusion, is inconvenient, and lacks precision. For these reasons, PAH clearance is now rarely used to measure renal function [69].

As with GFR measurements, many methods of ERPF measurements have been reported in the literature. Most of the variety is between the number of plasma samples and the timing of these blood samples (up to six plasma samples). The model of $^{131}$I-01H distribution and secretion follows biexponential decay according to the same dual-compartmental model that the GFR agent $^{99m}$Tc-DTPA follows. The first portion of the decay curve represents the distribution of $^{131}$I-OIH in the extracellular fluid (the first compartment) and dominates the initial 10 to 15 minutes after $^{131}$I-OIH administration. The second portion of the curve represents the intravascular (second compartment) clearance of $^{131}$I-OIH by the kidney and begins about 15 to 20 minutes after $^{131}$I-OIH injection. The complete plasma concentration curve can be plotted when multiple blood samples are obtained over approximately 60 minutes, although the minimal gain in accuracy of the additional samples and the inconvenience to both the technologist and patient make this technique unfeasible clinically. The most common technique of ERPF measurement is a single bolus administration of $^{131}$I-OIH followed by either one or two plasma samples [79].

For an agent to measure renal plasma flow, it must have an extraction efficiency of 100%. PAH is the nearest to the ideal agent with an extraction efficiency of 90% and with tubular excretion. Because PAH is not completely extracted, the term effective renal plasma flow is used when this agent quantitates renal plasma flow. The two radionuclides that most closely resemble the incomplete extraction and tubular
excretion of PAH are $^{131}$I-OIH and $^{99m}$Tc-MAG3 [67]. $^{131}$I-OIH clearance is slightly less than that of PAH. When using a single injection technique, however, the measurements obtained with $^{131}$I-OIH correlate well with those obtained from constant infusion of PAH. The correlation is felt to be secondary to the competing effects of $^{131}$I-OIH's lower clearance and the inability of the single injection technique to accurately quantitate the first few minutes of the plasma time activity curve. These errors tend to cancel [69].

Since 1982, the single injection, single-sample method for ERPF measurements has been an established method according to Dubovsky and Russell. The single sample is drawn about 44 minutes after $^{131}$I-OIH is administered and, therefore, discounts the extracellular distribution phase by assuming equilibrium has been obtained. This method is the simplest and least time consuming of the plasma techniques [79].

The two-plasma sample technique has been reported to be more accurate. Russell et al. [80] compared the one- and two-plasma sample techniques to a complete reference curve. The reference data was obtained from six to nine plasma samples drawn between 10 and 90 minutes. The single-sample ERPF measurement was obtained from a 44-minute postinjection sample. The two-sample method ERPF was obtained by calculating the ERPF from two samples in the reference curve. Russell et al. found that the residual standard deviation of the two-plasma sample method (20 mL/minute) was approximately half that obtained from a single sample (48 mL/minute). In addition, the optimal time interval for the two samples was 8.7 minutes and 92 minutes postbolus injection. This group recommended the single injection, two-plasma sample method of ERPF calculation only when accuracy is critical (research) and further advised obtaining the samples at 10 to 15 minutes and at 60 to 90 minutes postinjection.

The slope intercept method also uses two plasma samples after a single bolus injection of $^{131}$I-OIH. However, the two samples are drawn between 30 and 60 minutes. These samples can be used only to estimate the clearance portion of the decay curve and, like the single-sample method, it disregards the extracellular equilibration. Consequently, the volume of distribution and the ERPF is overestimated. This method offers little advantage over the single-sample method and furthermore requires an additional plasma sample.

Lear et al. [79] proposed a new two-compartment, two-sample technique and compared this technique to the single 44-minute sample technique and to the slope
intercept technique. This group based their new technique on the volume of distribution and on the exchange between the intravascular and extravascular space observed in healthy and unhealthy patients. The volume of distribution is the sum of the intravascular and extravascular volumes. They noted that the intravascular (V1) and extravascular (V2) components had a stable rate of exchange (k/V1, k/V2) over a wide spectrum of renal function. The fraction of the volume of distribution contained in V1 ranged from 0.5 to 0.6 with the V1 = 0.6 X Vd in healthy individuals and V1 = 0.6 X Vd in patients with severe renal disease. In this model, V1 was assumed to equal to V2, and the sum was equal to the volume of distribution (Vd). Following is the biexponential decay curve of the two-compartment model.

\[
\frac{dC_1}{dt} = -ERPF\left(\frac{C_1}{V_1}\right) - \frac{k}{V_1}C_1 + \left(\frac{k}{V_1}\right)C_2
\]

\[
\frac{dC_2}{dt} = \left(\frac{k}{V_2}\right)(C_1 - C_2)
\]

where \(C_1\) is the \(^{131}\text{I}-\text{OIH}\) concentration in compartment 1; \(C_2\) is the \(^{131}\text{I}-\text{OIH}\) concentration in compartment 2; \(k\) is the rate constant of intercompartmental exchange; and ERPF is the effective renal plasma flow.

When assuming that \(V_1 = V_2\), and \(V_i = 0.5 \times V_d\) and \(k/ V_1 = 0.5\), the equation is simplified to

\[
\frac{dC_1}{dt} = -ERPF\left(\frac{C_1}{V_1}\right) - 0.05(C_1 - C_2)
\]

\[
\frac{dC_2}{dt} = 0.05(C_1 - C_2)
\]

A personal computer then set certain conditions and generated a time concentration curve that best fit the data obtained at 40 and 60 minutes. The ERPF and volume of distribution was then calculated. With this method there were certain assumptions that do not always hold true. \(V_i\) will not always equal 0.5\(V_d\) and \(k\) will not be constant in all patients. This group reported, however, that resulting errors in ERPF values were smaller than errors found in other techniques. In addition, adjustments to \(V_i\) and \(V_d\) were suggested in different clinical settings and the computer program was provided to accomplish the corresponding calculations. The advantage of this technique over
the slope intercept method is that this method accounts for the extravascular distribution time [79].

ERPF has been measured by a gamma-camera method both globally and differentially. Chachati et al. [76] examined a gamma-camera method of ERPF calculations following $^{131}$I-OIH injection and compared this to the PAH infusion method. The basis of the gamma-camera method was to determine the fraction of the injected dose of $^{131}$I-OIH 1-2 minutes after administration according to Schlegel's equation.

$$\text{Relative uptake} = \frac{\text{kidney count - background} \times Y^2}{\text{1 minute count of injected dose}} \times 100$$

where $Y$ is the renal depth calculated thus; left kidney: 13.2 (weight/height) + 0.7; and right kidney: 13.3 (weight/height) + 0.7.

The renal depth calculation was developed by Tonnesen and cited by Schlegel and Hamway [81]. Chachati and his group [76] found a good correlation between PAH clearance and ERPF ($r = 0.84$, $n = 22$, $p < 0.001$). The gamma-camera methods are infrequently used to measure global function and are discussed more fully during the review of differential renal function.

$^{99m}$Tc-MAG3 has a clearance that is nearly half that of $^{131}$I OIH. However, ERPF measurements reported with $^{99m}$TcMAG3 have correlated with those of $^{131}$I-OIH (58). Using a dual-channel technique, ERPF was calculated following simultaneous administration of $^{131}$I-OIH and $^{99m}$Tc-MAG3 and after obtaining a 44-minute plasma sample. The proportionality constant between $^{131}$I-OIH and $^{99m}$Tc-MAG3 was 0.563. By taking the product of the $^{99m}$Tc-MAG3 activity and 0.563 and substituting this value for $^{131}$I-OIH activity, the ERPF values in 50 patients agreed with those obtained with $^{131}$I-OIH ($r = 0.96$) [83].

One- and two-plasma sample methods for evaluating ERPF with $^{99m}$Tc-MAG3 were compared by Russell et al [84]. The single plasma sample was drawn at 43 minutes and resulted in an error of 19 mL/minute (residual standard deviation). The 43-minute sample time was the optimum over a large range of renal function. Longer sample times in poor renal function and shorter sample times in patients with good renal function can be used when renal function is known in advance. The 43-minute sample time is preferred by these investigators in cases of unknown renal function. The two-plasma sample technique resulted in an error of 7 ml iminute (standard residual
(deviation) when the samples were obtained at 12 and 94 minutes. Note that the suggested sample times for $^{99}$mTc-MAG3 are almost identical to those recommended for $^{131}$I-OIH. Finally, these investigators felt that the accuracy needed for clinical decision making was provided by the single-sample technique and that the two-sample method should be reserved for research purposes when accuracy is essential.

Muller-Suur et al. [85] found that a single sampling time of 60 minutes provided a smaller error of 15 mL/minute as compared with the 19 mL/minute found by Russell et al. at 43 minutes. Furthermore, this group reported a regression equation to convert the ERPF values obtained with $^{99}$mTc-MAG3 to the more familiar corresponding $^{131}$I-OIH values. Muller-Suur et al. used the equation

$$ERPF = 1.86 \times C \ (MAG3) + 4.6$$

The obvious advantage of the superior dosimetry of $^{99}$mTc-MAG3 over $^{131}$I-OIH makes $^{99}$mTc-MAG3 the ideal agent for ERPF measurements. The normal ERPF value obtained with $^{131}$I-OIH is 600 mL/minute, and the normal clearance of $^{99}$mTc-MAG3 is 370 mL/minute.

Following bolus injection of a tubular agent ($^{131}$I-OIH or $^{99}$mTc-MAG3), serial images of the kidney are obtained every 2 to 3 minutes (refer to section 5.7). To minimize tissue attenuation, these images are anterior images in the transplant patient and posterior images in native kidneys. Renogram represents several different components of radionuclide distribution, the vascular phase, the concentration phase, and the excretory phase. Because the kidneys receive approximately 20% of the cardiac output, the initial phase of the curve is rapidly upsloping and represents renal perfusion. This begins about 15 to 20 seconds after injection and reaches an inflection point at 20 to 40 seconds. Renal tubular function and background activity also affect the slope. The second portion of the renogram curve has milder increase in activity reaching a peak within 3 to 5 minutes. This portion of the curve represents tubular accumulation. By about 3 to 5 minutes, the activity in the kidney begins to accumulate in the bladder via the collecting system. This is represented by a rapidly falling curve (Figure 5.4). In addition, a curve can be generated that represents the perfusion only. Rapidly acquired frames immediately following the bolus of either $^{99}$mTc-MAG3 or $^{99}$mTc-DTPA delineate the aorta and the kidneys. Normally, activity is seen in the kidneys within 3.5 seconds of being seen in the aorta.
The shape of the renogram curve is affected by many factors. Prerenal insults will affect the perfusion portion of the curve. Renal diseases such as glomerulonephritis will affect the tubular function portion of the curve, whereas postrenal diseases such as obstruction will prevent activity from reaching the bladder and affect the excretory portion of the curve [86].

5.11.2 Differential Function

The disadvantage of the foregoing techniques for the measurement of GFR and ERPF is that the measurements are global measurements and individual kidney function is not addressed. Gamma-camera techniques have been developed to measure both global and differential GFR and ERPF. Most do not require urine samples, and, although most do not require plasma samples, several do use one plasma sample. The obvious advantage to gamma-camera techniques is that they are not invasive. However, this comes at a price. The accuracy of these techniques is not always comparable to the plasma clearance methods but is usually superior to creatinine clearance.

Global and differential GFR measurements use the gamma-camera to produce a renogram after $^{99}$mTc-DTPA bolus injection and apply this data to the following equation to obtain the individual kidney glomerular filtration rate (IKGFR).

$$\frac{dR}{dt} = \alpha P(t)$$

where $dR$ is the rate of renal uptake;
$P$ is the plasma concentration; and
$\alpha$ is the constant of proportionality and represents IKGFR.

Once correction has been made for background, the IKGFR should be constant for up to 2.5 minutes after injection. This is the minimum time it takes for the radionuclide to transit the renal ROI [87]. Many variations on this equation were reported separately by Rutland [88] and Rehling et al. [89] in 1985.

One of the problems of accurate gamma-camera imaging of $^{99}$mTc-DTPA is the low extraction efficiency and subsequent low target-to-background ratio. The background correction is the main source of error in this method. The liver, spleen, adrenals, renal hilar vessels, intestine, and soft tissue all contribute to background. These organs vary
in their ratio of intravascular to extravascular activity, and no single area accurately represents the intravascular and extravascular components of background. Perirenal, subrenal, supraparenal, and heart activity have all been used in an attempt to approximate the background correctly. Bell and Peters [90] reported that extravascular chest wall activity contributed to an error in background cardiac blood pool estimation and resulted in overestimation of IKGFR by a factor of 1.17.

Piepsz et al. [91] addressed the problem of background correction. This group reported a double background correction method that combines the area ratio method and the linear fit method. The area ratio method is stated as

\[ R_c(t) = R_b(t) + T(t) + aP(t) \]

where \( T(t) \) represents the extravascular component and \( aP(t) \) is the fraction of blood pool activity included in the background \( ROT \). \( R_b(t) \) is the noncorrected renal activity and \( R_c(t) \) is the background corrected renal activity. Thus, the background can be corrected by the area ratio as

\[ \text{Background activity} = T'(t) + a'P(t) \]

where \( T'(t) \) is the extravascular component in the perirenal space. Assuming that the activity in the perirenal space is an approximate of the extravascular component in the renal space, \( T = T' \). By subtracting the previous two equations and dividing them by \( P(t) \) one finds

\[ \frac{R_c(t)}{P(t)} = \frac{\int P(t)dt}{P(t)} + (a - a') \]

where \( a - a' \) is the fraction of the intravascular component not corrected for by the area ratio method. This is an equation for a straight line. The slope of this line is the clearance that has been corrected for both intravascular and extravascular activity. This method works well when the background ROI is the perirenal or subrenal space. The supraprenal space contains the liver, and the activity in this region is not all extravascular, as is assumed in both the perirenal and subrenal regions. This results in an overestimation of the GFR because this region is not corrected for the intravascular activity. Russell [68] compared a method that used cardiac activity as the background correction to one that used a deconvoluted least-square technique. He found that the cardiac correction had a standard deviation of 18.9 mL/minute as compared with the plasma clearance method, whereas the least-square technique had a standard deviation of 14.5 mL/minute.
Differential ERPF can also be measured with a gamma-camera technique following either $^{131}$I-OIH or $^{99}$mTc-MAG3 injection. Fine et al. [93] compared several gamma-camera techniques to two plasma clearance techniques using $^{131}$I-OIH. The three gamma-camera methods differed only in the ROI chosen to correct for background. The regions were either between the lower poles, upper poles, or crescents lateral to the kidneys. A two-plasma sample method was used as the reference with samples drawn at 20 and 45 minutes. An additional plasma method was included that required one blood sample at 45 minutes. The ERPF measured with the reference method and the one plasma sample method was 384 mL/minute and 319 mL/minute, respectively. None of the gamma-camera techniques were as accurate as the plasma methods.

The reproducibility of manually drawn ROIs was also examined and was found to be very high (correlation coefficient regardless of the observer was greater than 0.98). Fine et al. suggested using either ultrasound or lateral scintigrams to correct for tissue depth because the ERPF was not altered by more than 1% as a result of depth correction in any patient in this study. The algorithm developed by Schlegel [81] was used.

Tondeur et al. [94] examined ERPF gamma-camera clearance with $^{99}$mTc-MAG3. Tc-MAG3 is significantly protein bound and therefore has a smaller extravascular component [95]. It also has a higher renal clearance than $^{131}$I-OIH. This was expected to result in a more accurate time activity curve by the gammacamera and a higher target-to-background ratio. In this study, the ERPF was calculated by the double correction method discussed previously, and lateral scintigrams were used to correct for tissue depth. Cardiac activity was used to estimate plasma activity and a 20-minute plasma sample was drawn for the renal clearance calculation. Three different areas were used to correct for background: suprarenal, perirenal, and subrenal regions. The clearance calculated by suprarenal correction was repeatedly higher than clearances calculated with the other two regions. This was felt to be secondary to the unaccounted intravascular component in the suprarenal region. The cardiac plasma activity was also compared with plasma sample activity in 6- and 20-minute samples and was found to be lower with a mean difference of 19.2%. Even though the high protein binding of $^{99}$mTc-MAG3 was expected to diminish the error associated with extravascular activity in the precordium, the faster clearance of $^{99}$mTc-MAG3 produced rapidly decreasing plasma activity and may have made the precordial activity inaccurate except at very early measurements.
5.12 Author’s work RENOGRAPHY MODELLING [25-26]

In renography, a tracer is introduced into the blood circulation. The kidney extracts this tracer from the blood circulation in the glomeruli and for a transient period of time in a normal person, the tracer is found within the renal parenchyma. From the renal parenchyma, it is excreted into the collecting system of the kidney (mainly the renal pelvis), from whence it travels out of the kidney into the urinary bladder. In many conditions, there is abnormalities in this outflow part of the kidney. For example, renal stones can be found in the outflow tract and cause obstruction to urine flow. The result is that the tracer is trapped within the renal pelvis much longer than normal.

In this paper, the aim is to model the behavior of tracer from input to the washout from the renal pelvis. This results from the model will be compared to actual data from renography.
Figure 5.12 Compartmental Model. The control volume is the ROI in our work.
If a tracer is injected into the blood circulation and the amount of tracer is measured by radioactive means in the renal outflow, the following curve is seen in a normal person:
5.12.1 Control volume around the renal pelvis

\[ G_1: \text{Tracer mass in the chamber 1, renal parenchyma in Counts.} \]
\[ G_2: \text{Tracer mass in the chamber 2, renal pelvis in Counts.} \]
\[ C_1: \text{Concentration of tracer in the chamber 1, renal parenchyma in Counts/dl.} \]
\[ C_2: \text{Concentration of tracer in the chamber 2, renal pelvis in Counts/dl.} \]
\[ V_1: \text{Volume of chamber 1, renal parenchyma in dl.} \]
\[ V_2: \text{Volume of chamber 2, renal pelvis in dl.} \]
\[ I(t): \text{Tracer input function in Counts/sec.} \]
\[ F(t): \text{Blood Flow from chamber 1 to chamber 2 in dL/sec.} \]
\[ U(t): \text{Urine outflow in dl/sec.} \]

**Figure 5.14** Renogram showing the normal versus obstructed at the renal pelvis.

**Figure 5.15** The derived two-compartmental renal model.
\[
\frac{dG_1}{dt} = -FC_1 + I(t), \text{ for chamber 1} \quad (1)
\]
\[
\frac{dG_2}{dt} = FC_1 - C_2U(t), \text{ for chamber 2} \quad (2)
\]

where

(i) \( G_1(= C_1V_1) \) represents the tracer amount in chamber 1, and

(ii) \( G_2(= C_2V_2) \) represents the tracer amount in chamber 2.

In physiological studies of the kidney urine flow, the input function is a tracer bolus administered over a short period of time. Compared to the entire duration of the renal dynamics, this bolus injection of tracer is approximated by an impulse function (Dirac’s delta function). In the following derivation, whenever \( I(t) \) appears it will be assumed be equal to \( \delta(t) \).

Assuming that the volumes of distribution \( V_1 \) and \( V_2 \) are constants (which they generally are), and the urinary flow rate \( U \) to be a constant unknown (urine flowing out of the kidney into the ureters is physiologically continuous and constant with time, unless there are changes in body fluid status. Here we are only performing an intra-renal analysis for any obstruction to the outflow), we have from eq (1) and (2):

\[
\frac{V_1 dC_1}{dt} = -FC_1 + I(t) \quad (3)
\]
\[
\frac{V_2 dC_2}{dt} = FC_1 - C_2U \quad (4)
\]

Differentiate eq (4) to obtain :

\[
\frac{V_2 d^2C_2}{dt^2} = \frac{d}{dt} \left( FC_1 - C_2U \right) - U \frac{dC_2}{dt} \quad (5)
\]

Replace the first term on the right hand side with eq (3) :

\[
\frac{V_2 d^2C_2}{dt^2} = F \left( \frac{I - FC_1}{V_1} \right) - U \frac{dC_2}{dt}
\]
Replace the term with $C_1$ with eq (4) so as to get a differential equation in the variable of interest, $C_2$:

$$\frac{V_2 d^2 C_2}{dt^2} = F \left( \frac{I}{V_1} - \frac{FC_1}{V_1} \right) - U \frac{dC_2}{dt}$$

$$= F \left( \frac{I}{V_1} - \frac{V_2 \frac{dC_2}{dt} + UC_2}{V_1} \right) - U \frac{dC_2}{dt}$$

$$= \left( \frac{F}{V_1} \right) I - \left( \frac{F}{V_1} \right) \left( \frac{V_2 \frac{dC_2}{dt} + UC_2}{V_1} \right) - U \frac{dC_2}{dt}$$

$$= \left( \frac{F}{V_1} \right) I - \frac{dC_2}{dt} \left( \frac{FV_2}{V_1} + U \right) - \left( \frac{FU}{V_1} \right) C_2$$

Eq (6) is a linear second-order differential equation, which we can rearrange as follows, where the subscript 2 for $C_2$ has been suppressed, as all the $C$ terms are referring to the same concentration of compartment 2 (the renal pelvicalyceal compartment).

$$V_2 \ddot{C} = \left( \frac{F}{V_1} \right) I - \dot{C} \left( \frac{FV_2}{V_1} + U \right) - \left( \frac{FU}{V_1} \right) C$$

Let the following indices be defined:

$$\left( \frac{FV_2}{V_1} + U \right) = \beta$$

$$\left( \frac{FU}{V_1} \right) = \gamma$$

Using the indices as defined above, eq (7) becomes

$$V_2 \ddot{C}_2 = \left( \frac{F}{V_1} \right) I(t) - \beta \dot{C}_2 - \gamma C_2$$

or,

$$V_2 \ddot{C}_2 + \beta \dot{C}_2 + \gamma C_2 = \left( \frac{F}{V_1} \right) I \delta(t)$$
This is a standard form for a linear second-order ordinary differential equation, with $I$ as the impulse function. This is the governing differential equation for the behaviour of tracer within the renal pelvicalyceal compartment.

Solution by Laplace transform method yields the following analytical result:

$$L\{V_2\ddot{C} + \beta \dot{C} + \gamma C\} = L\left\{\frac{F}{V_1}\right\}I\delta(t)$$

$$\therefore \left(V_2s^2 + \beta s + \gamma\right)C_2(s) = \frac{F}{V_1}$$

$$C_2(t) = C(t) = \left(\frac{F}{V_1}\right)\left(\frac{1}{V_2s^2 + \beta s + \gamma}\right) = \frac{F}{V_1}V_2s\left(s + \frac{\beta}{V_2s} + \frac{\gamma}{V_2}\right)^\frac{1}{2}$$

Solving the above Laplace transform and taking care of the characteristics of the roots (which is now in standard form, by looking up standard tables), we obtain the results for the dynamic behavior of the tracer concentration in the renal pelvis for this physiological system. The term underneath the square root is the determinant of the behavior of the system with regards to whether there is underdamped, critically damped or overdamped behaviour.

This term can be expressed as $\beta^2 - 4V_2\gamma$ and it yields a significant functional index for assessing the outflow status of the kidney. We will classify the observed physiological behaviours of renogram systems into underdamped, overdamped or critically damped systems based on the index, as follows:

**Case 1:**

If $\beta^2 - 4V_2\gamma < 0$, the condition is underdamping, and (7) yields the solution:
As can be seen from equation (8), the terms which describe urine outflow and determine the shape of the tracer-concentration curve of the renogram during the tracer wash-out phase are the $e^{-\beta t/V_2}$ and $\sin \left( \frac{\gamma - \beta^2}{V_2 4V_2^2} t \right)$. The important dynamic information captured in these two terms can be succinctly found in the physiological index that we have described. We will demonstrate the discriminatory nature of this index (which will be extracted as $A$) in section IV when we analyse correlation with actual renogram studies.

Equation (8) is a linear second-order ordinary differential equation, very similar to that of the linear oscillator with damping. In a functioning renal system, the characteristic oscillating-underdamped conditions do not exist.

**Case 2:**

Whenever there is outflow obstruction, the key term

$$\beta^2 - 4V_2 \gamma = \left( \frac{FV_2}{V_1} + U \right)^2 - 4V_2 \left[ \frac{FU}{V_1} \right] = \left( \frac{FV_2}{V_1} - U \right)^2 > 0$$

and the condition is overdamping. Then,

$$C(t) = \left( \frac{F}{V_2 V_1} \right) e^{-\beta t/V_2} \sinh \left( \frac{\gamma - \beta^2}{V_2 4V_2^2} t \right)$$

We can express output segment of the tracer curve of compartment 2 looks different from that of the tracer input.
\[ \beta^2 - 4V_2' \gamma = \left( \frac{FV_2}{V_1} + U \right)^2 - 4V_2 \left( \frac{FU}{V_1} \right) = \left( \frac{FV_2}{V_1} - U \right)^2 \]

so the key term actually reflects the rate of tracer input \((FC_1)\) minus the rate of tracer output \((UC_2)\).
Case 3:

In the normal case, most physiological systems are well-compensated, and hence the output are fairly similar, hence,

\[ \beta^2 - 4V_2 \gamma = \left( \frac{FV_2}{V_1} + U \right)^2 - 4V_2 \left( \frac{FU}{V_1} \right) = \left( \frac{FV_2}{V_1} - U \right)^2 = 0 \]

In other words, the renal system is critically damped.

The governing equations for this will be

\[ C(t) = \left( \frac{F}{V_1V_2} \right) e^{-\frac{\beta}{2V_2} t} \]  \hfill (12)

For model analysis, because of complications involved in monitoring $U$ (urine flow rate), $F$ (plasma flow rate into the renal pelvis) and $V_1$ control volume, we propose that our model parameters will be lumped parameters $k$ and $A$. Next our parameters identification will be carried out for $k$, $A$, $V_2$ and $\beta$. It is important to point out that only for critically damped case, we can separate the $V_2$ and $\beta$ individually during the parameters identification process.
\[ k = \frac{F}{V V_2} \]  \hspace{1cm} (20)

\[ A = \sqrt{\frac{\gamma - \frac{\beta^2}{4V_2^2}}{V_2}} \]

\[ A^2 = \frac{\gamma - \frac{\beta^2}{4V_2^2}}{V_2} \]

\[ \gamma = \left( A^2 + \frac{\beta^2}{4V_2^2} \right) V_2 \]

From (21):

\[ \gamma = \left( A^2 + \frac{\beta^2}{4V_2^2} \right) V_2 \]

From (8):

\[ \beta = \frac{FV_2}{V_1} + U \]  \hspace{1cm} (22)

\[ \gamma = \frac{FU}{V_1} \]  \hspace{1cm} (23)

From (23):

\[ \frac{\gamma}{U} = \frac{F}{V_1} \]  \hspace{1cm} (24)

From (24) & (20):

\[ \frac{\gamma}{U} = \frac{F}{V_1} = kV_2 \]

\[ F = \frac{\gamma V_1}{U} \]  \hspace{1cm} (25)

Sub (25) into (22):

\[ \beta = V_2 \left( kV_2 \right) + U \]

\[ U = \beta - kV_2^2 \]  \hspace{1cm} (26)
From the parameters identifications, we obtain $k, A, \beta$ & $V_2$.

Hence, $U(t) \text{ dl/sec.}$ (urine outflow) can be determined. Note that at this point of our work, we can only determine the $U$ for critically damped case because only this case we can separate the $V_2$ and $\beta$ individually.
5.13 CLINICAL DATA & EVALUATION

We will demonstrate and verify the application of our models using the renograms obtained from the Nuclear Medicine and PET Department. The radionuclide used are $^{99m}$Tc-DTPA and $^{99m}$Tc-MAG3. The degree of match with the governing equations is based on the area under the left and right kidney curves against the clinical curves between 60 and 120 seconds.

5.13.1 Model Application:

We will first digitalize and normalized the renograms. Next, we will perform parameters identification and obtain the system parameters: $k$, $A$, $\beta$ and $V_2$. We will only accept the results of the best fit.

Figure 5.16 Clinical renograms of volunteer coded Patient 7. Note that the $(Q_R-R_R)$ segment of the tracer curve for the right kidney is similar to the $(P_R-Q_R)$ segment and demonstrates good outflow-rate compared to the $(Q_L-R_L)$ segment of the obstructative curve for the left kidney.
Figure 5.17 Simulated results based on the clinical data of Patient 7 in Figure 5.15.

TABLE 5.2 Comparison of clinical and calculated results of Patient 7. We can observe that the errors for each kidney is less than 1%.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Left Kidney</th>
<th>Fitting</th>
<th>Right Kidney</th>
<th>Fitting</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SSE</td>
<td>R Sq</td>
<td>SSE</td>
<td>R Sq</td>
</tr>
<tr>
<td>k</td>
<td>0.0124</td>
<td>0.0221</td>
<td>0.0118</td>
<td>0.9879</td>
<td>LT(O)</td>
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<tr>
<td>A</td>
<td>5.48E-03</td>
<td>8.68E-03</td>
<td>0.9966</td>
<td>0.9879</td>
<td>RT(O)</td>
</tr>
<tr>
<td>β/ V²</td>
<td>0.01235</td>
<td>0.0021</td>
<td>0.0118</td>
<td>0.9966</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.9966</td>
<td>0.9879</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calculated Area</td>
<td>39.64</td>
<td>50.72</td>
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<tr>
<td>Calculated U</td>
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<td>44.00</td>
<td>0.29%</td>
<td>56.13</td>
<td>-0.23%</td>
</tr>
<tr>
<td>Relative Area</td>
<td>44.00</td>
<td>0.29%</td>
<td>56.00</td>
<td>-0.23%</td>
<td></td>
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</table>
Figure 5.18 Clinical renograms of volunteer coded Patient 19. Left kidney is normal while the right kidney has minor obstruction.
Figure 5.19 Simulated results based on the clinical data of Patient 19 in Figure 5.17.

TABLE 5.3 Comparison of clinical and calculated results of Patient 19. We can observe that the errors for each kidney is less than 3%.

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<tr>
<td></td>
<td>SSE R Sq</td>
<td>SSE R Sq</td>
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<td>SSE R Sq</td>
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<td>A</td>
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<tr>
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<td>0.0620</td>
<td>0.007</td>
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<tr>
<td>V₂</td>
<td>0.5389</td>
<td>0.9462</td>
<td>0.0872</td>
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<tr>
<td>Calculated Area*</td>
<td>38.52</td>
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<tr>
<td>Calculated/ Clinical (%)</td>
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<td>51.00</td>
<td>-2.39</td>
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<td>49.00</td>
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<td>Relative Area*</td>
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<tr>
<td>U</td>
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<tr>
<td>Relative U (%)</td>
<td>45.77</td>
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Figure 5.20 Clinical renograms of volunteer coded Patient 11. Left and right kidneys are normal.
Figure 5.21 Simulated results based on the clinical data of Patient 11 in Figure 5.19.

TABLE 5.4 Comparison of clinical and calculated results of Patient 11. We can observe that the errors for each kidney is less than 5%.

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<th>Remarks</th>
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</thead>
<tbody>
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<td>SSE</td>
<td>R Sq</td>
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<tr>
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<td></td>
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</tr>
<tr>
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<td>0.0255</td>
<td>0.9818</td>
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<tr>
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<td>0.9852</td>
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<tr>
<td></td>
<td>Calculated</td>
<td>Calculated</td>
<td>Calculated</td>
<td>LT(C)</td>
<td>RT(C)</td>
</tr>
<tr>
<td>Area</td>
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<td>43.58</td>
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<td></td>
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</tr>
<tr>
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<td>48.00</td>
<td>4.49</td>
<td>54.16</td>
<td>52.00</td>
</tr>
<tr>
<td>Calculated/ Clinical (%)</td>
<td>43.24</td>
<td>56.76</td>
<td></td>
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</table>
Refer to Appendix G for more simulation and clinical data.

5.14 Non-Dimensional Indices for Kidney Obstructions

In our discussions in the previous sections, we can observe that the $U(t)$ can only be calculated for normal cases. Hence, the NDI that we are proposing will be based on the area under the curve between 60 sec and 120 sec.

In clinical practice, the clinician will determine if the patient has obstructed kidneys based on the range beyond 45:55 or 55:45 (Area of Left Kidney : Area of Right Kidney).

$$\text{NDI} = \frac{\text{Area under the curve between 60 sec and 120 sec for left kidney}}{\text{Area under the curve between 60 sec and 120 sec for right kidney}}$$

![Figure 5.22 Ranges for indicating the left or right or both kidneys and normal ranges.](image-url)
5.15 CONCLUSION

We have demonstrated modeling of kidney-renal outflow tract compartments with derivation of the governing equations from second-order differential equations and assessed the clinical relevance with comparison with clinical renogram studies. From which, we can derive the urine outflow noninvasively for normal kidneys. NDI for identifying kidneys obstruction has also been discussed.
Reference On Modeling Of Renal Obstructions


Chapter 6 Non-dimensional Physiological Indices for Clinical Assessment

Purpose of Non-Dimensional Indices

This chapter concerns systematic application of dimensional analysis in human physiology, in which use is made of parameters of functional second order linear differential equations of physiological systems, to develop non-dimensional physiological indexes (NDPIs) to qualify patient health and diseases status as well as patient improvement. We have developed NDPIs for several physiological phenomena and systems, and indicated as to how they can be employed diagnostically. We have formulated NDPIs for:

(i) In Chapter 1, we have used the results of Oral Glucose Tolerance Test, to classify the patients into non-diabetic, diabetic or at-risk. The NDPIs can also distinguish the patients who are at-risk from non-diabetic and diabetic. Then they can undergo pre-emptive medications.

(ii) Chapter 3, Lung Ventilatory function, to enable us to diagnose lung diseases in terms of just one non-dimensional lung-ventilatory index ($VTI$) number, incorporating the lung parameters resistance ($R$) and compliance ($C$) as well as the lung breathing rate.

(iii) Chapter 4, Lung Gases Metabolism, to enable us to determine the lung efficiency in oxygen consumption and carbon dioxide rates, by one NDPI incorporating oxygen diffusion coefficient $D_{O_2}$ and carbon dioxide diffusion coefficient $D_{CO_2}$.

(iv) Chapter 5, Kidney Renal Dysfunctions, to enable us to quantify the severity of renal obstructions of both the patient’s kidneys by a NDPI.
6.1 Summary of Author’s work Non Dimensional Physiological Indices

From the previous chapters, we have realized that dimensional analysis has contribution to make to almost any problem and especially those where analytic methods fail. The ability to get dimensional and dimensionless relationships from differential equations is of great importance when the later too complex for analytic solution. Derivation of suitable dimensionless terms yields major insights into physical nature of particular problem. We have developed NDPIs for:

(i) Chapter 1, Oral Glucose Tolerance Test, to classify the patients into non-diabetic, diabetic or at-risk. The NDPIs can also distinguish the patients who are at-risk from non-diabetic and diabetic. Then they can undergo preemptive medications [2-3].

\[
G_{-NDI} = \frac{y_{\text{max}} \times y_2}{G^2} \times \frac{T_d}{A} \times \frac{T_{\text{max}}}{T_2} \times 10^6
\]

\[
l_{-NDI} = \frac{\beta \gamma \delta}{\alpha}
\]

\[
NDI = G_{-NDI} \times l_{-NDI}
\]

\[
= \frac{y_{\text{max}} \times y_2}{G^2} \times \frac{T_d}{A} \times \frac{T_{\text{max}}}{T_2} \times 10^6 \times \frac{\beta \gamma \delta}{\alpha}
\]

\(\alpha\): increases means insulin removed

\(\beta\): increases means insulin responsive to glucose concentration

\(\gamma\): decreases means blood glucose increases and not enough glucose absorbed by tissues.

\(\delta\): decreases means blood glucose increases and inadequate tissue glucose utilization.

(ii) Chapter 3, Lung Ventilatory function, to enable us to diagnose lung diseases in terms of just one non-dimensional lung-ventilatory index (VTI) number, incorporating the lung parameters resistance \((R)\) and compliance \((C)\) as well as the lung breathing rate \([1, 5, 8]\).
\[ NDPI = \frac{D_{CO_2}}{D_{O_2}} \times \frac{O_2 \text{ consumption rate}}{CO_2 \text{ production rate}} \]

Checking dimensions:

\[ NDPI = \frac{D_{CO_2}}{D_{O_2}} \times \frac{O_2 \text{ consumption rate}}{CO_2 \text{ production rate}} = \frac{mlCO_2/\text{min}/mmHg}{mlO_2/\text{min}/mmHg} \times \frac{mlO_2/\text{min}}{mlCO_2/\text{min}} \]

Example:

\[ NDPI = \frac{417.68 \text{ mlCO}_2/\text{min}/mmHg}{21.90 \text{ mlO}_2/\text{min}/mmHg} \times \frac{283.2 \text{ ml/min}}{226.8 \text{ ml/min}} = 23.8 \]

(iii) Chapter 4, Lung Gases Metabolism, to enable us to determine the lung efficiency in oxygen consumption and carbon dioxide rates, by one NDPI incorporating oxygen diffusion coefficient \( D_{O_2} \) and carbon dioxide diffusion coefficient \( D_{CO_2} \) [4,6-7, 9-11].

\[ VTI_1 = \left[ (Ra \cdot Ca) \cdot \text{(Ventilatory rate in s}^{-1}) \cdot 60 \right]^2 = \tau_a^2 \cdot (BR)^2 \cdot 60^2 \]

where \( BR \) is the breathing rate.

\[ VTI_2 = \frac{(BR) \cdot TV}{[P_1] \cdot [P_2] \cdot [P_3]} = \frac{(BR) \cdot [TV]}{[P_1] \cdot [P_2] \cdot [P_3] \cdot \tau_a^2} \]

(iv) Chapter 5, Kidney Renal Dysfunctions, to enable us to quantify the severity of renal obstructions of both the patient’s kidneys by a NDPI [12-13].

\[ NDI = \frac{\text{Area under the curve between 60 sec and 120 sec for left kidney}}{\text{Area under the curve between 60 sec and 120 sec for right kidney}} \]

Each Physiological Non-Dimensional Indexes (PNDIs), serves its own functions in discriminating the normal from diseasing or diseased physiological organ system. The ranges of each indices which represent each class has been discussed in their respective chapters.
6.2 Conclusions

The author has demonstrated in Chapter 2, how the insulin infusion system has used the results of the NDIs from Chapter 1 to bring down the blood glucose concentration within the 2-hour critical period. He has used the blood glucose concentration of truly diabetic patients in the system model to bring the concentrations of blood glucose concentration by control infusion of insulin into the blood-stream. The resulting of the new blood glucose concentration is continuously monitored and sequence of infusion is spread across at every 0.5 hour intervals. The author wishes to build the system and perform clinical in the near future. He believes that this system can definitely benefit more diabetic patients and system has no means of invasive techniques in measuring the blood glucose concentration and control insulin-infusion into the blood stream. He has realized the serious in over or under dosing of insulin, as a result, the negative feed-back from the system is a very important safety mechanism.

The NDIs from Chapter 3 and 4 can help clinicians and equipment manufacturers to determine the type of pulmonary diseases, such as SARs, emphysema and chronic bronchitis and COPD. Each type of lung diseases attacked the lungs in different ways such as emphysema has very high compliance and the metabolism is very poor. COPD will be very high resistance and metabolism is very poor. The author hopes to realize the system. In fact a preliminary version of the system has been patented [14].

At the moment, the renograms collected does not contain the amount of tracers were introduced during the procedures. Many a times, the amount was introduced by experienced PET radiographers themselves. The author hope that his partners at the local government hospitals can convenience them to keep the record so that the actual urine outflow can be calculated instead of the relative urine outflow rate. The current system model equations were only good for normal flow, more work has to be carried out for diseased urine flow-rates so that we can develop a quick and accurate expert system.

We have seen how we can formulate and evaluate Non-Dimensional Physiological Indices (NDPNs) to serve as physiological-system disorder indices, and hence represent health-status. These non-dimensional health-status indicators of diabetic risky patients.
NDPIs require multi-disciplinary analyses of physiological and/or systems, and provides a convenient basis for medical diagnosis in terms of just one number. Thus NDPIs can also constitute the basis of effective classification of prognosis.
References On Non-Dimensional Physiological Indices


5. Loh Kah Meng, Dhanjoo N. Ghista and Heiko Rudolph, Determination of O2 and CO2 Metabolic-Rates and Lung Diffusion Coefficients, based on the Data of Inspired and Expired Air Compositions, Annals, Academy of Medicine, Singapore.


9. Loh Kah Meng, Dhanjoo N. Ghista and Heiko Rudolph, Determination of O2 and CO2 Metabolic-Rates and Lung Diffusion Coefficients, based on the Data of Inspired and Expired Air Compositions, Annals, Academy of Medicine, Singapore.


Appendix A

Underdamp Responses for Subjects N01-N20

These 40 subjects (N01 to N20) were diagnosed by physician as normal and (D01 to D20) were diagnosed by physician as diabetic.

Characteristic equation for glucose fitting for underdamp (healthy and non-diabetic) subjects:

\[ y(t) = \left( \frac{G}{\omega} \right) e^{-\alpha t} \sin \omega t \]

Characteristic equation for insulin fitting for underdamp (healthy and non-diabetic) subjects:

\[
x(t) = \frac{-\beta G(t)e^{-\alpha t} - t\alpha e^{-\alpha t} + e^{(-\alpha t)} - e^{-(-\alpha t)}}{(A - \alpha)^2}
\]

G: glucose administered to the system in gram/liter hour

A: attenuation constant in 1/hour

x: blood insulin concentration (from its fasting level)

y : blood glucose concentration (from its fasting level)

α: represents pancreatic insulin sensitivity to insulin (average insulin removal-rate independent of glucose) in (hr)^{-1}

β: pancreatic insulin sensitivity to elevated glucose blood concentrations (net increase in insulin release-rate due to glucose) in (Units) (hr)^{-1}(gms)^{-1}

γ : liver glycogen storage to elevated blood-glucose concentrations (net increase in glucose removal due to insulin) in (gms)(hr)^{-1} (Units)^{-1}

δ: tissue glucose utilisation to elevated blood-glucose concentrations (average glucose removal-rate independent of insulin) in (hr)^{-1}
## Summary of the fit

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<thead>
<tr>
<th>Best Fitted (R-Square &gt; 95%)</th>
<th>No Fit</th>
</tr>
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<tr>
<td>N02</td>
<td>N09</td>
</tr>
<tr>
<td>N05</td>
<td>N20</td>
</tr>
<tr>
<td>N11</td>
<td></td>
</tr>
<tr>
<td>N14</td>
<td></td>
</tr>
<tr>
<td>N16</td>
<td></td>
</tr>
<tr>
<td>N19</td>
<td></td>
</tr>
<tr>
<td>D03</td>
<td></td>
</tr>
<tr>
<td>Parameters</td>
<td>Values</td>
</tr>
<tr>
<td>------------</td>
<td>---------</td>
</tr>
<tr>
<td>A</td>
<td>1.537</td>
</tr>
<tr>
<td>G</td>
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S01 actually is diabetic even the clinician diagnosed him as normal.
<table>
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S03 is in a dangerous rim. The insulin response is too little.
### Parameters and Values

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<td>---------</td>
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### Parameters and Fitting

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G | 2.366 | Glucose Fit | SSE | 0.005696
ω | 2.332e-6 | | R-Square | 0.9192
α | 1.5885 | Insulin Fit | SSE | 1.851e-005
β | 0.05113 | | |
γ | 3.1715 | R-Square | 0.9951
δ | 3.4638 | | |
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S14 is classified as normal. But S14 is hyperinsulinemia. S14 fits all 3 classes.
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S15 is at the rim. S15 is classified as normal by clinician.
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S16 is normal just as diagnosed by clinician.
Parameters | Values | Fitting | Remarks
---|---|---|---
A | 1.043 | Glucose Fit | SSE 0.003526 S17 is normal just as diagnosed by clinician.
G | 1.838 | | |
ω | 1.363 | | |
α | 1.7481 | Insulin Fit | R-Square 0.9832 |
β | 0.03522 | | |
γ | 0.3379 | | |
δ | 1.6783 | | |
### Parameters, Values, Fitting, Remarks

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The diagram shows the glucose and insulin response over time, highlighting the fit for S18 and the key parameters associated with these responses.
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S19 is at the rim even though S19 is diagnosed as normal.
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S20 is at the rim even though S20 is diagnosed as normal.
Underdamp Responses for Subjects D01-D20

These 20 subjects were diagnosed by physician as diabatic.
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<tr>
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<td>Insulin</td>
<td>Fit, R-Square, 0.9002</td>
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<td>Insulin</td>
<td>SSE, 0.0002618</td>
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<tr>
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<td>Fit, R-Square, 0.9002</td>
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<tr>
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<td>Fit, R-Square, 0.9002</td>
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Parameters & Values

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D02 fits both the underdamp and critical damp but D02 is classified as diabetic by clinician.
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D03 fit both the criticaldamp & overdamp cases and D03 is classified as diabetic.
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<tr>
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D04 is diabetic just as diagnosed as diabetic by the clinician.
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<td>SSE</td>
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<td>β</td>
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<td>Values</td>
<td>Values</td>
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<tr>
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<td>α</td>
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D06 is diabetic just as diagnosed.
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<td>R-Square 0.9835</td>
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<tr>
<td>β</td>
<td>0.01869</td>
<td>Fit</td>
<td>SSE 0.0004136</td>
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<tr>
<td>γ</td>
<td>0.1146</td>
<td></td>
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<tr>
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<td>53.8405</td>
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Parameters | Values | Fitting | Remarks
--- | --- | --- | ---
A | 2.527e-7 | Glucose | SSE | 0.009778 | D08 is diabetic as diagnosed.
G | 1.673 | Fit | | | |
\( \omega \) | 1.044 | | R-Square | 0.9943 | |
\( \alpha \) | -0.2083 | Insulin | SSE | 9.636e-006 | |
\( \beta \) | 0.00446 | | | | |
\( \gamma \) | 0.2083 | Fit | R-Square | 0.986 | |
\( \delta \) | -5.2292 | | | | |
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<tr>
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<td></td>
<td></td>
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<tr>
<td>α</td>
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<td>Insulin</td>
<td>D09 is hyperinsulinemia which made him</td>
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<td>diabetic.</td>
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## Parameters, Values, Fitting, Remarks

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<th>Remarks</th>
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D10 is diabetic as diagnosed.
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D11 is diabetic as diagnosed due to hypoinsulinemia.
### Parameters

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<td>Fitting</td>
<td>Remarks</td>
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<td>--------</td>
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<td>---------</td>
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<tr>
<td>A</td>
<td>0.3872</td>
<td>Glucose Fit</td>
<td>D15 fits both underdamp and overdamp. But the poor insulin response make D15 diabetic.</td>
</tr>
<tr>
<td>G</td>
<td>1.314</td>
<td>Glucose SSE</td>
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<tr>
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<tr>
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<tr>
<td>γ</td>
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Parameters | Values | Fitting | Remarks
--- | --- | --- | ---
A | 0.6194 | Glucose | SSE 2.986e-010 | D16 fits all 3 classes. But the poor insulin response make D16 diabetic.
G | 1.749 | Fit | |
ω | 0.8981 | |
α | 0.2250 | Insulin | SSE 0.0002776 |
β | 0.0422 | Fit | |
γ | 1.0138 | |
δ | 5.0993 | |

D16 Glucose & Insulin Response

![Graph showing glucose and insulin response over time]

- **A**: 0.6194, SSE 2.986e-010
- **G**: 1.749
- **ω**: 0.8981
- **α**: 0.2250, SSE 0.0002776
- **β**: 0.0422
- **γ**: 1.0138
- **δ**: 5.0993
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<tbody>
<tr>
<td>A</td>
<td>1.493</td>
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<td>SSE</td>
<td>D17 is diabetic because the glucose did not come down after 2 hours.</td>
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<td>G</td>
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<td>γ</td>
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<td>SSE</td>
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<tr>
<td>γ</td>
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<tr>
<td>δ</td>
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</tbody>
</table>
Parameters | Values     | Fitting | Remarks
---|------------|---------|--------
A  | 1.395e-8   | Glucose Fit | SSE 0.004518 | D19 is at the rim of being diabetic due to hypoinsulinemia and the glucose cannot go down after 2 hours.
G  | 0.8465     |          |        |
ω  | 0.6069     |          |        |
α  | -0.6275    | Insulin Fit | SSE 2.913e-005 |
β  | 0.01634    |          |        |
γ  | 0.6275     |          | R-Square 0.9945 |
δ  | -0.5707    |          |        |
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D20 is diabetic due to hypoinsulinemia and the glucose cannot go down after 2 hours.
Appendix B

Overdamp Responses for Subjects N01-N20

These 40 subjects (N01 to N20) were diagnosed by physician as normal and (D01 to D20) were diagnosed by physician as diabetic.

Characteristic equation for glucose fitting for underdamp (healthy and non-diabetic) subjects :

\[ y(t) = \left( \frac{G}{\omega} \right) e^{-At} \sin \omega t \]

Characteristic equation for insulin fitting for underdamp (healthy and non-diabetic) subjects :

\[ x(t) = \frac{\left( \frac{1}{2} (\cosh(\omega t - At)A + \sinh(-\omega t + At)A - \cosh(-\omega t + At)A - \sinh(\omega t - At)A + \sinh(\omega t - At)w - \cosh(\omega t - At)w - \sinh(-\omega t - At)A + \sinh(\omega t + At)A - \cosh(\omega t + At)A - \sinh(-\omega t + At)A + 2w + \sinh(-\omega t + At)w)e^{-\omega t}}{-w^2 + A^2 - 2A\alpha + \alpha^2} \right) \]

G: glucose administered to the system in gram/liter hour
A: attenuation constant in 1/hour
x: blood insulin concentration (from its fasting level)
\( y \): blood glucose concentration (from its fasting level)
\( \alpha \): represents pancreatic insulin sensitivity to insulin (average insulin removal-rate independent of glucose) in (hr)
\( \beta \): pancreatic insulin sensitivity to elevated glucose blood concentrations (net increase in insulin release-rate due to glucose) in (Units) (hr) (gms)
\( \gamma \): liver glycogen storage to elevated blood-glucose concentrations (net increase in glucose removal due to insulin) in (gms)(hr) (Units)
\( \delta \): tissue glucose utilisation to elevated blood-glucose concentrations (average glucose removal-rate independent of insulin) in (hr)
### Summary of the fit

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No Fit!
### Parameters, Values, Fitting, Remarks

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<td>δ</td>
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**Remarks:**
- S03 is in a dangerous rim.
- The insulin response is too little.
<table>
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No Fit!
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<td>γ</td>
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**Graph:**

- **Glucose & Insulin Response**
- Time/Hour
- Glucose in g/L
- Insulin in U/L
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<th>Remarks</th>
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<tr>
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<td>0.05334</td>
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S06 is normal. Just as diagnosed by the clinician.
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</tr>
<tr>
<td>α</td>
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<td>β</td>
<td>0.0485</td>
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<td>γ</td>
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<td>38.8710</td>
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<tr>
<td>δ</td>
<td></td>
<td>R-Square</td>
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</table>

Parameters | Fitting | Remarks |
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<td>G</td>
<td>R-Square</td>
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<td>0.001322</td>
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<td>0.0485</td>
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### Parameters, Values, Fitting, Remarks

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<th>Fitting</th>
<th>Remarks</th>
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<tr>
<td>A</td>
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<tr>
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![Graph of N08 Glucose & Insulin Response](image)
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<td>δ</td>
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S10 is normal. Just as diagnosed by the clinician.
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<td>SSE</td>
<td>S12 is at the rim of being diabetic due to</td>
</tr>
<tr>
<td>G</td>
<td>Fit</td>
<td>R-Square</td>
<td>hyperinsulinemia.</td>
</tr>
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<td>ω</td>
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<td>α</td>
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<td>Fit</td>
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<td>γ</td>
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No Fit!
S13 Glucose & Insulin Response

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<td>δ</td>
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N15 Glucose & Insulin Response

S15 is at the rim.
S15 is classified as normal by clinician.
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<td>SSE</td>
<td>S16 is normal just as diagnosed by clinician.</td>
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<td>R-Square</td>
<td></td>
</tr>
<tr>
<td>ω</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α</td>
<td>Insulin</td>
<td>SSE</td>
<td>0.001593</td>
</tr>
<tr>
<td>β</td>
<td>Fit</td>
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</tr>
<tr>
<td>γ</td>
<td></td>
<td>R-Square</td>
<td>0.812</td>
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<tr>
<td>δ</td>
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No Fit!
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<th>Fitting</th>
<th>Remarks</th>
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S17 is normal just as diagnosed by clinician.
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<td>S18 fit all classes.</td>
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<tr>
<td>G</td>
<td>7.435</td>
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<td>S18 suffers from hyperinsulinemia.</td>
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<tr>
<td>ω</td>
<td>1.562</td>
<td>R-Square 0.9997</td>
<td>The pancreas will not be able to sustain the insulin requirement as age catches up.</td>
</tr>
<tr>
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<td>1.8827</td>
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<td></td>
</tr>
<tr>
<td>β</td>
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<tr>
<td>γ</td>
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<td>δ</td>
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<td>Values</td>
<td>Fitting</td>
<td>Remarks</td>
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S19 is at the rim even though S19 is diagnosed as normal.
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<th>Remarks</th>
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<td>SSE</td>
<td>S20 is at the rim even though S20 is diagnosed as normal.</td>
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<td>Fit</td>
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<td>ω</td>
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<td>R-Square</td>
<td>0.9992</td>
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No Fit!
Overdamp Responses for Subjects D01-D20

These 20 subjects were diagnosed by physician as diabatic.
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<td>Glucose comes down very slowly. D01 is diabetic.</td>
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D03 fit both the criticaldamp & overdamp cases and D03 is classified as diabetic.
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![Graph of Glucose & Insulin Response](image)

**Graph Notes:**
- Green markers: x vs. t
- Blue fit: fit 170
- Red markers: y vs. t
- Red fit: fit 1 copy 1

**Graph Details:**
- X-axis: Time/Hour
- Y-axis: Glucose in g/l, Insulin in U/l

**Graph Description:**
- The graph illustrates the response of glucose and insulin over time, with parameters fitting and remarks noted.
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D08 is diabetic as diagnosed.
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### Parameters Values Fitting Remarks

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### Graph

The graph shows the glucose and insulin response over time, with fits labeled as follows:
- `x vs. y`: Glucose response
- `fit1 copy 1`: Insulin fit
- `fit1 copy 1`: Glucose fit
- `fit5 copy 1`: Overdamped fit
- `y vs. x`: Underdamped fit

The graph includes data points for both glucose and insulin, with a clear distinction between the fits and their respective R-square values.
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D16 Glucose & Insulin Response

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![D18 Glucose & Insulin Response](image-url)
### Parameters and Values

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D19 is at the rim of being diabetic due to hypoinsulinemia and the glucose cannot go down after 2 hours.
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Appendix C

Critical Damp Responses for Subjects N01-N20

These 40 subjects (N01 to N20) were diagnosed by physician as normal and (D01 to D20) were diagnosed by physician as diabetic.

Characteristic equation for glucose fitting for underdamp (healthy and non-diabetic) subjects:

\[ y(t) = Gte^{-At} \]

Characteristic equation for insulin fitting for underdamp (healthy and non-diabetic) subjects:

\[ x(t) = \frac{-\beta G(tAe^{(-At)} - t\alpha e^{(-At)} + e^{(-At)} - e^{(-\gamma t)})}{(A - \alpha)^2} \]

G: glucose administered to the system in gram/liter hour
A: attenuation constant in 1/hour
x: blood insulin concentration (from its fasting level)
y: blood glucose concentration (from its fasting level)
α: represents pancreatic insulin sensitivity to insulin (average insulin removal-rate independent of glucose) in (hr)^{-1}
β: pancreatic insulin sensitivity to elevated glucose blood concentrations (net increase in insulin release-rate due to glucose) in (Units) (hr)^{-1}(gms)^{-1}
γ: liver glycogen storage to elevated blood-glucose concentrations (net increase in glucose removal due to insulin) in (gms)(hr)^{-1}(Units)^{-1}
δ: tissue glucose utilisation to elevated blood-glucose concentrations (average glucose removal-rate independent of insulin) in (hr)^{-1}
### Summary of the fit

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The diagram shows the glucose and insulin response over time. The graph indicates a peak in glucose levels followed by a drop, which is typical of an insulin response. The parameters are fitted to the data, with R-Square values indicating the goodness of fit. The table provides values for the parameters and their corresponding fitting methods along with remarks noting the health status related to hyperinsulinemia.
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![Graph showing glucose and insulin response over time](image-url)
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No Fit!

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S15 is at the rim. S15 is classified as normal by clinician.
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Glucose: Fit $SSE = 0.00122$

Insulin: Fit $R\text{-Square} = 0.8561$

Note: S16 is normal just as diagnosed by the clinician.

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<td>$\delta$</td>
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S19 is at the rim even though S19 is diagnosed as normal.
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<tr>
<td>α</td>
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<td>SSE 1.541e-006</td>
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No Fit!
Critical Damp Responses for Subjects D01-D20

These 20 subjects were diagnosed by physician as diabatic.
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<td>R-Square 0.999</td>
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<td>2.153e-005</td>
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D03 Glucose & Insulin Response

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<tr>
<td>α</td>
<td>2.3</td>
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<tr>
<td>A</td>
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<td>G</td>
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</tr>
<tr>
<td>ω</td>
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<td></td>
<td>D04 is diabetic just as diagnosed as diabetic by the clinician.</td>
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<td>α</td>
<td>1.3700</td>
<td>Insulin</td>
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<tr>
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<td>---------</td>
</tr>
<tr>
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<td>1.3530</td>
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<td>SSE 0.01169 D05 fits both the underdamp and overdamp classes even though D05 has been diagnosed as diabetic.</td>
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<tr>
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<tr>
<td>( \alpha )</td>
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</tr>
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</tr>
<tr>
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<tr>
<td>( \delta )</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>Values</td>
<td>Fitting</td>
<td>Remarks</td>
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</tr>
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<tr>
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D06 is diabetic just as diagnosed.
<table>
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<th>Function</th>
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<th>Remarks</th>
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<tr>
<td>A</td>
<td>0.9793</td>
<td>Glucose</td>
<td>SSE</td>
<td>0.05622</td>
</tr>
<tr>
<td>G</td>
<td>4.895</td>
<td>Fit</td>
<td>R-Square</td>
<td>0.9741</td>
</tr>
<tr>
<td>ω</td>
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<td></td>
<td>R-Square</td>
<td>0.9741</td>
</tr>
<tr>
<td>α</td>
<td>1.639</td>
<td>Insulin</td>
<td>SSE</td>
<td>0.0002503</td>
</tr>
<tr>
<td>β</td>
<td>0.1128</td>
<td>Fit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>γ</td>
<td>3.8582</td>
<td></td>
<td>R-Square</td>
<td>0.9787</td>
</tr>
<tr>
<td>δ</td>
<td>0.3196</td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>

D07 is diabetic as diagnosed.
### Parameters | Values | Fitting | Remarks
--- | --- | --- | ---
A | 0.6559 | Glucose Fit | D08 is diabetic as diagnosed.
G | 2.544 | | 
ω | 0 | | 
α | 1.3000 | Insulin Fit | 
β | 0.5800 | | 
γ | 0.7153 | | 
δ | 0.0118 | |
### Parameters and Values

<table>
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<th>Values</th>
<th>Fitting</th>
<th>Remarks</th>
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<td>SSE 0.08382</td>
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<td>R-Square 0.896</td>
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<td>D09 is both underdamp and overdamp. But</td>
</tr>
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<td>α</td>
<td>1.6500</td>
<td>Insulin Fit</td>
<td>D09 is hyperinsulinemia which made him</td>
</tr>
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<td>β</td>
<td>0.6853</td>
<td>Insulin Fit</td>
<td>diabetic.</td>
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**Graph:**
- D09 Glucose & Insulin Response
- Graph shows the relationship between glucose and insulin over time/hour.
- Key points indicate specific data points for glucose and insulin levels.

---

**Remark:**
- D09 is both underdamped and overdamped, suggesting a complex response.
- Hyperinsulinemia is indicated, which led to D09 becoming diabetic.
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<tr>
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<tr>
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D10 is diabetic as diagnosed.
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<td>4.949</td>
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D11 is diabetic as diagnosed due to hypoinsulinemia.
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<td>SSE 0.004315 D12 fits all the 3 classes. But D12 is hyperinsulinemia which make D12 diabetic.</td>
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**D15 Glucose & Insulin Response**

![Graph showing glucose and insulin response over time]

- **SSE**: 0.00341
- **R-Square**: 0.9903
- **SSE**: 0.0001411
- **R-Square**: 0.9181
<table>
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</tr>
<tr>
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<tr>
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<tr>
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![Graph showing glucose and insulin response over time](image)

**Graph Description:**
- The graph titled "D16 Glucose & Insulin Response" illustrates the changes in glucose and insulin levels over time.
- The x-axis represents time in hours, ranging from 0 to 2.
- The y-axis shows glucose (g/L) on the left and insulin (U/L) on the right.
- The graph includes fitted curves for both glucose and insulin, with markers indicating specific data points.
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
<th>Fitting</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.3169</td>
<td>Glucose Fit</td>
<td>SSE 0.01966</td>
</tr>
<tr>
<td>G</td>
<td>1.112</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ω</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α</td>
<td>0.6000</td>
<td>Insulin Fit</td>
<td>SSE 0.004513</td>
</tr>
<tr>
<td>β</td>
<td>0.7800</td>
<td></td>
<td></td>
</tr>
<tr>
<td>γ</td>
<td>0.1028</td>
<td></td>
<td>R-Square 0.0771</td>
</tr>
<tr>
<td>δ</td>
<td>0.0338</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parameters</td>
<td>Values</td>
<td>Fitting</td>
<td>Remarks</td>
</tr>
<tr>
<td>------------</td>
<td>--------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>A</td>
<td>0.4489</td>
<td>Glucose Fit</td>
<td>SSE 1.563e-005</td>
</tr>
<tr>
<td>G</td>
<td>1.252</td>
<td>Glucose Fit</td>
<td>R-Square 1</td>
</tr>
<tr>
<td>( \omega )</td>
<td>0</td>
<td>Insulin Fit</td>
<td>SSE 2.796e-006</td>
</tr>
<tr>
<td>( \alpha )</td>
<td>0.8900</td>
<td>Insulin Fit</td>
<td>R-Square 0.9998</td>
</tr>
<tr>
<td>( \beta )</td>
<td>0.3504</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \gamma )</td>
<td>0.5553</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \delta )</td>
<td>0.0078</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

D18 fits both the underdamp and overdamp classes and D18 is diabetic because glucose did not go down after 2 hour and hypoinulinemia.
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
<th>Fitting</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.1892</td>
<td>Glucose Fit</td>
<td>SSE 0.003993 D19 is at the rim of being diabetic due to hypoinsulinemia and the glucose cannot go down after 2 hours.</td>
</tr>
<tr>
<td>G</td>
<td>0.9563</td>
<td>Fit</td>
<td>R-Square 0.9965</td>
</tr>
<tr>
<td>ω</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α</td>
<td>0.3700</td>
<td>Insulin Fit</td>
<td>SSE 5.421e-005</td>
</tr>
<tr>
<td>β</td>
<td>0.6064</td>
<td></td>
<td></td>
</tr>
<tr>
<td>γ</td>
<td>0.0539</td>
<td></td>
<td>R-Square 0.9898</td>
</tr>
<tr>
<td>δ</td>
<td>0.0084</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The graph shows the response of glucose and insulin over time. The fitting parameters and their corresponding SSE and R-Square values are listed in the table above. The remarks note that D19 is at the rim of being diabetic due to hypoinsulinemia and the glucose cannot go down after 2 hours.
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
<th>Fitting</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.3942</td>
<td>Glucose Fit</td>
<td>SSE 0.0124</td>
</tr>
<tr>
<td>G</td>
<td>2.046</td>
<td>Fit</td>
<td>SSE 0.0124</td>
</tr>
<tr>
<td>ω</td>
<td>0</td>
<td>R-Square 0.9948</td>
<td></td>
</tr>
<tr>
<td>α</td>
<td>0.7600</td>
<td>Insulin Fit</td>
<td>SSE 1.256e-005</td>
</tr>
<tr>
<td>β</td>
<td>0.2282</td>
<td></td>
<td></td>
</tr>
<tr>
<td>γ</td>
<td>0.5864</td>
<td>R-Square 0.9633</td>
<td></td>
</tr>
<tr>
<td>δ</td>
<td>0.0284</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix D

Non-Dimensional Indices Distribution of Patients

$G_{-NDI} \times I_{-NDI} = \left( \frac{y_{\text{max}} \times y_{2} \times T_{d} \times T_{\text{max}}}{G^2} \times \frac{T_{\text{max}}}{32} \times 10^6 \right) \times \left( \frac{B \gamma \delta}{\alpha} \right)$

for all the 40 patients with some data removed due to experimental errors.
Figure E.2 Non-dimensional plot of Figure 100 Non-dimensional plot of

\[
\frac{G_{\text{NDI}}}{I_{\text{NDI}}} = \left( A \times \frac{\alpha_0 G}{y_m} \times \frac{(y_m - y_2)}{y_m} \right) \left( \frac{y_m}{\beta} \times \frac{\alpha^2}{G} \right)
\]

for all the 40 patients with some data removed due to experimental errors.
Figure E.3 Non-dimensional plot of Figure 100

Non-dimensional plot of

\[ G_{NDI} \times I_{NDI} = \left( \frac{A \times \omega_0 \times G}{y_m} \times \left( \frac{y_m - y_2}{y_m} \right) \right) \times \left( \frac{x_{\text{max}}}{\beta} \times \frac{\alpha^2}{G} \right) \]

for all the 40 patients with some data removed due to experimental errors.
TABLE – 1: Nomenclature

<table>
<thead>
<tr>
<th>SYMBOL</th>
<th>MEANING</th>
<th>UNITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T$</td>
<td>Time</td>
<td>Hour (hr)</td>
</tr>
<tr>
<td>$V$</td>
<td>Extra-cellular fluid volume</td>
<td>Liter (l)</td>
</tr>
<tr>
<td>$I$</td>
<td>Rate of insulin injection</td>
<td>Units/hour (U/hr)</td>
</tr>
<tr>
<td>$G$</td>
<td>Rate of Glucose Injection</td>
<td>Grams/hour (gm/hr)</td>
</tr>
<tr>
<td>$X$</td>
<td>Extra-cellular insulin concentration</td>
<td>Units/liter (U/l)</td>
</tr>
<tr>
<td>$Y$</td>
<td>Extra-cellular glucose concentration</td>
<td>Grams/liter (gm/hr)</td>
</tr>
<tr>
<td>$X_{ss}$</td>
<td>Steady-state insulin concentration</td>
<td>Units/liter (U/l)</td>
</tr>
<tr>
<td>$Y_{ss}$</td>
<td>Steady-state glucose concentration</td>
<td>Grams/liter (gm/hr)</td>
</tr>
<tr>
<td>$F_1(x)$</td>
<td>Rate of insulin destruction</td>
<td>Units/hour (U/hr)</td>
</tr>
<tr>
<td>$F_2(y)$</td>
<td>Rate of insulin production</td>
<td>Units/hour (U/hr)</td>
</tr>
<tr>
<td>$F_3(X,Y)$</td>
<td>Rate of linear accumulation of glucose</td>
<td>Grams/hour (gm/hr)</td>
</tr>
<tr>
<td>$F_4(X,Y)$</td>
<td>Rate of tissue utilization of glucose</td>
<td>Grams/hour (gm/hr)</td>
</tr>
</tbody>
</table>
**TABLE 2: Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVGTT</td>
<td>Intravenous Glucose Tolerance Test</td>
</tr>
<tr>
<td>OGGT</td>
<td>Oral Glucose Tolerance Test</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>BGCS</td>
<td>Blood Glucose Control System</td>
</tr>
<tr>
<td>GIRS</td>
<td>Glucose-Insulin Regulatory System</td>
</tr>
</tbody>
</table>

**SYMBOLS**

- $\dot{Y}$: First derivative of $y$ with respect to time
- $\ddot{Y}$: Second derivative of $y$ with respect to time
- $y(t)$: Time dependent function of $y$
- $y(0)$: Initial value of $y$ at time $t=0$
- $Y(s)$: Laplace transform of $y(t)$
- $sY(s)$: Laplace transform of $y'$ if $y(0) = 0$
- $s^2Y(s)$: Laplace transform of $y''$ if $y'(0) = y(0) = 0$
- $q$: Rate of intestinal glucose flow or exogenously injected) into blood
- $h$: Height of rectangular pulse
- $x_0$: Blood Insulin Concentration at $t=0$, due to intestinal hormonal effect of anticipatory control
- $t_0$: Duration of the above Glucose flow = pulse width
- $e$: Exponential constant
- $L$: Operational symbol for Laplace transformation
- $u(t)$: Unit step function
- $v$: Blood-Glucose compartment volume
- $\alpha V$: Sensitivity of insulinase activity to elevated insulin concentration.
- $\beta V$: Sensitivity of pancreatic insulin output to elevated glucose concentration.
- $\gamma V$: Combined Sensitivity of liver glycogen storage and tissue glucose utilization to elevated insulin concentration.
- $\delta V$: Combined sensitivity of liver glycogen storage and tissue glucose
utilization to elevated glucose concentration.
### TABLE – 3: Symbols & Units

<table>
<thead>
<tr>
<th>SYMBOL</th>
<th>MEANING</th>
</tr>
</thead>
<tbody>
<tr>
<td>$X_0$</td>
<td>Mean physiological value of X Units/liter</td>
</tr>
<tr>
<td>$Y_0$</td>
<td>Mean physiological value of Y Grams/liter</td>
</tr>
<tr>
<td>$x$</td>
<td>$x = X - X_0$ Units/liter</td>
</tr>
<tr>
<td>$y$</td>
<td>$y = Y - Y_0$ Grams/liter</td>
</tr>
<tr>
<td>$x(\text{ss})$</td>
<td>$x(\text{ss}) = X(\text{ss}) - X_0$ (ss=steady state) Units/liter</td>
</tr>
<tr>
<td>$y(\text{ss})$</td>
<td>$y(\text{ss}) = Y(\text{ss}) - Y_0$ (ss=steady state) Grams/liter</td>
</tr>
<tr>
<td>$y(0)$</td>
<td>$y(0) = Y(0) - Y_0$ Grams/liter</td>
</tr>
<tr>
<td>$p$</td>
<td>$p = \left(\frac{I'}{N}\right)$ Units (lit)$^{-1}$ (hr)$^{-1}$</td>
</tr>
<tr>
<td>$q$</td>
<td>$q = \left(\frac{G}{N}\right)$ Grams (lit)$^{-1}$ (hr)$^{-1}$</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>$\left(\frac{1}{V}\right)\left(\frac{\partial F_1}{\partial X}\right)_{atX_0}$ (hr)$^{-1}$</td>
</tr>
<tr>
<td>$\beta$</td>
<td>$\left(\frac{1}{V}\right)\left(\frac{\partial F_2}{\partial y}\right)_{atY_0}$ (units) (hr)$^{-1}$ (gms)$^{-1}$</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>$\left(\frac{1}{V}\right)\left[\frac{\partial F_3}{\partial x} + \frac{\partial F_4}{\partial y}\right]_{atX_0,Y_0}$ (gms) (hr)$^{-1}$</td>
</tr>
<tr>
<td>$\delta$</td>
<td>$\left(\frac{1}{V}\right)\left[\frac{\partial F_3}{\partial y} + \frac{\partial F_4}{\partial y}\right]_{atX_0,Y_0}$ (hr)$^{-1}$</td>
</tr>
</tbody>
</table>
Appendix F

This appendix contains the results of the Insulin Infusion System based on PD controller.
G.1 Subject D01

Data

<table>
<thead>
<tr>
<th>Time</th>
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<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose Conc.</td>
<td>0</td>
<td>1.44</td>
<td>2.03</td>
<td>2.35</td>
<td>2.2</td>
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</tbody>
</table>

From Curve-Fitting

<table>
<thead>
<tr>
<th>A</th>
<th>G</th>
<th>ω</th>
<th>γ</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6417</td>
<td>3.969</td>
<td>0.0003</td>
<td>23.0383</td>
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Parameters

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<th>2 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>0.003</td>
<td>0.004</td>
<td>0.003</td>
<td>0</td>
</tr>
<tr>
<td>kp</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>kd</td>
<td>0</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE:
1) kp and kd are fixed while I varies.
2) kp >> kd
3) Output response is dependant on previous output response, ie. No level off.
G.2 Subject D02

Data

<table>
<thead>
<tr>
<th>Time</th>
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<th>0.5</th>
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<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose Conc.</td>
<td>0</td>
<td>0.92</td>
<td>0.93</td>
<td>0.81</td>
<td>0.08</td>
</tr>
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</table>

From Curve-Fitting

<table>
<thead>
<tr>
<th>A</th>
<th>G</th>
<th>$\omega$</th>
<th>$\gamma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.423</td>
<td>3.861</td>
<td>1.4e-8</td>
<td>71.9693</td>
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</tbody>
</table>

Parameters

<table>
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<th>1.5 hr</th>
<th>2 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
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<td>0.002</td>
<td>0.003</td>
<td>0.002</td>
<td>0</td>
</tr>
<tr>
<td>$k_p$</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>$k_d$</td>
<td>0</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0</td>
</tr>
</tbody>
</table>

**NOTE:**
4) $k_p$ and $k_d$ are fixed while $I$ varies.
5) $k_p >> k_d$
6) Output response is **dependant** on previous output response, i.e. No level off.
G.3 Subject D04

Data

<table>
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<tr>
<th>Time</th>
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<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose Conc.</td>
<td>0</td>
<td>0.77</td>
<td>1.54</td>
<td>1.49</td>
<td>1.41</td>
</tr>
</tbody>
</table>

From Curve-Fitting

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>G</th>
<th>ω</th>
<th>γ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.625</td>
<td>2.549</td>
<td>0.0023</td>
<td>104.3761</td>
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</table>

Parameters

<table>
<thead>
<tr>
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<th>1.5 hr</th>
<th>2 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
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<td>0.0007</td>
<td>0.0008</td>
<td>0.0007</td>
<td>0</td>
</tr>
<tr>
<td>kp</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>kd</td>
<td>0</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE:
7) $k_p$ and $k_d$ are fixed while $I$ varies.
8) $k_p >> k_d$
9) Output response is dependant on previous output response, ie. No level off.
G.4 Subject D08

Data

<table>
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<tr>
<th>Time</th>
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<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose Conc.</td>
<td>0</td>
<td>0.82</td>
<td>1.32</td>
<td>1.67</td>
<td>1.37</td>
</tr>
</tbody>
</table>

From Curve-Fitting

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>G</th>
<th>ω</th>
<th>γ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.6559</td>
<td>2.544</td>
<td>1.6e-8</td>
<td>23.7478</td>
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</tbody>
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Parameters

<table>
<thead>
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<th>1 hr</th>
<th>1.5 hr</th>
<th>2 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>0.003</td>
<td>0.004</td>
<td>0.003</td>
<td>0</td>
</tr>
<tr>
<td>kp</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>kd</td>
<td>0</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE:
10) kp and kd are fixed while I varies.
11) kp >> kd
12) Output response is dependant on previous output response, ie. No level off.
G.5 Subject D09

Data

<table>
<thead>
<tr>
<th>Time</th>
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<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose Conc.</td>
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<td>0.62</td>
<td>1.02</td>
<td>1.03</td>
<td>0.31</td>
</tr>
</tbody>
</table>

From Curve-Fitting

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>G</th>
<th>ω</th>
<th>γ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.8842</td>
<td>2.469</td>
<td>4e-7</td>
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</tbody>
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Parameters

<table>
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<th>0.5 hr</th>
<th>1 hr</th>
<th>1.5 hr</th>
<th>2 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
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<td>0.007</td>
<td>0.008</td>
<td>0.007</td>
<td>0</td>
</tr>
<tr>
<td>k_p</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>k_d</td>
<td>0</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE:
13) k_p and k_d are fixed while I varies.
14) k_p >> k_d
15) Output response is dependant on previous output response, ie. No level off.
G.6 Subject D10

Data

<table>
<thead>
<tr>
<th>Time</th>
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<th>1</th>
<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose Conc.</td>
<td>0</td>
<td>0.72</td>
<td>1.04</td>
<td>0.55</td>
<td>0.52</td>
</tr>
</tbody>
</table>

From Curve-Fitting

<table>
<thead>
<tr>
<th>A</th>
<th>1.141</th>
</tr>
</thead>
<tbody>
<tr>
<td>G</td>
<td>2.548</td>
</tr>
<tr>
<td>\omega</td>
<td>0.0024</td>
</tr>
<tr>
<td>\gamma</td>
<td>16.3837</td>
</tr>
</tbody>
</table>

Parameters

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<td>0.008</td>
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</tr>
<tr>
<td>kp</td>
<td>0</td>
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<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>kd</td>
<td>0</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE:

16) \( kp \) and \( kd \) are fixed while \( I \) varies.
17) \( kp >> kd \)
18) Output response is dependant on previous output response, ie. No level off.
G.7 Subject D11

Data

<table>
<thead>
<tr>
<th>Time</th>
<th>Glucose Conc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
<td>0.91</td>
</tr>
<tr>
<td>1</td>
<td>1.18</td>
</tr>
<tr>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>2</td>
<td>1.36</td>
</tr>
</tbody>
</table>

From Curve-Fitting

<table>
<thead>
<tr>
<th>A</th>
<th>G</th>
<th>ω</th>
<th>γ</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6071</td>
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Parameters

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<tbody>
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<td>0.001</td>
<td>0.0015</td>
<td>0.001</td>
<td>0</td>
</tr>
<tr>
<td>k_p</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>k_d</td>
<td>0</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE:
19) \(k_p\) and \(k_d\) are fixed while \(I\) varies.
20) \(k_p >> k_d\)
21) Output response is dependant on previous output response, ie. No level off.
G.8 Subject D13

Data

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
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<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose Conc.</td>
<td>0</td>
<td>0.91</td>
<td>1.16</td>
<td>1</td>
<td>0.67</td>
</tr>
</tbody>
</table>

From Curve-Fitting

<table>
<thead>
<tr>
<th>A</th>
<th>G</th>
<th>(\omega)</th>
<th>(\gamma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.064</td>
<td>3.289</td>
<td>0.0001</td>
<td>30.1855</td>
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</tbody>
</table>

Parameters

<table>
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<th>2 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>0.003</td>
<td>0.004</td>
<td>0.003</td>
<td>0</td>
</tr>
<tr>
<td>(k_p)</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>(k_d)</td>
<td>0</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE:

22) \(k_p\) and \(k_d\) are fixed while \(I\) varies.
23) \(k_p \gg k_d\)
24) Output response is dependant on previous output response, ie. No level off.
G.9 Subject D14

Data

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose Conc.</td>
<td>0</td>
<td>0.5</td>
<td>0.77</td>
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</tbody>
</table>

From Curve-Fitting

<table>
<thead>
<tr>
<th>A</th>
<th>G</th>
<th>ω</th>
<th>γ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.138</td>
<td>2.446</td>
<td>4e-12</td>
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</tbody>
</table>

Parameters

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<th>1.5 hr</th>
<th>2 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>kp</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>kd</td>
<td>0</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE:

25) kp and kd are fixed while I varies.
26) kp >> kd
27) Output response is dependant on previous output response, ie. No level off.
G.10 Subject D15

Data

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose Conc.</td>
<td>0</td>
<td>0.53</td>
<td>0.72</td>
<td>0.73</td>
<td>0.51</td>
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</tbody>
</table>

From Curve-Fitting

<table>
<thead>
<tr>
<th>A</th>
<th>G</th>
<th>(\omega)</th>
<th>(\gamma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.8598</td>
<td>1.701</td>
<td>0.0012</td>
<td>36.4844</td>
</tr>
</tbody>
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Parameters

<table>
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<th>1.5 hr</th>
<th>2 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>0.002</td>
<td>0.003</td>
<td>0.002</td>
<td>0</td>
</tr>
<tr>
<td>(k_p)</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>(k_d)</td>
<td>0</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE:

28) \(k_p\) and \(k_d\) are fixed while \(I\) varies.
29) \(k_p \gg k_d\)
30) Output response is dependant on previous output response, ie. No level off.
G.11 Subject D16

Data

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose Conc.</td>
<td>0</td>
<td>0.01</td>
<td>0.82</td>
<td>0.75</td>
<td>0.55</td>
</tr>
</tbody>
</table>

From Curve-Fitting

<table>
<thead>
<tr>
<th>A</th>
<th>G</th>
<th>(\omega)</th>
<th>(\gamma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9321</td>
<td>2.024</td>
<td>2.4e-6</td>
<td>15.2168</td>
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Parameters

<table>
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<th>1.5 hr</th>
<th>2 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>(I)</td>
<td>0</td>
<td>0.006</td>
<td>0.007</td>
<td>0.006</td>
<td>0</td>
</tr>
<tr>
<td>(k_p)</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>(k_d)</td>
<td>0</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE:

31) \(k_p\) and \(k_d\) are fixed while \(I\) varies.
32) \(k_p \gg k_d\)
33) Output response is dependant on previous output response, ie. No level off.
G.12 Subject D18

Data

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose Conc.</td>
<td>0</td>
<td>0.5</td>
<td>1.44</td>
<td>0.95</td>
<td>1.02</td>
</tr>
</tbody>
</table>

From Curve-Fitting

<table>
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<tr>
<th>A</th>
<th>G</th>
<th>ω</th>
<th>γ</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4891</td>
<td>1.272</td>
<td>0.3127</td>
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Parameters

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<th>2 hr</th>
</tr>
</thead>
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<td>0.05</td>
<td>0.04</td>
<td>0</td>
</tr>
<tr>
<td>kp</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>kd</td>
<td>0</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE:
34) kp and kd are fixed while I varies.
35) kp >> kd
36) Output response is dependant on previous output response, ie. No level off.
G.13 Subject N01

Data

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<th>2</th>
</tr>
</thead>
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<td>Glucose Conc.</td>
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<td>0.57</td>
<td>0.36</td>
<td>0.36</td>
<td>0.3</td>
</tr>
</tbody>
</table>

From Curve-Fitting

<table>
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<th>G</th>
<th>ω</th>
<th>γ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>23.81</td>
<td>16.6</td>
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Parameters

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</tr>
</thead>
<tbody>
<tr>
<td>I</td>
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<td>0.1</td>
<td>0.15</td>
<td>0.15</td>
<td>0</td>
</tr>
<tr>
<td>k_p</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>k_d</td>
<td>0</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE:
37) $k_p$ and $k_d$ are fixed while $I$ varies.
38) $k_p > k_d$
39) Output response is dependant on previous output response, ie. No level off.
G.13 Subject N07

Data

<table>
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<tr>
<th>Time</th>
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<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose Conc.</td>
<td>0</td>
<td>0.68</td>
<td>0.57</td>
<td>0.61</td>
<td>0.56</td>
</tr>
</tbody>
</table>

From Curve-Fitting

<table>
<thead>
<tr>
<th>A</th>
<th>G</th>
<th>ω</th>
<th>γ</th>
</tr>
</thead>
<tbody>
<tr>
<td>19.49</td>
<td>26.79</td>
<td>19.38</td>
<td>0.8</td>
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</tbody>
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Parameters

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<th>2 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>0.2</td>
<td>0.25</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>kp</td>
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<td>100</td>
<td>100</td>
<td>100</td>
<td>0</td>
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<tr>
<td>kd</td>
<td>0</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE:

40) kp and kd are fixed while I varies.
41) kp >> kd
42) Output response is dependant on previous output response, ie. No level off.
Appendix G

Renogram Simulations Results

This chapter contains the simulated results of the renograms. The clinical renograms were provided by PET Centre at SGH.

Definition/Abbreviation

Area is obtained by obtaining the area under the curve from 60 to 120 seconds. Deviation is obtained by: (Clinical – Calculated)/Clinical * 100%
### Patient 1

#### Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Left Kidney</th>
<th>Fitting</th>
<th>Right Kidney</th>
<th>Fitting</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SSE R Sq</td>
<td></td>
<td>SSE R Sq</td>
<td></td>
<td></td>
</tr>
<tr>
<td>k</td>
<td>0.0174</td>
<td>0.0189</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>1.50E-02</td>
<td>7.83E-03</td>
<td></td>
<td></td>
<td>LT(O)</td>
</tr>
<tr>
<td>β</td>
<td>0.0232</td>
<td>0.0132</td>
<td>0.0132</td>
<td>0.9813</td>
<td>RT(O)</td>
</tr>
<tr>
<td>V_2</td>
<td>0.7692</td>
<td>0.0023</td>
<td>0.6923</td>
<td>0.9813</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calculated</td>
<td></td>
<td>Calculated</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area*</td>
<td>31.91</td>
<td>49.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calculated</td>
<td></td>
<td>Calculated</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative Area*</td>
<td>39.39</td>
<td>35.00</td>
<td>-12.54</td>
<td>60.61</td>
<td>65.00</td>
</tr>
<tr>
<td></td>
<td>Calculated</td>
<td></td>
<td>Calculated</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U</td>
<td>0.0129</td>
<td>0.0032</td>
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<td></td>
</tr>
<tr>
<td>Relative U (%)</td>
<td>79.94</td>
<td>20.06</td>
<td></td>
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</tr>
</tbody>
</table>

#### Diagram

A graph showing the tracer concentration over time for both left and right kidneys, with fitting curves and remarks.
### Patient 2

#### Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Left Kidney</th>
<th>Fitting</th>
<th>Right Kidney</th>
<th>Fitting</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>k</td>
<td>0.0098</td>
<td>SSE</td>
<td>0.0175</td>
<td>SSE</td>
<td>LT(C)</td>
</tr>
<tr>
<td>A</td>
<td>8.60E-03</td>
<td>R Sq</td>
<td>0.0123</td>
<td>R Sq</td>
<td>RT(O)</td>
</tr>
<tr>
<td>β</td>
<td>0.0047</td>
<td></td>
<td>0.0073</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V₂</td>
<td>0.5280</td>
<td>0.0613</td>
<td>0.7027</td>
<td>0.9284</td>
<td></td>
</tr>
</tbody>
</table>

#### Calculated/Clinical (%)

| Relative Area* | 42.73 | 46.00 | 7.10 | 57.27 | 54.00 | -6.05 |
| Calculated     |       |       |      | Calculated | |

#### U (%)

| U (%)       | 35.37 | 64.63 |

#### Graph

The graph shows the tracer concentration over time for both left and right kidneys, with fitting parameters indicated.
Patient 3

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Left Kidney</th>
<th>Fitting</th>
<th>Right Kidney</th>
<th>Fitting</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SSE</td>
<td>R Sq</td>
<td>SSE</td>
<td>R Sq</td>
</tr>
<tr>
<td>k</td>
<td>0.0123</td>
<td></td>
<td></td>
<td>0.0149</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>6.06E-03</td>
<td></td>
<td></td>
<td>5.80E-03</td>
<td></td>
</tr>
<tr>
<td>β</td>
<td>0.0180</td>
<td></td>
<td></td>
<td>0.0112</td>
<td></td>
</tr>
<tr>
<td>V₂</td>
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<td>0.0046</td>
<td>0.9915</td>
<td>0.8187</td>
<td>0.0061</td>
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<tr>
<td>Area*</td>
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<td></td>
<td></td>
<td></td>
</tr>
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<td>Calculated</td>
<td>35.44</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Calculated/ Clinical (%)</td>
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<td>44.00</td>
<td>-0.13%</td>
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<td>56.00</td>
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### Graph

- **Patient 4 Curves**
  - Left and Right Kidney curves are plotted over time (in seconds).
  - Key points include:
    - Tracer Concentration (y-axis) vs. Time (x-axis).
    - SSE and R² values for fitting parameters are indicated on the graph.
## Patient 5

### Patient 5 Curves

![Graph showing tracer concentration over time for Patient 5](image)

### Parameters

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<td>SSE</td>
<td>R Sq</td>
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### Calculated/Clinical (\%)

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### Calculated

| U               | 0.0268      |          | -0.0020       |           |          |               |               |
| Relative U (%)  | 92.95       |          | -7.05         |           |          |               |               |
### Patient 6

#### Parameters

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### Diagram

Patient 6 Curves

- **Tracer Conc.** vs **Time/Sec**
- **Left Kidney** vs **Right Kidney**
- Fitting curves: `LT vs t`, `RT vs t`, `fit 1 copy 3`, `fit 2 copy 2`
### Parameters

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| Calculated | Calculated | Calculated | Calculated |
|            |            |            |            |
| U          | 0.0013     | 0.0049     |
| Relative U (%) | 21.45 | 78.55 |
### Patient 8

#### Patient 8 Curves

![Patient 8 Curves](image)

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| Area*      | Calculated  | 52.25   | Calculated   | 52.89   |
| Relative Area* | 49.69 | 50.00 | 0.61 | 50.31 | 50.00 | -0.61 |

| U          | 0.0043      |         |             |         |
| Relative U (%) | 53.16 |         |             |         |
## Patient 9

### Parameters

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### Patient 10

#### Patient 10 Curves

![Graph showing tracer concentration over time for left and right kidneys.](image)

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#### Calculated/Clinical

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#### Area

- Left: 21.48
- Right: 48.72

#### Calculated/Clinical Deviation

- Left: -10.17%
- Right: -10.17%
### Patient 11

#### Parameters

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#### Calculated vs. Clinical Deviation (%)

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#### U (%)

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### Patient 12

#### Patient 12 Curves

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### Patient 13

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**Patient 13 Curves**

- LT vs. t
- fit 19 copy 1
- RT vs. t
- fit 19 copy 2
## Patient 14

### Patient 14 Curves

![Patient 14 Curves](image)

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<th>Fitting</th>
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| Calculated U (%) | 0.0014 | 0.0054 |
| Relative U (%)   | 21.02 | 78.98 |

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### Parameters

- **Parameters**: Kidney Fitting
- **Remarks**: Left (LT) vs. Right (RT) fitting
- **Areas** calculated and clinical deviation
- **U (%)**: Relative

---

15
Patient 15

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Appendix H

Clinical Renogram

Patient 1
Patient 2
Patient 3
Patient 4

(KIDNEY CURVES Diagram)

[Graph showing kidney curves with X-axis: 0.00 - 1440.00, Y-axis: 168.00 - 308.00, 1st kidney graph, 2nd kidney graph, F = 15]
Patient 6
Patient 7

**KIDNEY CURVES**

F - 15
Patient 8

KIDNEY CURVES
F - 15
Patient 9

KIDNEY CURVES

MAG3 STUDY
F-15 STUDY

RT
LT
Patient 11
Patient 12
Patient 13
Patient 14
Patient 16
Patient 18
Patient 19

KIDNEY CURVES

MAG3 STUDY

MIN
Patient 20
Appendix I

Published Papers and Book Chapters
7th Annual NTU-SGH Symposium 2005
Moving Technology Towards Better Patient Care

11–12 August 2005
Singapore National Eye Centre Auditorium

Programme & Abstracts

Organised by

Singapore General Hospital
Nanyang Technological University
## Daily Programme

### 11 August 2005

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<td><strong>SYMPOSIUM – MEDICAL INFORMATICS 1</strong></td>
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<td>1015–1045</td>
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<td>1145–1215</td>
<td><strong>LUNCH SYMPOSIUM</strong></td>
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<td>Biotechnological Inventions &amp; Intellectual Property: A Challenge for Patent Law(s)</td>
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<tr>
<td>1215–1315</td>
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<td><strong>FREE PAPERS 3 (MEDICAL INFORMATICS/MEDICAL SIGNAL PROCESSING)</strong></td>
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<td>IT Security in Biomedical Imaging Informatics: The Hidden Vulnerability</td>
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<td>Advanced Integrative Approach for Breast Thermogram</td>
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<td>Orthopaedics Surgery Simulation</td>
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<td>Modeling of Brain Response to External Stimuli</td>
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<td><em>Mr Lo Chong Chiah (NTU)</em></td>
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<td>1415–1455</td>
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<tr>
<td>1455–1525</td>
<td>Tea Break and Exhibition</td>
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<tr>
<td>1525–1625</td>
<td><strong>FREE PAPERS 5 (NURSING)</strong></td>
</tr>
<tr>
<td>1625–1630</td>
<td>Closing Remarks</td>
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</table>
## Development of an Electrocardiographic Diagnostic Tool using Frontal Plane Vectorcardiogram

Mr Nagenthiran Thurairaj (NTU)

Chair: Asst/Prof Kwek Leong Chuan & Dr Philip Wong

### FREE PAPERS 4 (ADVANCED BIOMATERIALS/MODELLING/TISSUE ENGINEERING)

- **Fabrication and Near-Physiological Testing of a Biodegradable Metallic Coronary Stent**
  - A/Prof Lim Chu Sing (NTU)
- **A New Concept of Active and Passive Elastance to Explain Left Ventricular Pressure Dynamics**
  - Dr Zhong Liang (NTU)
- **Non-invasive Contractility Indices Based on the Left Ventricular Shape**
  - Dr Zhong Liang (NTU)
- **Implantation of an Autologous Pericardial Valve in a Sheep Model**
  - Dr Tan Teing Ee (National Heart Centre)

Chair: A/Prof Frank Fuss & Dr Guo Chang Ming

### 1415–1455

- **FREE PAPERS 4 (ADVANCED BIOMATERIALS/MODELLING/TISSUE ENGINEERING)**

### 1455–1525

- **Tea Break and Exhibition**

### 1525–1625

- **FREE PAPERS 5 (NURSING)**

  - **An Analysis of the Skin Prick Test Results of Rhinitis Patients at ENT Centre, SGH**
    - Ms Aishah bte Abdul Latiff
  - **To Facilitate Early Ambulation for Patients who Require Walking Aids after Surgery**
    - Ms Norhayati Ahmad
  - **To Reduce Time in Levelling Transducer to Axis Point**
    - Ms Kamsiah Jaafar
  - **Comparison of Temperature Readings between Tympanic and Oral Mercury-In-Glass Thermometer**
    - Ms Josephine Teo
  - **Use of a Modified Trolley By Nurses to Save Time and Ensure Safekeeping of Patients Record**
    - Ms Tamilchelvi Sinnapan
  - **Perineal Cold Pads Vs Oral Analgesics in the Relief of Post Partum Perineal Wound Pain**
    - Ms Punasundri Thangaraju

Chair: Ms Kaldip Kaur & Ms Cheam Boon See

### 1625–1630

- **Closing Remarks**
  - A/Prof Kwoh Chee Keong, Co-chairman

### 1630

- **End of Scientific Sessions**
Determination of urine outflow and renal function quantitatively

Loh Kah Meng, David Ng, Dhanjoo N Ghista, Heiko Rudolph

1 School of Engineering (Electronics), Nanyang Polytechnic, Singapore; 2 Department of Nuclear Medicine and PET, Singapore General Hospital, Singapore; 3 Department of Biomedical Engineering, Nanyang Technological University, Singapore; 4 School of Electrical and Computer Engineering, Biomedical, KMIT, Australia

Summary—In this paper, we provide a noninvasive methodology to assess physiological function of the kidneys. We analyze the renograms with 2-compartmental modeling of the kidney-renal outflow system, and therefore compute the amount of flow of renal radionuclide into and out of the renal pelvis compartment.

Index Terms—glomerular filtration rate, GFR, renal outflow obstruction, renal function

I. MOTIVATION

Currently there is no mathematical model for renal function and urine outflow rate based on non-invasive renography.

II. METHODOLOGY

We will first digitalize and normalized the renograms. The 2-compartmental modeling of the kidney outflow system was performed with derivation of system parameters: \( k_a \) and \( v_1 / v_r \) [1]. We will only accept the results of the best fit (R-Square > 95%). From these parameters, we will determine the urine outflow \( (U(t)) \) dl/sec.

III. RESULTS

![Figure 1. Clinical renograms of volunteer coded Patient 7.](image)

Note that the \( (Q_o, R_r) \) segment of the tracer curve for the right kidney is similar to the \( (P, Q_o) \) segment and demonstrates good outflow-rate compared to the \( (Q_r, R_r) \) segment of the obstructive curve for the left kidney.

We have performed parametric identification for equations (9) and (10) using MatLab 7 in the paper [1]. The following are the best fitted results for patients 7.

<table>
<thead>
<tr>
<th>Identify</th>
<th>Clinical %</th>
<th>Calculated %</th>
<th>% Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 7</td>
<td>44</td>
<td>56</td>
<td>43.87</td>
</tr>
</tbody>
</table>

IV. CONCLUSION

We have demonstrated the techniques of using the two-compartment model of kidney-renal outflow tract [1] to assess the clinical relevance with comparison with clinical renogram studies.

REFERENCES

ACTIVITY-BASED DYNAMIC INSULIN INFUSION SYSTEM
Loh Kah Meng¹, Chan Ting Kwan², Dhanjoo N. Ghista³, Heiko Rudolph⁴
¹ School of Engineering (Electronics), Nanyang Polytechnic, Singapore, ² TechSource Systems Pte Ltd, Singapore, ³ Department of Biomedical Engineering, Nanyang Technological University, Singapore, ⁴ School or Electrical and Computer Engineering, Biomedical, RMIT, Australia

Summary – This paper has demonstrated the operation of an activity-based dynamic insulin infusion system. The amount of insulin infused to bring the blood glucose concentration down is regulated by a closed-loop PD (Proportional-Derivative) control algorithm.

Index Terms – dynamic, clinical diagnosis, insulin release, systems-engineering model

I. MOTIVATION
The current insulin infusion systems are based on the previously known individual’s activities history to estimate the required insulin amount. The techniques adopted do not allow the patients to deviate too much from their normal daily activities [3]. Our work focuses on regular sampling of diabetic patients’ blood glucose concentration through a sensor to compute the required amount of insulin to be released into the bloodstream.

II. METHODOLOGY
The closed loop system will continuously monitor the blood glucose concentration at 0.5h interval. Once the system detects that the blood glucose concentration exceeds a predetermined threshold e.g. 120mg/dl [1], the system will be armed and calculate the amount of insulin required [2] to bring the blood glucose concentration below the threshold.

Figure 1. System Block diagram of the insulin release system. The error is generated from glucose sensor and computed glucose concentration after the release of insulin into the blood stream at 0.5h interval.

III. RESULTS
The result 2 shows the results of the insulin infusion system. The diabetic subject D18’s unaided glucose clinical data is fed into the system. After the release of insulin at 0.5h, 1h and 1.5h intervals, the final blood glucose concentration drops below the threshold and the controller will stop releasing insulin into the blood stream.

Figure 2. The subject’s unaided blood glucose concentration at time 0 is above 120mg/dl. The system is armed and re-sampled the blood glucose concentration at 0.5h (170 mg/dl). The system will send a bolus of insulin; 10mU/dl into the blood stream. The system will keep monitoring the resulting blood glucose concentration at 1.0h and 1.5 hour intervals. If the blood glucose concentration is above the threshold, the system will infuse a computed insulin bolus into blood stream.

IV. CONCLUSION
We have demonstrated the capabilities of an activities-adaptive dynamic real-time insulin release system. The system is able to protect the users from hypoglycemia and hyperglycemia. As we continue this work, we will develop a clinically-implementable hardware system for diabetic patients.

REFERENCES
CHAPTER 3

Lung-gas composition and transfer analysis: O₂ and CO₂ diffusion coefficients and metabolic rates

D.N. Ghista¹, K.M. Loh² & D. Ng³
¹School of Mechanical and Production Engineering, Nanyang Technological University, Singapore 639798; email:mdnghista@ntu.edu.sg
²School of Engineering (Electronics), Nanyang Polytechnic, Singapore.
³Department of Nuclear Medicine and PET, Singapore General Hospital, Singapore.

Abstract

The primary function of the lung is to (i) oxygenate the blood and thereby provide oxygen to the cells for metabolism purposes, and (ii) to remove the collected CO₂ from the pulmonary blood. Herein, we will analyze the compositions of the inspired and expired air per breath, and from there compute the O₂ consumption and CO₂ production rates. Next, we derive expressions for diffusion coefficients $D_{O₂}$ and $D_{CO₂}$ in terms of the evaluated cardiac output, O₂ and CO₂ concentrations in arterial and venous blood, alveolar and blood O₂ and CO₂ partial pressures. We then take up a typical case study, and demonstrate the computation of $D_{O₂}$ and $D_{CO₂}$, to represent the lung-performance capability to oxygenate the blood.

1 Introduction

The lung-functional performance is characterized by (i) its ventilatory capacity, to bring air (and hence O₂) into the alveoli, and (ii) its capacity to transfer O₂ and CO₂ into and from the pulmonary capillary bed. Hence, the O₂ and CO₂ diffusion coefficients as well as the O₂ consumption rate and the CO₂ production rate represent the lung-performance indices.
2 Lung-air composition analysis (and O₂ consumption and CO₂ production rates)

We carry out a mass-balance analysis, involving:

(i) compositions of air breathed in and out
(ii) consumption or losses of O₂, CO₂ and H₂O.

Table 1 provides clinical data on partial pressures and volumes of N₂, O₂, CO₂ and H₂O of atmospheric air breathed in and expired out, one breath cycle. The monitored breathing rate (BR) = 12 breaths/min, and we assume \( P_{\text{H}_2\text{O}} \) at 37°C = 47 mmHg.

It can be noted that the expired air volume exceeds the inspired air volume for this particular breath cycle. The H₂O loss of 30.1 ml (=32.6–2.5 ml) contributes the major portion of this difference.

2.1 Calculation of O₂ consumption rate and CO₂ production rate

We now determine the O₂ consumption rate and CO₂ production rates from the inspired and expired gases.

Assuming the patient breathes at 12 times per minute we have

\[
O_2 \text{ Consumption Rate} = (\text{Inspired } O_2 - \text{Expired } O_2) \times 12
\]

\[
= (104.2 - 80.6) \times 12
\]

\[
= 283.2 \text{ ml/min}
\]

<table>
<thead>
<tr>
<th>Respiratory gases</th>
<th>Atmospheric air</th>
<th>Expired air</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmHg</td>
<td>ml/%</td>
</tr>
<tr>
<td>N₂</td>
<td>597</td>
<td>393.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>78.55%</td>
</tr>
<tr>
<td>O₂</td>
<td>159</td>
<td>104.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20.84%</td>
</tr>
<tr>
<td>CO₂</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.04%</td>
</tr>
<tr>
<td>H₂O</td>
<td>3.7</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.49%</td>
</tr>
<tr>
<td>Total</td>
<td>760</td>
<td>500</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100%</td>
</tr>
</tbody>
</table>
Figure 1: Dead-space volume

\[
\text{CO}_2 \text{ Production Rate} = (\text{Expired CO}_2 - \text{Inspired CO}_2) \times 12 \\
= (19.1 - 0.2) \times 12 \\
= 226.8 \text{ ml/min}
\]

The amount of water vapor in the humidified expired air amounts to 6.2% of the expired air (compared to 0.49% of the dry inspired air) corresponding to the partial-pressure ratio of water vapor in the expired air (\(\approx 47/760\)). The volume of the dry expired air is \((525.3 - 32.6) \text{ ml} = 492.7 \text{ ml}\).

Now, assume that out of 500 ml of inspired air, the dead-space air volume (not taking part in the gas-transfer process) is 150 ml and the alveolar air volume is 350 ml. We next compute the dead-space air volume composition.

### 2.2 Dead-space air composition

The clinical data of expired air composition is:

- \(\text{N}_2 = 393.1 \text{ ml}\)
- \(\text{O}_2 = 83.36 \text{ ml}\)
- \(\text{CO}_2 = 16.87 \text{ ml}\)
- \(\text{H}_2\text{O} = 34.15 \text{ ml}\)
- Total = 527.49 ml

Now, the dead-space air will be made up of (i) a dry air portion from the inspired air (assumed to be \(= 141 \text{ ml}\)), plus (ii) the water vapor taken up by the dry air
(estimated to be \( = 9 \text{ ml} \)) since the expired air portion of 141 ml will not have undergone \( \text{O}_2 \) and \( \text{CO}_2 \) transfer, its composition is the same as that of the inspired air:

\[
\begin{align*}
\text{N}_2 & = 111 \text{ ml (78.55\%)} , \quad \text{O}_2 = 29.40 \text{ ml (20.84\%)} , \quad \text{CO}_2 = 0.06 \text{ ml (0.04\%)} , \\
\text{H}_2\text{O} & = 0.69 \text{ ml (0.49\%)} .
\end{align*}
\]

When this inspired air (in the dead space) of 141 ml is fully humidified, it will take up a further \( X \) ml of \( \text{H}_2\text{O} \) vapor, in the ratio of the partial-pressures, as:

\[
\frac{X}{141} = \frac{47}{713} = 0.0659
\]

\[
\therefore X = 0.0659 \times 141 = 9.29 \text{ ml of } \text{H}_2\text{O} \text{ vapor (which is close to our estimate)}.
\]

So, by adding 9.29 ml of \( \text{H}_2\text{O} \) vapor to 0.69 ml of water vapor in the inspired air volume of 141 ml, the total water vapor in the dead-space air is 9.98 ml. The humidified dead-space air composition will be:

\[
\begin{align*}
\text{N}_2 & = 111.00 \text{ ml (}= 73.78\%) \\
\text{O}_2 & = 29.40 \text{ ml (}= 19.55\%) \\
\text{CO}_2 & = 0.06 \text{ ml (}= 0.04\%) \\
\text{H}_2\text{O} & = 9.98 \text{ ml (}= 6.63\%) \\
\text{Total} & = 150.44 \text{ ml}
\end{align*}
\]

### 2.3 Alveolar-air composition and partial pressures

We can now compute the alveolar air composition, by subtracting the dead-space air from the expired air. These values are tabulated in column 4 of the table below.

Finally, we compute the partial pressure of \( \text{O}_2 \) and \( \text{CO}_2 \) (as well as of \( \text{N}_2 \) and \( \text{H}_2\text{O} \)), so that we can determine next the diffusion coefficients of \( \text{O}_2 \) and \( \text{CO}_2 \) based on the monitoring of arterial and venous blood concentrations. These values are tabulated in column 5 of the below table.

<table>
<thead>
<tr>
<th></th>
<th>Expired air (ml)</th>
<th>Dead-space air (ml)</th>
<th>Alveolar air (ml)</th>
<th>Alveolar-air partial pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{N}_2 )</td>
<td>393.1</td>
<td>111.00</td>
<td>282.1</td>
<td>569.41</td>
</tr>
<tr>
<td>( \text{O}_2 )</td>
<td>80.53</td>
<td>29.40</td>
<td>51.13</td>
<td>103.21</td>
</tr>
<tr>
<td>( \text{CO}_2 )</td>
<td>19.12</td>
<td>0.06</td>
<td>19.06</td>
<td>38.47</td>
</tr>
<tr>
<td>( \text{H}_2\text{O} )</td>
<td>34.21</td>
<td>9.98</td>
<td>24.23</td>
<td>48.91</td>
</tr>
<tr>
<td>Total</td>
<td>526.96</td>
<td>150.44</td>
<td>376.52</td>
<td>760</td>
</tr>
</tbody>
</table>
3 Lung gas-exchange model and parametric analysis

3.1 Expressions for \( D_{O_2} \) and \( D_{CO_2} \)

The gas exchange between the alveolar air and pulmonary capillary blood is represented by the following \( O_2 \) and \( CO_2 \) conservation equations (Fig. 2):

\[
Q^{VE}C^{VE}_{O_2} = Q^{AE}C^{AE}_{O_2} + \dot{V}_O \quad \text{(from the alveolar air to capillary blood)}
= Q^{AE}C^{AE}_{O_2} + (\Delta P_{av})D_{O_2}; \quad P_{O_2}^{cap} = P_{O_2}^{AE},
\]

(1)

in which \( P_{O_2}^{cap} = P_{O_2}^{PRB} \) (\( O_2 \) concentration of the preoxygenated blood)

\[
Q^{VE}C^{VE}_{CO_2} = Q^{AE}C^{AE}_{CO_2} - \dot{V}_CO_2
= Q^{AE}C^{AE}_{CO_2} - (\Delta P_{av})D_{CO_2}; \quad P_{CO_2}^{cap} = P_{CO_2}^{VE},
\]

(2)

in which \( P_{CO_2}^{cap} = P_{CO_2}^{PRB} \) (\( CO_2 \) concentration of the preoxygenated blood), wherein

(i) \( Q^{AB} \) and \( Q^{VB} \) are arterial and venous blood flow-rates;
\( Q^{AB} = Q^{VE} \) (at venous end), \( Q^{VB} = Q^{AE} \) (at arterial end)

(ii) \( P_{O_2}^{al} \) and \( P_{O_2}^{cap} \) are the alveolar and capillary \( O_2 \) partial pressures

(iii) \( P_{CO_2}^{al} \) and \( P_{CO_2}^{cap} \) are the alveolar and capillary \( CO_2 \) partial pressure

(iv) \( D_{O_2} \) and \( D_{CO_2} \) are the \( O_2 \) and \( CO_2 \) diffusion coefficients

(v) \( \Delta P_{av}^{O_2} \) = average of \( (P_{O_2}^{al} - P_{O_2}^{cap}) \) over the capillary length;
\( \Delta P_{av}^{CO_2} \) = average of \( (P_{CO_2}^{al} - P_{CO_2}^{cap}) \) over the capillary length.

Now we can equate the arterial and venous blood flow rates, as

\[
Q^{AB} = Q^{VB} = Q = (SV)/(EP) \simeq CO/60,
\]

SV, EP and CO being the stroke volume, ejection period and cardiac output, respectively. Hence the above equations can be rewritten as:

(vi) \( \dot{V}_{O_2} \) is the \( O_2 \) transfer rate from alveolar air to capillary blood (= \( O_2 \) consumption rate), \( \dot{V}_{CO_2} \) is the \( CO_2 \) transfer rate from capillary blood to alveolar air.

![Figure 2: Schematic of blood-gas concentration in the pulmonary capillary.](image-url)
From eqn. (1):

$$Q^{VE}C_{O_2}^{VE} = Q^{AB}C_{O_2}^{AB} + (\Delta P_{O_2}^{O_2})D_{O_2}; \quad P_{O_2}^{cap} = P_{O_2}^{AE} = P_{O_2}$$

$$Q^{VE}C_{O_2}^{VB} = Q^{AB}C_{O_2}^{AB} + (\Delta P_{O_2}^{O_2})D_{O_2}$$

$$D_{O_2} = \frac{Q(C_{O_2}^{VE} - C_{O_2}^{AE})}{(\Delta P_{O_2}^{O_2})} = \frac{Q(C_{O_2}^{AB} - C_{O_2}^{VB})}{(\Delta P_{O_2}^{O_2})}.$$  \hspace{1cm} (3)

From eqn. (2):

$$Q^{VE}C_{CO_2}^{VE} = Q^{AE}C_{CO_2}^{AE} - (\Delta P_{CO_2}^{CO_2})D_{CO_2}; \quad P_{CO_2}^{cap} = P_{CO_2}^{AE} = P_{CO_2}^{VB}$$

$$Q^{VE}C_{CO_2}^{VB} = Q^{AE}C_{CO_2}^{AE} - (\Delta P_{CO_2}^{CO_2})D_{CO_2}$$

$$D_{CO_2} = \frac{Q(C_{CO_2}^{VE} - C_{CO_2}^{AE})}{(\Delta P_{CO_2}^{CO_2})}.$$  \hspace{1cm} (4)

wherein

(i) $Q$, $C_{O_2}^{VE}$ and $C_{CO_2}^{VE}$, $C_{O_2}^{AE}$ and $C_{CO_2}^{AE}$ can be monitored because $C_{O_2}^{VE}$ and $C_{CO_2}^{VE}$ = $C_{O_2}^{AB}$ and $C_{CO_2}^{AB}$, and $C_{O_2}^{AE}$ and $C_{CO_2}^{AE}$ = $C_{O_2}^{VB}$ and $C_{CO_2}^{VB}$

(ii) $D_{O_2}$ and $D_{CO_2}$ (eqns. (3) and (4)) represent the lung gas-exchange parameters.

Now from eqns. (3) and (4), if we want to evaluate the diffusion coefficients $D_{O_2}$ and $D_{CO_2}$, we need to also express $P_{O_2}^{al}$, $P_{O_2}^{cap}$ and $P_{CO_2}^{al}$, $P_{CO_2}^{cap}$ in terms of monitorable quantities. In this regard,

(i) Alveolar $P_{O_2}^{al}$ can be expressed in terms of $\dot{V}$ (the ventilation rate) and $\dot{V}_{O_2}$ (the $O_2$ consumption rate) as Fig. 3:

$$P_{O_2}^{al} = k_1 \left[ 1 - e^{-k_2 \left( \frac{\dot{V} / \dot{V}_m}{\dot{V}_{O_2}} \right) } \right],$$ \hspace{1cm} (5)

where $\dot{V}_m$ is the maximum ventilation rate and $\dot{V}_{O_2}$ (the $O_2$ consumption rate or absorption rate from the alveoli) = $Q(C_{O_2}^{AB} - C_{O_2}^{VB})$. Equation (5) implies that as $(\dot{V} / \dot{V}_m)$ increases, (the exponential term decreases, and) $P_{O_2}^{al}$ increases (as in Fig. 3), and as $\dot{V}_{O_2}$ increases $P_{O_2}^{al}$ decreases (as in Fig. 3).

(ii) Alveolar $P_{CO_2}^{al}$ can be expressed in terms of $\dot{V}$ and $\dot{V}_{CO_2}$ as in Fig. 4.

$$P_{CO_2}^{al} = k_3 e^{-k_4 \left( \frac{\dot{V} / \dot{V}_m}{\dot{V}_{CO_2}} \right)}.$$ \hspace{1cm} (6)

where $\dot{V}_{CO_2}$ (the $CO_2$ production rate or excretion rate from the blood) = $Q(C_{CO_2}^{VB} - C_{CO_2}^{AB})$. This equation implies that as $\dot{V} / \dot{V}_m$ increases, $P_{CO_2}^{al}$ decreases; also, as $\dot{V}_{CO_2}$ increases (the exponential term decreases, and hence) $P_{CO_2}^{al}$ increases.
Figure 3: Effect on alveolar $P_{O_2}$ of (i) alveolar ventilation, and (ii) rate of oxygen absorption from alveolar $P_{O_2}$ or $O_2$ consumption rate [from Guyton (1971), p. 476].

Figure 4: Effect on alveolar $P_{CO_2}$ of alveolar ventilation and rate of carbon dioxide excretion from the blood or $CO_2$ production rate [from Guyton (1971), p. 476].

(iii) Blood $P_{O_2}$ can be obtained in terms of blood $CO_2$, from the $O_2$ disassociation curve (providing concentrations in arterial and venous blood), is represented in Fig. 5 as:

$$C_{O_2} = C_{O_2}^{m} \left(1 - e^{-k_5^{P_{O_2}}}ight), \quad \text{or} \quad C_{O_2} = 1 - e^{-k_5^{P_{O_2}}},$$

(7)
Figure 5: $O_2$ dissociation curves, showing the total oxygen in each 100 ml of normal blood, the portion dissolved in the water of the blood [from Guyton [2], p. 485].

Figure 6: The carbon dioxide dissociation curve [from Guyton [2], p. 491].

where

- $C_{O_2}^m$ and $P_{O_2}^m$ are the maximum values of blood $O_2$ partial pressure
- $CO_2^* = CO_2 / CO_2^m$
- $P_{O_2}^* = P_{O_2} / P_{O_2}^m$.

(iv) Blood $P_{CO_2}$ can be obtained in terms of $C_{CO_2}$, from the $CO_2$ disassociation curve or $CO_2$ concentration in arterial and venous blood can be represented
as per Fig. 6 as:

\[ C_{CO_2} = C_{O_2}^m \left( 1 - e^{-k_6 \left( P_{CO_2} / P_{CO_2}^m \right)} \right) \]

or, \[ C_{CO_2}^* = 1 - e^{-k_6 \left( P_{CO_2} / P_{CO_2}^m \right)} = 1 - e^{-k_6 P_{CO_2}^*} \]  \hspace{1cm} (8)

### 3.2 Alveolar O\(_2\) and CO\(_2\) partial-pressure expressions

Now, let us refer eqn. (4) for the \( P_{O_2}^{al} \) partial pressure curve (Fig. 3), represented by the equation:

\[ P_{O_2}^{al} = k_1 \left[ 1 - e^{-k_2 \left( (V \circ / V_m) / \dot{V}_{O_2} \right)} \right] \]

\[ = k_1 \left[ 1 - e^{-k_2 \left( \dot{V}^* / \dot{V}_{O_2} \right)} \right], \text{ where } \dot{V}^* = \frac{\dot{V}}{\dot{V}_m} \]  \hspace{1cm} (9)

where \( \dot{V} \) is the alveolar ventilation rate (in liters/min), \( \dot{V}_m \) is the maximum ventilation rate (= 50 l/min) and \( \dot{V}_{O_2} \) is the \( O_2 \) consumption rate (in liters/min). Herein, the coefficients \( k_1 \) and \( k_2 \) can be determined by having this equation match the Fig. 3 data. Note, in this equation, when \( \dot{V} = 0, P_{O_2}^{al} = 0 \) from the equation, which satisfies the data.

Now for \( \dot{V}_{O_2} = 0.25 \text{ l/min}, \) \( \dot{V}^* = \frac{\dot{V}}{\dot{V}_m} = 0.5, \) \( P_{O_2}^{al} = 140 \text{ mmHg.} \) Hence,

\[ 140 = k_1 \left[ 1 - e^{-k_2 \left[ \frac{0.5}{0.25} \right]} \right] = k_1 (1 - e^{-2k_2}). \]  \hspace{1cm} (10)

Also, when \( \dot{V}_{O_2} = 11/\text{min}, \dot{V}^* = 0.31/\text{min}, \) \( P_{O_2}^{al} = 100 \text{ mmHg.} \) Hence

\[ 100 = k_1 \left[ 1 - e^{-k_2 \left[ \frac{0.31}{1} \right]} \right] = k_1 (1 - e^{-0.3k_2}). \]  \hspace{1cm} (11)

From eqns. (10) and (11), we get:

\[ \frac{140}{100} = \frac{k_1 (1 - e^{-2k_2})}{k_1 (1 - e^{-0.3k_2})} = \frac{1 - e^{-2k_2}}{1 - e^{-0.3k_2}} \]

\[ \therefore 140 - 140e^{-0.3k_2} = 100 - 100e^{-2k_2} \]

or, \( 40 = 100e^{-2k_2} + 140e^{-0.3k_2} \), so that \( k_2 = 4.18 \text{ min/l.} \)  \hspace{1cm} (12)

Upon substituting \( k_2 = 4.18 \text{ min/l} \) into eqn. (10) we obtain:

\[ 140 = k_1 (1 - e^{-\left(2 \times 4.18\right)}), \text{ so that } k_1 \approx 140 \text{ mmHg.} \]  \hspace{1cm} (13)
Hence, the $P_{\text{O}_2}^{\text{al}}$ curve can be represented by:

$$P_{\text{O}_2}^{\text{al}} = 140 \left[ 1 - e^{-4.18 \left( \frac{\dot{V}^*}{\dot{V}_{\text{O}_2}} \right)} \right],$$  \hspace{1cm} (14)$$

where, $\dot{V}_{\text{O}_2} = Q(C_{\text{O}_2}^{\text{AB}} - C_{\text{O}_2}^{\text{VB}})$ and $\dot{V}^* = \dot{V}/501/\text{min}$.

Now, let us look at the $P_{\text{CO}_2}^{\text{al}}$ expression:

$$P_{\text{CO}_2}^{\text{al}} = k_3 e^{-k_4 \left( \frac{\dot{V}}{V_{\text{m}}} \right) / \dot{V}_{\text{CO}_2}} = k_3 e^{-k_4 \left( \frac{\dot{V}^*}{\dot{V}_{\text{CO}_2}} \right)}.
$$

We note from Fig. 4 that for $\dot{V}_{\text{CO}_2} = 0.2 \text{ l/min}$ and $\dot{V}_{\text{m}} = 0.2$, $P_{\text{CO}_2}^{\text{al}} = 12$. Hence, from the above equation, we get:

$$12 = k_3 e^{-k_4}$$  \hspace{1cm} (15)$$

Also, for $\dot{V}_{\text{O}_2} = 0.8 \text{ l/min}$ and $\dot{V}_{\text{m}} = 0.2$, $P_{\text{CO}_2}^{\text{al}} = 62 \text{ mmHg}$. Hence

$$62 = k_3 e^{-k_4 \left[ \frac{0.20}{0.80} \right]} = k_3 e^{-\frac{k_4}{4}}. \hspace{1cm} (16)$$

From eqns. (15) and (16), we get:

$$\frac{12}{62} = \frac{e^{-k_4}}{e^{-\frac{k_4}{4}}} = e^{-\frac{2}{3}k_4}$$

$$\ln \left( \frac{12}{62} \right) = -\frac{2}{3}k_4, \hspace{0.5cm} \text{so that } k_4 = 2.46.$$  \hspace{1cm} (17)$$

Substituting $k_4 = 2.46$ into eqn. (16), we obtain:

$$62 = k_3 e^{-\frac{2.46}{4}}, \hspace{0.5cm} \therefore k_3 = 114.68.$$  \hspace{1cm} (18)$$

Hence, the $P_{\text{CO}_2}^{\text{al}}$ curve can be represented as

$$P_{\text{CO}_2}^{\text{al}} = 114.68e^{-2.46 \left( \frac{\dot{V}}{V_{\text{m}}} \right) / \dot{V}_{\text{CO}_2}},$$  \hspace{1cm} (19)$$

where $\dot{V}^* = \dot{V}/501 \text{ l/min}$ and $\dot{V}_{\text{CO}_2} = Q(C_{\text{CO}_2}^{\text{VB}} - C_{\text{CO}_2}^{\text{AB}})$.

3.3 Arterial and venous $\text{O}_2$ and $\text{CO}_2$ partial-pressure expressions

We now need to express $P_{\text{O}_2}^{\text{AB}}$ and $P_{\text{CO}_2}^{\text{VB}}$ in terms of $C_{\text{O}_2}^{\text{AB}}$ and $C_{\text{CO}_2}^{\text{VB}}$. 
So that let us look at the $O_2$ disassociation curve, as shown in Fig. 5.

$$C_{O_2} = C_{O_2|\text{max}} \left[ 1 - e^{-k_5 P_{O_2}^*} \right],$$
or,

$$C_{O_2}^* = 1 - e^{-k_5 P_{O_2}^*},$$

where $C_{O_2}^* = \frac{C_{O_2}}{C_{O_2|\text{max}}}$, $P_{O_2}^* = \frac{P_{O_2}}{P_{O_2|\text{max}}}$. \(\text{(20)}\)

From Fig. 5, at $P_{O_2}^* = \frac{40 \text{ mmHg}}{140 \text{ mmHg}} = 0.29$ (for normal venous blood), and

$$C_{O_2}^* = \frac{15}{20} = 0.75.$$

Hence from eqn. (20):

$$0.75 = 1 - e^{-0.29k_5} \Rightarrow k_5 = 4.78. \quad \text{(21)}$$

Also, $P_{O_2}^* = \frac{95 \text{ mmHg}}{140 \text{ mmHg}} = 0.68$ (for normal arterial blood), and

$$C_{O_2}^* = \frac{19}{20} = 0.95.$$

Hence from eqn. (20):

$$0.95 = 1 - e^{-0.68k_5}, \text{ or } k_5 = 4.4. \quad \text{(22)}$$

So, we take the average value of $k_5$:

$$k_5 = \frac{(4.78 + 4.4)}{2} = 4.59. \quad \text{(23)}$$

Then the $O_2$ disassociation curve is given by:

$$C_{O_2} = C_{O_2}^B = 0.2 \left[ 1 - e^{-4.59\frac{P_{O_2}}{140}} \right], \quad \text{(24)}$$

and

$$P_{O_2} = \frac{140}{4.59} \ln \left[ \frac{0.2}{0.2 - C_{O_2}^B} \right] = 30.5 \ln \left[ \frac{0.2}{0.2 - C_{O_2}^B} \right]. \quad \text{(25)}$$

Finally, we look at the $CO_2$ disassociation curve

$$C_{CO_2} = C_{CO_2|\text{max}} \left( 1 - e^{-k_6 P_{CO_2}^*} \right),$$
or,

$$C_{CO_2}^* = 1 - e^{-k_6 P_{CO_2}^*} = 1 - e^{-k_6 P_{CO_2}^*}. \quad \text{(26)}$$
Based on Fig. 6, when $P_{CO_2}^* = \frac{20 \text{ mmHg}}{140 \text{ mmHg}} = 0.14$, $C_{CO_2}^* = \frac{38}{80} = 0.475$, so that

$$0.475 = 1 - e^{-0.14k_6}, \quad k_6 = 4.60,$$

and when $P_{CO_2}^* = \frac{70 \text{ mmHg}}{140 \text{ mmHg}} = 0.5$, $C_{CO_2}^* = \frac{60}{80} = 0.75$, so that

$$0.75 = 1 - e^{-0.5k_6}, \quad k_6 = 2.77.$$

So, we take the average value of $k_6$:

$$k_6 = \frac{(4.60 + 2.77)}{2} = 3.69.$$  

Then the CO$_2$ concentration is given (from eqns. (26–29) by:

$$C_{CO_2} = C_{CO_2}^B = 0.8 \left[ 1 - e^{-4.71 \left[ \frac{P_{CO_2}}{140} \right]} \right]$$

(30)

and

$$P_{CO_2} = 29.72 \ln \left[ \frac{0.8}{0.8 - C_{CO_2}^B} \right].$$

(31)

3.4 Sequential procedure to compute $D_{O_2}$ and $D_{CO_2}$

1. We first monitor: $V(t)$, $\dot{V}(t)$, SV (stroke volume), EP (cardiac ejection period), $C_{O_2}^B$, $C_{O_2}^{AB}$, $C_{CO_2}^B$ and $C_{CO_2}^{AB}$ (O$_2$ and CO$_2$ concentrations in pre oxygenated and post oxygenated blood).

2. We substitute the values of $C_{O_2}^{AB} (= C_{O_2}^{VE})$ and $C_{O_2}^{VB} (= C_{O_2}^{AE})$ into eqn. (3), and the values of $C_{CO_2}^{AB} (= C_{CO_2}^{VE})$ and $C_{CO_2}^{VB} (= C_{CO_2}^{AE})$ into eqn. (4).

3. We next determine:

$$Q = SV / \text{ejection period},$$

(32)

$$\dot{V}_O_2(t) = Q(C_{O_2}^{AB} - C_{O_2}^{VB}),$$

(33)

$$\dot{V}_{CO_2}(t) = Q(C_{CO_2}^{VB} - C_{CO_2}^{AB}).$$

(34)

4. We then substitute the expressions for $\dot{V}_O_2(t)$ and $\dot{V}_{CO_2}(t)$ into the equations for $P_{O_2}^{al}$ (eqn. (14)) and $P_{CO_2}^{al}$ (eqn. (19)).

5. We substitute the monitored values of $C_{O_2}^{VB} (= C_{O_2}^{AE})$ and $C_{CO_2}^{VB} (= C_{CO_2}^{AE})$ into eqns. (25) and (31), to obtain the values of $P_{O_2}^{AE}$ and $P_{CO_2}^{AE}$.

6. Now, in order to determine the values of the lung gas-exchange parameters $D_{O_2}$ and $D_{CO_2}$, we substitute into eqns. (3) and (4) for $Q$ from eqn. (32), $P_{O_2}^{al}$ from eqn. (14), $P_{CO_2}^{al}$ from eqn. (19), $P_{O_2}^{VE}$ from eqn. (26), and $P_{CO_2}^{VE}$ from eqn. (31).
3.5 Determining $D_{O_2}$ and $D_{CO_2}$

Figure 7 illustrates the variation of $\Delta P^{O_2} (= P_{O_2}^{al} - P_{O_2}^{cap} = P_{O_2}^{al} - P_{O_2}^{AB})$ along the length ($l$) of the capillary bed.

Let $l^* = l / l_m$.

Then we can express:

$$\Delta P^{O_2} = \Delta P^{O_2}_{\text{max}} f_{O_2}(l^*).$$  \hspace{1cm} (35)

Then,

$$\Delta P^{O_2}_{\text{av}} = \Delta P^{O_2}_{\text{max}} \left( \int_0^1 f_{O_2}(l^*) \, dl^* \right) = \Delta P^{O_2}_{\text{max}} \left( F_{O_2} \right).$$ \hspace{1cm} (36)

Based on data [3], since $\Delta P^{O_2}_{\text{av}} = 12$ mmHg for $\Delta P^{O_2}_{\text{max}} = 65$ mmHg, we have $F_{O_2} = 0.185$.

We can similarly determine the average value of $\Delta P^{CO_2}$ from Fig. 8 as:

Let $l^* = l / l_m$.

Then, we can represent Fig. 8 as:

$$\Delta P^{CO_2} = \Delta P^{CO_2}_{\text{max}} f_{CO_2}(l^*).$$ \hspace{1cm} (37)

Then,

$$\Delta P^{CO_2}_{\text{av}} = \Delta P^{O_2}_{\text{max}} \left( \int_0^1 f_{CO_2}(l^*) \, dl^* \right) = \Delta P^{CO_2}_{\text{max}} \left( F_{CO_2} \right).$$ \hspace{1cm} (38)

![Diagram showing alveolar and pulmonary oxygen partial pressures](image)

**Figure 7:** Uptake of oxygen by the pulmonary capillary blood. (The curve in this figure was constructed from data in Mihorn and Pulley: Biophys. J., 8: 337, 1968). [from Guyton (1971), p. 434.]
Figure 8: Diffusion of carbon dioxide from the pulmonary blood into the alveolus. (The curve in this figure was constructed from data in Mihorn and Pulley: Biophys. J., 8: 337, 1968). [from Guyton (1971), p. 435.]

Based on data [3], since $\Delta P_{\text{av}}^{\text{CO}_2} = 0.5 \text{ mmHg}$ for $\Delta P_{\text{max}}^{\text{CO}_2} = 5 \text{ mmHg}$, we have $F_{\text{CO}_2} = 0.1$.

From the $\Delta P_{\text{av}}^{\text{O}_2}$ and $\Delta P_{\text{av}}^{\text{CO}_2}$ expressions, we can determine the $\text{O}_2$ consumption and the $\text{CO}_2$ production rates, as follows:

$$D_{\text{O}_2} = \frac{\text{Total } \text{O}_2 \text{ consumed}}{\Delta P_{\text{av}}^{\text{O}_2}} = \frac{V_{\text{O}_2}}{\Delta P_{\text{av}}^{\text{O}_2}} = \frac{Q \left( C_{\text{O}_2}^{\text{AB}} - C_{\text{O}_2}^{\text{VB}} \right)}{\Delta P_{\text{av}}^{\text{CO}_2}} \quad (39)$$

$$D_{\text{CO}_2} = \frac{\text{Total } \text{CO}_2 \text{ produced}}{\Delta P_{\text{av}}^{\text{CO}_2}} = \frac{V_{\text{CO}_2}}{\Delta P_{\text{av}}^{\text{CO}_2}} = \frac{Q \left( C_{\text{CO}_2}^{\text{AB}} - C_{\text{CO}_2}^{\text{VB}} \right)}{\Delta P_{\text{av}}^{\text{CO}_2}} \quad (40)$$

4 Case studies

(A) We monitor the partial pressures blood concentrations of $\text{O}_2$ and $\text{CO}_2$ as:

$$C_{\text{O}_2}^{\text{AE}} = C_{\text{O}_2}^{\text{VB}} = 0.13, \quad C_{\text{O}_2}^{\text{VE}} = C_{\text{O}_2}^{\text{AB}} = 0.18, \quad C_{\text{CO}_2}^{\text{AE}} = C_{\text{CO}_2}^{\text{VB}} = 0.525,$$

$$C_{\text{CO}_2}^{\text{VE}} = C_{\text{CO}_2}^{\text{AB}} = 0.485.$$

From eqn. (26), we obtain:

$$P_{\text{O}_2}^{\text{VB}} = 30.5 \ln \left[ \frac{0.2}{0.2 - C_{\text{O}_2}^{\text{VB}}} \right] = 29.72 \ln \left[ \frac{0.2}{0.2 - 0.13} \right]$$

$$= 32.02 \text{ mmHg}. \quad (41)$$
From eqn. (31), we obtain:

\[ P_{CO_2}^{VB} = 37.94 \ln \left[ \frac{0.8}{0.8 - C_{CO_2}^{VB}} \right] = 37.94 \ln \left[ \frac{0.8}{0.8 - 0.525} \right] = 40.51 \text{ mmHg}. \]  

(42)

We now also monitor \( Q = 51/\text{min}, \hat{V}^* = 0.1 \) and \( \hat{\dot{V}} = 51/\text{min} \).

Then, from eqn. (33):

\[ \dot{V}_{O_2}(t) = Q \left( C_{O_2}^{AB} - C_{O_2}^{VB} \right), \]

so that from the above data,

\[ \dot{V}_{O_2}(t) = 5000 \times 0.05 = 250 \text{ ml O}_2/\text{min Consumption rate} \]  

(43)

From eqn. (34):

\[ \dot{V}_{CO_2}(t) = Q \left( C_{CO_2}^{VB} - C_{CO_2}^{AB} \right) = 5000(0.04) = 200 \text{ ml CO}_2/\text{min production rate}. \]  

(44)

Now, from eqn. (14),

For \( \hat{V}^* = 0.1 \) and \( \hat{\dot{V}} = 0.251 \), we obtain \( P_{O_2}^{al} \):

\[ P_{O_2}^{al} = 140 \left[ 1 - e^{-4.18 \left( \frac{\hat{V}^*}{\hat{V}_{O_2}} \right)} \right], \]

\[ = 140 \left[ 1 - e^{-4.18[0.1/0.25]} \right] = 113.7 \text{ mmHg}. \]  

(45)

From eqn. (19), for \( \hat{V}^* = 0.1 \) and \( \hat{V}_{CO_2} = 0.20 \), we obtain \( P_{CO_2}^{al} \):

\[ P_{CO_2}^{al} = 107.18 e^{-2.19 \left( \frac{\hat{V}^*}{\hat{V}_{CO_2}} \right)} = 107.18 e^{-2.19[0.1/0.2]} \]

\[ = 35.86 \text{ mmHg}. \]  

(46)

Now, we can evaluate the diffusion coefficients:

From eqns. (3), (36), (41), and (45):

\[ D_{O_2} = \frac{Q(C_{O_2}^{AB} - C_{O_2}^{VB})}{\Delta P_{O_2}^{av}} \]

\[ = \frac{5000(0.18 - 0.13)}{(113.7 - 31.2) \times 0.18} = 16.84 \text{ ml O}_2/\text{min/mmHg}. \]  

(47)
From eqn. (4):

\[
D_{CO_2} = \frac{Q(C^V_{CO_2} - C^{AB}_{CO_2})}{\Delta P^{CO_2}_{av}} = \frac{5000(0.04)}{(40.51 - 35.86) \times 0.1} = 430.11 \text{ ml CO}_2/\text{min/mmHg}. \quad (48)
\]

(B) Alternately, we derive data from:

(i) the inspired and expired air analysis (such as that carried out in Section 2.3):

- O\textsubscript{2} consumption rate = 283.2 ml/min,
- CO\textsubscript{2} production rate = 226.8 ml/min,
- \(P_{O_2}^{al} = 103.03\text{ mmHg}\) and \(P_{CO_2}^{al} = 38.41\text{ mmHg}\)

and

(ii) venous blood gas analysis:

- \(C^{VB}_{O_2} = 0.13, C^{VB}_{CO_2} = 0.548\).

Then, as per eqn. (41),

\[
P^{VB}_{O_2} = 31.2\text{ mmHg}, \quad (49)
\]

corresponding to \(C^{VB}_{O_2} = 0.13\) and, as per eqn. (42):

\[
P^{VB}_{CO_2} = 37.94 \ln \left(\frac{0.8}{0.8 - C^{VB}_{CO_2}}\right) = 37.94 \ln \left(\frac{0.8}{0.8 - 0.548}\right) = 43.84\text{ mmHg}. \quad (50)
\]

We obtain, from air-composition analysis, that \(\dot{V}_{O_2}(t) = 283.3\text{ ml/min}\) \(\dot{V}_{CO_2}(t) = 226.8\text{ ml/min}\). \(\quad (51)\)

Hence,

\[
D_{O_2} = \frac{\dot{V}_{O_2}}{\Delta P^{O_2}_{av}} = \frac{283.2}{(103.03 - 31.2) \times 0.18} = 21.90\text{ mlO}_2/\text{min/mmHg}, \quad (53)
\]

and

\[
D_{CO_2} = \frac{\dot{V}_{CO_2}}{\Delta P^{CO_2}_{av}} = \frac{226.8}{(43.84 - 38.41) \times 0.1} = 417.68\text{ mlCO}_2/\text{min/mmHg}. \quad (54)
\]

The advantage of this method (B) over (A) is that it does not require monitoring of the cardiac output, and is hence simpler to implement clinically.
References


Dear Colleagues:

I would like to cordially thank all of you for your contributions.

According to the review received on our book: Human Respiration: Anatomy and Physiology, Mathematical Modeling, Numerical Simulation and Applications, all the chapters submitted by us are accepted for publication. Congratulations!!!

However, we need to make some minor additions and amendments.

The reviewer's comment is attached to this message (see below). In summary, we need to take the following steps:

1. All equations are to be numbered and typed by means of MS Word Equation Editor. Each equation should be a single object but not a mixture of text symbols and equations in one line.
2. All symbols that are used in equations and appear in text must be typed by means of MS Word Equation Editor within the text.
3. All repetitions among the chapters contributed by the same principal author should be removed.
4. Each principal author has to provide me with nomenclature (in a separate MS Word file), so that the same symbols were used by one principal author in all his/her chapters.
5. Each principal author has to provide me with key words to be included into Subject Index that will follow our book.
6. Each principal author has to send me the amended version of his/her contribution(s) in MS Word format together with the nomenclature and key words file by e-mail: mvvkulish@ntu.edu.sg. Please ensure that each chapter is formatted according to the template that was sent to you previously [otherwise, the production of the book can be delayed].

The deadline set by the publisher (WIT Press) is September 20, 2004. Hence, I have to receive all your amended...

I am looking forward to hearing from you.

With kindest regards,

Vladimir V. Kulish, Ph. D.

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'Relevance

The bio-engineering discipline is now recognised as being of substantial importance. Human respiration is a significant, challenging and rewarding field: significant because of the increase in airborne pollutants and congenital respiratory diseases; challenging because of the wide range of scales in the pulmonary system, which span about three orders of magnitude (or five, if the thickness of the alveolar membrane is included); and rewarding

because of the marvellous ingenuity that characterises the system. A text that covers highlights of the application of bio-engineering techniques to the study of human respiration is to be welcomed.
This text comprises twelve chapters dealing with various topics in human respiration, from fundamental aspects of anatomy and physiology through to numerical modelling of processes such as gas diffusion and practical applications in the field of respiratory physiotherapy. As such, there is material here that will be of interest to seasoned bio-engineers and clinical practitioners, as well as novices to the study of human respiration. **There should be a good market for the text** – WIT should use the success of their publication “Medical Application of Computer Modelling – the Respiratory System” as a guide.

**Technical Correctness**

The text encompasses such a wide range of material that I cannot comment on all of it. Nevertheless, I am satisfied that in the field that I do have some knowledge (fluid mechanics) the material presented is correct. Moreover, each chapter appears to be a distillation of a large body of work which has been presented and reviewed for publication in technical journals, and this gives me confidence that the whole work is accurate and reliable. There are several papers that deal with modelling of gas transfer across that alveolar lumen. **The nomenclature employed in each paper (or group of papers, where a group is characterised by having the same principal author) is slightly different. It would be very helpful if a common nomenclature could be employed. A formal definition of nomenclature after the Table of Contents would be useful.**

There are instances where relatively complex equations have been poorly constructed. For example, dots above symbols to represent differentiation with respect to time (e.g. _) have been replaced by small “o”s (e.g. _); in some instances the “o”s have been badly misplaced. This is not correct, and is unnecessary – the text appears to have been written using Microsoft Word, and Word includes an equation editor that has all the functionality required to produce neat equations employing standard notation. The final text should not contain any ambiguities in its formulae.

**Quality of Text**

The text is written in generally good English. While I am not sure whether it is the reviewer’s role to flag (what he thinks may be) grammatical errors, I have annotated the text where I think it might be improved. I offer these corrections not critically (they are few in number), but in the hope that through such minor corrections to the text, I might contribute to its acceptance in the academic community.

There are some instances of repetition of material between chapters by the same principal authors; there is also duplication of introductory material on respiratory anatomy between different authors. It would be beneficial to the ease with which the text can be used if (a) the repetitions were removed, (b) the duplication was minimised, and (c) the introductory material was brought forward to the first and second chapters (see below for more detail).

**Order of Chapters**
If the original 12 chapters are to be retained as they are, then I would suggest the following re-ordering of the text:

Anatomy and Physiology

1. Anatomy and Physiology of the Human Respiratory System

2. Fundamentals of Alveolar Gas Diffusion Mathematical Modelling and Numerical Simulation

3. Lung Gas Composition and Transfer Analysis: O2 and CO2 Diffusion Coefficients and Metabolic Rates

4. Lung Ventilation Modelling and Assessment

5. Visualisation of Alveolar Diffusion

6. Modelling of Two-Phase Flow in the Human Respiratory System

7. Impact of Microscopic Solid Particles on Alveolar Diffusion

8. Quantification of Human Physiological Response to Toxic Substances

9. Anatomically-based Modelling of Pulmonary Structure Applications

10. Applied Chest-Wall Vibration Therapy for Patients with Obstructive Lung Disease

11. Indicator for Lung Status in a Mechanically Ventilated COPD Patient using Lung Ventilation Modelling and Assessment

12. Mechanics of Proportional Assist Ventilation

I have suggested that “Anatomy and Physiology of the Human Respiratory System” should come before “Fundamentals of Alveolar Gas Diffusion”, and that “Lung Gas Composition and Transfer Analysis” and “Lung Ventilation Modelling and Assessment” should precede “Visualisation of Alveolar Diffusion”, “Modelling of Two-Phase Flow in the Human Respiratory System” and “Impact of Microscopic Solid Particles on Alveolar Diffusion”. This is because it may be easier for the reader to deal with the more general issue of lung respiration before approaching the topic of alveolar respiration. However, if some reordering of the material in chapters 2 and 5 can be allowed, then I would recommend the following titles for these chapters: 2. Fundamentals of Alveolar Gas Diffusion – Physiological Aspects 5. Alveolar Gas Diffusion – Numerical Modelling and Visualisation Here, chapter 2 would deal with the physiology of alveolar gas diffusion, and the modelling aspects would be placed in chapter 5. This would have the advantages that: (a) the first section is a relatively easy introduction of the topic of human respiration; and (b) the visualisation of the calculations by Kulish et al is presented in the best context.

It should also be possible to combine the chapters “Modelling of Two-Phase Flow in the Human Respiratory System” and “Impact of Microscopic Solid Particles on Alveolar Diffusion” into a single chapter, e.g. “Modelling the Impact of Microscopic Solid Particles on Alveolar Diffusion”. Certainly,
the material in “Impact of Microscopic Solid Particles on Alveolar Diffusion” which is a repetition of material in “Visualisation of Alveolar Diffusion” should be deleted.

I cannot decide whether the chapter entitled “Quantification of Human Physiological Response to Toxic Substances” should be left in the section on “Mathematical Modelling and Numerical Simulation” or placed in the section on “Applications”. Perhaps Kulish as the author is the deciding factor, and it should remain where it is in proximity to Kulish’s other papers. Thus, the chapter order becomes:

1. Anatomy and Physiology of the Human Respiratory System
2. Fundamentals of Alveolar Gas Diffusion – Physiological Aspects Mathematical Modelling and Numerical Simulation
3. Lung Gas Composition and Transfer Analysis: O2 and CO2 Diffusion Coefficients and Metabolic Rates
4. Lung Ventilation Modelling and Assessment
5. Alveolar Gas Diffusion – Numerical Modelling and Visualisation
6. Impact of Microscopic Solid Particles on Alveolar Diffusion
7. Quantification of Human Physiological Response to Toxic Substances
8. Anatomically-based Modelling of Pulmonary Structure Applications
9. Applied Chest-Wall Vibration Therapy for Patients with Obstructive Lung Disease
10. Indicator for Lung Status in a Mechanically Ventilated COPD Patient using Lung Ventilation Modelling and Assessment
11. Mechanics of Proportional Assist Ventilation
Human Respiration

Anatomy and Physiology, Mathematical Modeling, Numerical Simulation and Applications

Series: Advances in Bioengineering Volume 3

Even in ancient times, breathing was believed to be the most important feature of life itself. The very Universe was viewed as a huge breathing organism, within which every part was related to everything else through a process of vibration — or breath. Nowadays, our understanding of the laws governing the Universe and life has advanced tremendously. Yet this has not changed our perception of breathing as one of the most important mechanisms of life support.

Books on human respiration are usually written either by physicians or engineers. This book became possible as a result of a decade of research collaboration between physicians, engineers, physicists and applied mathematicians. Consequently, this volume presents the latest developments and major challenges in the area of biomedical engineering concerned with studies of the human respiratory system.

The contributors cover the anatomy and physiology of human respiration, some of the newest macro- and microscopic models of the respiratory system, numerical simulation and computer visualisation of gas transport phenomena, and applications of these models to medical diagnostics, treatment and safety.

Titles of related interest:

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Editors: X. Y. XU & M. W. COLLINS
Series: Advances in Computational Bioengineering, Volume 1

ISSN: 1464-9292
Chapter 3
Lung-gas composition and transfer analysis: O₂ and CO₂ diffusion coefficients and metabolic rates ................................................................. 77
D.N. Ghista, K.M. Loh & D. Ng

1 Introduction .................................................................................. 77
2 Lung-air composition analysis (and O₂ consumption and CO₂ production rates) ................................................................. 78
   2.1 Calculation of O₂ consumption rate and CO₂ production rate ...... 78
   2.2 Dead-space air composition ....................................................... 79
   2.3 Alveolar air composition and partial pressures ......................... 80
3 Lung gas-exchange model and parametric analysis ......................... 81
   3.1 Expressions for $D_O$ and $D_{CO₂}$ .............................................. 81
   3.2 Alveolar O₂ and CO₂ partial-pressure expressions ...................... 85
   3.3 Arterial and venous O₂ and CO₂ partial-pressure expressions ......... 86
   3.4 Sequential procedure to compute $D_O$ and $D_{CO₂}$ .................... 88
   3.5 Determining $D_O$ and $D_{CO₂}$ .................................................. 89
4 Case studies .................................................................................. 90

Chapter 4
Lung ventilation modeling and assessment ....................................... 95
D.N. Ghista, K.M. Loh & M. Damodaran

1 Introduction .................................................................................. 95
   1.1 Role of lung ventilation ............................................................. 95
2 Lung ventilation performance using a linear first-order model ............ 96
3 Ventilatory Index ......................................................................... 101
   3.1 Noninvasively determinable ventilatory index .............................. 101
4 Variations in R and C during a respiratory cycle (towards nonlinear) ................................................................. 103
   4.1 Nonlinear compliance .............................................................. 104
5 Work of breathing (WOB) ............................................................ 106
6 Second-order model for single-compartment lung model .................. 108
7 Two-compartmental linear model ............................................... 110
   7.1 Two compartmental model using first order ventilatory model ........ 112
      7.1.1 Stiff right lung (with compliance problems) ......................... 115
      7.1.2 Right lung with R problems ............................................... 115

Chapter 5
Modeling of two-phase flow in the human respiratory system ............ 117
V.V. Kulish, B. Wijayanto & C.S. Lim

1 Introduction .................................................................................. 117
2 Methodology .............................................................................. 118
   2.1 Geometry of the human respiratory duct .................................. 118
CHAPTER 3

Lung-gas composition and transfer analysis: 
O₂ and CO₂ diffusion coefficients and 
metabolic rates

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Abstract

The primary function of the lung is to (i) oxygenate the blood and thereby provide oxygen to the cells for metabolization purposes, and (ii) to remove the collected CO₂ from the pulmonary blood. Herein, we will analyze the compositions of the inspired and expired air per breath, and from there compute the O₂ consumption and CO₂ production rates. Next, we derive expressions for diffusion coefficients \(D_{O₂}\) and \(D_{CO₂}\) in terms of the evaluated cardiac output, O₂ and CO₂ concentrations in arterial and venous blood, alveolar and blood O₂ and CO₂ partial pressures. We then take up a typical case study, and demonstrate the computation of \(D_{O₂}\) and \(D_{CO₂}\), to represent the lung-performance capability to oxygenate the blood.

1 Introduction

The lung-functional performance is characterized by (i) its ventilatory capacity, to bring air (and hence O₂) into the alveoli, and (ii) its capacity to transfer O₂ and CO₂ into and from the pulmonary capillary bed. Hence, the O₂ and CO₂ diffusion coefficients as well as the O₂ consumption rate and the CO₂ production rate represent the lung-performance indices.
2 Lung-air composition analysis (and O₂ consumption and CO₂ production rates)

We carry out a mass-balance analysis, involving:

(i) compositions of air breathed in and out
(ii) consumption or losses of O₂, CO₂ and H₂O.

Table 1 provides clinical data on partial pressures and volumes of N₂, O₂, CO₂ and H₂O of atmospheric air breathed in and expired out, one breath cycle. The monitored breathing rate (BR) = 12 breaths/min, and we assume \( P_{H₂O} \) at 37°C = 47 mmHg.

It can be noted that the expired air volume exceeds the inspired air volume for this particular breath cycle. The H₂O loss of 30.1 ml (=32.6–2.5 ml) contributes the major portion of this difference.

2.1 Calculation of O₂ consumption rate and CO₂ production rate

We now determine the O₂ consumption rate and CO₂ production rate from the inspired and expired gases.

Assuming the patient breathes at 12 times per minute we have

\[
O₂ \text{ Consumption Rate} = (\text{Inspired} \ O₂ - \text{Expired} \ O₂) \times 12
\]

\[
= (104.2 - 80.6) \times 12
\]

\[
= 283.2 \text{ ml/min}
\]

Table 1: Inspired air composition and partial pressures.

<table>
<thead>
<tr>
<th>Respiratory gases</th>
<th>Atmospheric air</th>
<th>Expired air</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmHg</td>
<td>ml/%</td>
</tr>
<tr>
<td>N₂</td>
<td>597</td>
<td>393.1</td>
</tr>
<tr>
<td></td>
<td>78.55%</td>
<td></td>
</tr>
<tr>
<td>O₂</td>
<td>159</td>
<td>104.2</td>
</tr>
<tr>
<td></td>
<td>20.84%</td>
<td></td>
</tr>
<tr>
<td>CO₂</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>0.04%</td>
<td></td>
</tr>
<tr>
<td>H₂O</td>
<td>3.7</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>0.49%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>760</td>
<td>500</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>
The amount of water vapor in the humidified expired air amounts to 6.2% of the expired air (compared to 0.49% of the dry inspired air) corresponding to the partial-pressure ratio of water vapor in the expired air (≈ 47/760). The volume of the dry expired air = (525.3 – 32.6) ml = 492.7 ml.

Now, assume that out of 500 ml of inspired air, the dead-space air volume (not taking part in the gas-transfer process) is 150 ml and the alveolar air volume is 350 ml. We next compute the dead-space air volume composition.

### 2.2 Dead-space air composition

The clinical data of expired air composition is:

\[ \begin{align*}
N_2 & = 393.1 \, \text{ml} \\
O_2 & = 83.36 \, \text{ml} \\
CO_2 & = 16.87 \, \text{ml} \\
H_2O & = 34.15 \, \text{ml} \\
\text{Total} & = 527.49 \, \text{ml}
\end{align*} \]

Now, the dead-space air will be made up of (i) a dry air portion from the inspired air (assumed to be = 141 ml), plus (ii) the water vapor taken up by the dry air
(estimated to be \( = 9 \text{ ml} \)) since the expired air portion of 141 ml will not have undergone \( \text{O}_2 \) and \( \text{CO}_2 \) transfer, its composition is the same as that of the inspired air:

\[
\begin{align*}
\text{N}_2 &= 111 \text{ ml (78.55\%)} , \\
\text{O}_2 &= 29.40 \text{ ml (20.84\%)} , \\
\text{CO}_2 &= 0.06 \text{ ml (0.04\%)} , \\
\text{H}_2\text{O} &= 0.69 \text{ ml (0.49\%)}. \\
\end{align*}
\]

When this inspired air (in the dead space) of 141 ml is fully humidified, it will take up a further \( X \) ml of \( \text{H}_2\text{O} \) vapor, in the ratio of the partial pressures, as:

\[
\frac{X}{141} = \frac{47}{713} = 0.0659 \\
\therefore X = 0.0659 \times 141 = 9.29 \text{ ml of } \text{H}_2\text{O} \text{ vapor (which is close to our estimate)}. 
\]

So, by adding 9.29 ml of \( \text{H}_2\text{O} \) vapor to 0.69 ml of water vapor in the inspired air volume of 141 ml, the total water vapor in the dead-space air is 9.98 ml. The humidified dead-space air composition will be:

\[
\begin{align*}
\text{N}_2 &= 111.00 \text{ ml (73.78\%)} , \\
\text{O}_2 &= 29.40 \text{ ml (19.55\%)} , \\
\text{CO}_2 &= 0.06 \text{ ml (0.04\%)} , \\
\text{H}_2\text{O} &= 9.98 \text{ ml (6.63\%)}. \\
\end{align*}
\]

Total = 150.44 ml

### 2.3 Alveolar-air composition and partial pressures

We can now compute the alveolar air composition, by subtracting the dead-space air from the expired air. These values are tabulated in column 4 of the table below.

Finally, we compute the partial pressure of \( \text{O}_2 \) and \( \text{CO}_2 \) (as well as of \( \text{N}_2 \) and \( \text{H}_2\text{O} \)), so that we can determine next the diffusion coefficients of \( \text{O}_2 \) and \( \text{CO}_2 \) based on the monitoring of arterial and venous blood concentrations. These values are tabulated in column 5 of the below table.

<table>
<thead>
<tr>
<th></th>
<th>Expired air (ml)</th>
<th>Dead-space air (ml)</th>
<th>Alveolar air (ml)</th>
<th>Alveolar-air partial pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{N}_2 )</td>
<td>393.1</td>
<td>111.00</td>
<td>282.1</td>
<td>569.41</td>
</tr>
<tr>
<td>( \text{O}_2 )</td>
<td>80.53</td>
<td>29.40</td>
<td>51.13</td>
<td>103.21</td>
</tr>
<tr>
<td>( \text{CO}_2 )</td>
<td>19.12</td>
<td>0.06</td>
<td>19.06</td>
<td>38.47</td>
</tr>
<tr>
<td>( \text{H}_2\text{O} )</td>
<td>34.21</td>
<td>9.98</td>
<td>24.23</td>
<td>48.91</td>
</tr>
<tr>
<td>Total</td>
<td>526.96</td>
<td>150.44</td>
<td>376.52</td>
<td>760</td>
</tr>
</tbody>
</table>
3 Lung gas-exchange model and parametric analysis

3.1 Expressions for $D_O_2$ and $D_CO_2$

The gas exchange between the alveolar air and pulmonary capillary blood is represented by the following $O_2$ and $CO_2$ conservation equations (Fig. 2):

$$Q^VEC_{O_2} = Q^{AE}C^{AE}_{O_2} + \dot{V}_{O_2} \text{ (from the alveolar air to capillary blood)}$$

$$= Q^{AE}C^{AE}_{O_2} + (\Delta P_{O_2}^{av})D_{O_2}; \quad P^\text{cap}_{O_2} = P^{AE}_{O_2}, \quad (1)$$

in which $P^\text{cap}_{O_2} = P^{PBB}_{O_2}$ ($O_2$ concentration of the preoxygenated blood)

$$Q^VEC_{CO_2} = Q^{AE}C^{AE}_{CO_2} - \dot{V}_{CO_2}$$

$$= Q^{AE}C^{AE}_{CO_2} - (\Delta P_{CO_2}^{av})D_{CO_2}; \quad P^\text{cap}_{CO_2} = P^{VE}_{CO_2}, \quad (2)$$

in which $P^\text{cap}_{CO_2} = P^{PBB}_{CO_2}$ ($CO_2$ concentration of the preoxygenated blood).

wherein

(i) $Q^{AB}$ and $Q^{VB}$ are arterial and venous blood flow-rates;
(ii) $Q^{AB} = Q^{VE}$ (at venous end), $Q^{VB} = Q^{AE}$ (at arterial end)
(iii) $P^{al}_{O_2}$ and $P^{cap}_{O_2}$ are the alveolar and capillary $O_2$ partial pressures
(iv) $D_{O_2}$ and $D_{CO_2}$ are the $O_2$ and $CO_2$ diffusion coefficients
(v) $\Delta P_{O_2}^{av}$ = average of ($P^{al}_{O_2} - P^{cap}_{O_2}$) over the capillary length;
$\Delta P_{CO_2}^{av}$ = average of ($P^{al}_{CO_2} - P^{cap}_{CO_2}$) over the capillary length.

Now we can equate the arterial and venous blood flow rates, as

$$Q^{AB} - Q^{VB} - Q - (SV)/(EP) \simeq CO/60,$$

SV, EP and CO being the stroke volume, ejection period and cardiac output, respectively. Hence the above equations can be rewritten as:

(vi) $\dot{V}_{O_2}$ is the $O_2$ transfer rate from alveolar air to capillary blood ($\simeq O_2$ consumption rate), $\dot{V}_{CO_2}$ is the $CO_2$ transfer rate from capillary blood to alveolar air.

![Figure 2: Schematic of blood-gas concentration in the pulmonary capillary.](image-url)
From eqn. (1):

\[ Q^{\text{VE}}C^{\text{VE}}_\text{O}_2 = Q^{\text{AB}}C^{\text{AB}}_\text{O}_2 + (\Delta P^{\text{O}_2}_{\text{av}})D_{\text{O}_2}; \quad P^{\text{cap}}_{\text{O}_2} = P^{\text{AE}}_{\text{O}_2} = P_{\text{O}_2} \]

\[ Q^{\text{VE}}C^{\text{VE}}_\text{CO}_2 = Q^{\text{AE}}C^{\text{AE}}_\text{CO}_2 - (\Delta P^{\text{CO}_2}_{\text{av}})D_{\text{CO}_2}; \quad P^{\text{cap}}_{\text{CO}_2} = P^{\text{AE}}_{\text{CO}_2} = P_{\text{CO}_2} \]

\[ D_{\text{O}_2} = \frac{Q(C^{\text{VE}}_{\text{O}_2} - C^{\text{AE}}_{\text{O}_2})}{(\Delta P^{\text{O}_2}_{\text{av}})} = \frac{Q(C^{\text{AE}}_{\text{O}_2} - C^{\text{VE}}_{\text{O}_2})}{(\Delta P^{\text{O}_2}_{\text{av}})} \]  \hspace{1cm} (3)

From eqn. (2):

\[ Q^{\text{VE}}C^{\text{VE}}_\text{CO}_2 = Q^{\text{AE}}C^{\text{AE}}_\text{CO}_2 - (\Delta P^{\text{CO}_2}_{\text{av}})D_{\text{CO}_2}; \quad P^{\text{cap}}_{\text{CO}_2} = P^{\text{AE}}_{\text{CO}_2} = P_{\text{CO}_2} \]

\[ D_{\text{CO}_2} = \frac{Q(C^{\text{VE}}_{\text{CO}_2} - C^{\text{AE}}_{\text{CO}_2})}{(\Delta P^{\text{CO}_2}_{\text{av}})} \]  \hspace{1cm} (4)

wherein

(i) \( Q, C^{\text{VE}}_{\text{O}_2} \) and \( C^{\text{AE}}_{\text{CO}_2} \) can be monitored because
\( C^{\text{VE}}_{\text{CO}_2} \) and \( C^{\text{VE}}_{\text{O}_2} \) are \( C^{\text{AB}}_{\text{O}_2} \) and \( C^{\text{AB}}_{\text{CO}_2} \), and \( C^{\text{AE}}_{\text{CO}_2} \) and \( C^{\text{AE}}_{\text{O}_2} \) are \( C^{\text{AV}} \) and \( C^{\text{VB}} \), with \( C^{\text{VE}}_{\text{CO}_2} \) not being measured directly.

(ii) \( D_{\text{O}_2} \) and \( D_{\text{CO}_2} \) (eqns. (3) and (4)) represent the lung gas-exchange parameters.

Now from eqns. (3) and (4), if we want to evaluate the diffusion coefficients \( D_{\text{O}_2} \) and \( D_{\text{CO}_2} \), we need to also express \( P^{\text{al}}_{\text{O}_2}, P^{\text{cap}}_{\text{O}_2}, P^{\text{al}}_{\text{CO}_2}, P^{\text{cap}}_{\text{CO}_2} \) in terms of moniturable quantities. In this regard,

(i) Alveolar \( P^{\text{al}}_{\text{O}_2} \) can be expressed in terms of \( \tilde{V} \) (the ventilation rate) and \( \tilde{V}_{\text{O}_2} \) (the \( \text{O}_2 \) consumption rate) as Fig. 3:

\[ P^{\text{al}}_{\text{O}_2} = k_1 \left[ 1 - e^{-k_2 \left( \frac{\tilde{V}}{\tilde{V}_m} - \frac{\tilde{V}_{\text{O}_2}}{\tilde{V}_m} \right)} \right], \]  \hspace{1cm} (5)

where \( \tilde{V}_m \) is the maximum ventilation rate and \( \tilde{V}_{\text{O}_2} \) (the \( \text{O}_2 \) consumption rate or absorption rate from the alveoli) = \( Q(C^{\text{AB}}_{\text{O}_2} - C^{\text{VB}}_{\text{O}_2}) \). Equation (5) implies that as \( \tilde{V} / \tilde{V}_m \) increases, \( P^{\text{al}}_{\text{O}_2} \) decreases, and as \( \tilde{V}_{\text{O}_2} \) increases \( P^{\text{al}}_{\text{O}_2} \) increases as in Fig. 3, and as \( \tilde{V}_{\text{O}_2} \) increases \( P^{\text{al}}_{\text{O}_2} \) decreases as in Fig. 3.

(ii) Alveolar \( P^{\text{al}}_{\text{CO}_2} \) can be expressed in terms of \( \tilde{V} \) and \( \tilde{V}_{\text{CO}_2} \) as in Fig. 4:

\[ P^{\text{al}}_{\text{CO}_2} = k_3 e^{-k_4 \left( \frac{\tilde{V}_{\text{CO}_2}}{\tilde{V}_m} \right)}, \]  \hspace{1cm} (6)

where \( \tilde{V}_{\text{CO}_2} \) (the \( \text{CO}_2 \) production rate or excretion rate from the blood) = \( Q(C^{\text{VB}}_{\text{CO}_2} - C^{\text{AB}}_{\text{CO}_2}) \). This equation implies that as \( \tilde{V} / \tilde{V}_m \) increases, \( P^{\text{al}}_{\text{CO}_2} \) decreases; also, as \( \tilde{V}_{\text{CO}_2} \) increases (the exponential term decreases, and hence) \( P^{\text{al}}_{\text{CO}_2} \) increases.
Figure 3: Effect on alveolar $P_O_2$ of (i) alveolar ventilation, and (ii) rate of oxygen absorption from alveolar $P_O_2$ or $O_2$ consumption rate [from Guyton (1971), p. 476].

Figure 4: Effect on alveolar $P_CO_2$ of alveolar ventilation and rate of carbon dioxide excretion from the blood or $CO_2$ production rate [from Guyton (1971), p. 476].

(iii) Blood $P_O_2$ can be obtained in terms of blood $CO_2$, from the $O_2$ disassociation curve (providing concentrations in arterial and venous blood), is represented in Fig. 5 as:

$$C_{O_2} = C_{O_2}^m \left( 1 - e^{-k_{O_2} / P_{O_2}} \right), \quad \text{or} \quad C_{O_2}^v = 1 - e^{-k_{O_2} P_{O_2}}, \quad (7)$$
Figure 5: O₂ dissociation curves, showing the total oxygen in each 100 ml of normal blood, the portion dissolved in the water of the blood [from Guyton [2], p. 485].

Figure 6: The carbon dioxide dissociation curve [from Guyton [2], p. 491].

where

- \( C_{O_2}^m \) and \( P_{O_2}^m \) are the maximum values of blood O₂ partial pressure
- \( CO_2^* = CO_2 / CO_2^m \)
- \( P_{O_2}^* = P_{O_2} / P_{O_2}^m \).

(iv) Blood \( P_{CO_2} \) can be obtained in terms of \( C_{CO_2} \), from the CO₂ disassociation curve or CO₂ concentration in arterial and venous blood can be represented
LUNG-GAS COMPOSITION AND TRANSFER ANALYSIS

\[ C_{CO_2} = C_{O_2}^{ii} \left( 1 - e^{-k_2 \left( \frac{P_{CO_2}}{P_{CO_2}^{ii}} \right)} \right) \]

or, \[ C_{CO_2}^{ii} = 1 - e^{-k_2 \left( \frac{P_{CO_2}}{P_{CO_2}^{ii}} \right)} = 1 - e^{-k_2 P_{CO_2}^{*}}. \] (8)

3.2 Alveolar O₂ and CO₂ partial-pressure expressions

Now, let us refer eqn. (4) for the \( P_{O_2}^{al} \) partial pressure curve (Fig. 3), represented by the equation:

\[ P_{O_2}^{al} = k_1 \left[ 1 - e^{-k_2 \left( \frac{\dot{V}}{\dot{V}_m} / \dot{V}_{O_2} \right)} \right] \]

\[ = k_1 \left[ 1 - e^{-k_2 \left( \frac{\dot{V}^*}{\dot{V}_m} \right)} \right], \text{ where } \dot{V}^* = \frac{\dot{V}}{\dot{V}_m} \] (9)

where \( \dot{V} \) is the alveolar ventilation rate (in liters/min), \( \dot{V}_m \) is the maximum ventilation rate (= 50 l/min) and \( \dot{V}_{O_2} \) is the \( O_2 \) consumption rate (in liters/min). Herein, the coefficients \( k_1 \) and \( k_2 \) can be determined by having this equation match the Fig. 3 data. Note, in this equation, when \( \dot{V} = 0, P_{O_2}^{al} = 0 \) from the equation, which satisfies the data.

Now for \( \dot{V}_{O_2} = 0.25 \text{ l/min, when } \frac{\dot{V}^*}{\dot{V}_m} = 0.5, P_{O_2}^{al} = 140 \text{ mmHg. Hence,} \)

\[ 140 = k_1 \left[ 1 - e^{-k_2 \left( \frac{0.5}{0.5} \right)} \right] = k_1 (1 - e^{-2k_2}). \] (10)

Also, when \( \dot{V}_{O_2} = 11/\text{min, } \dot{V}^* = 0.31/\text{min, } P_{O_2}^{al} = 100 \text{ mmHg. Hence} \)

\[ 100 = k_1 \left[ 1 - e^{-k_2 \left( \frac{0.31}{0.35} \right)} \right] = k_1 (1 - e^{-0.3k_2}). \] (11)

From eqns. (10) and (11), we get:

\[ \frac{140}{100} = \frac{k_1 (1 - e^{-2k_2})}{k_1 (1 - e^{-0.3k_2})} = \frac{1 - e^{-2k_2}}{1 - e^{-0.3k_2}} \]

\[ \therefore 140 - 140e^{-0.3k_2} = 100 - 100e^{-2k_2} \]

or, \[ 40 = 100e^{-2k_2} + 140e^{-0.3k_2}, \text{ so that } k_2 = 4.18 \text{ min/l.} \] (12)

Upon substituting \( k_2 = 4.18 \text{ min/l} \) into eqn. (10) we obtain:

\[ 140 = k_1 (1 - e^{-2(4.18)}), \text{ so that } k_1 \approx 140 \text{ mmHg.} \] (13)
Hence, the \( P_{O_2}^{al} \) curve can be represented by:

\[
P_{O_2}^{al} = 140 \left[ 1 - e^{-4.18 \left( \frac{\tilde{V}^*}{\tilde{V}_{O_2}} \right)} \right],
\]

(14)

where \( \tilde{V}_{O_2} = Q(C^{AB}_{O_2} - C^{VB}_{O_2}) \) and \( \tilde{V}^* = \tilde{V}/50 \) l/min.

Now, let us look at the \( P_{CO_2}^{al} \) expression:

\[
P_{CO_2}^{al} = k_3 e^{-k_4} \left[ \left( \frac{\tilde{V}}{\tilde{V}_m} \right) \tilde{V}_{CO_2} \right] = k_3 e^{-k_4} \left[ \frac{\tilde{V}^*}{\tilde{V}_{CO_2}} \right].
\]

We note from Fig. 4 that for \( \tilde{V}_{CO_2} = 0.2 \) l/min and \( \tilde{V}_m = 0.2 \), \( P_{CO_2}^{al} = 12 \). Hence, from the above equation, we get:

\[
12 = k_3 e^{-k_4}
\]

(15)

Also, for \( \tilde{V}_{O_2} = 0.8 \) l/min and \( \tilde{V}_m = 0.2 \), \( P_{CO_2}^{al} = 62 \) mmHg. Hence

\[
62 = k_3 e^{-k_4} \left[ \frac{\tilde{V}}{\tilde{V}_m} \right] = k_3 e^{-k_4}. \quad (16)
\]

From eqns. (15) and (16), we get:

\[
\frac{12}{62} = \frac{e^{-k_4}}{e^{-k_4}} = e^{-\frac{k_4}{3}}
\]

\[
\ln \left( \frac{12}{62} \right) = -\frac{2}{3} k_4, \quad \text{so that} \quad k_4 = 2.46.
\]

(17)

Substituting \( k_4 = 2.46 \) into eqn. (16), we obtain:

\[
62 = k_3 e^{-\frac{2.46}{3}} \quad \therefore \quad k_3 = 114.68. \quad (18)
\]

Hence, the \( P_{CO_2}^{al} \) curve can be represented as

\[
P_{CO_2}^{al} = 114.68 e^{-2.46 \left( \frac{\tilde{V}}{\tilde{V}_m} \right) \tilde{V}_{CO_2}}, \quad (19)
\]

where \( \tilde{V}^* = \tilde{V}/50 \) l/min and \( \tilde{V}_{CO_2} = Q(C^{VB}_{CO_2} - C^{AB}_{CO_2}). \)

### 3.3 Arterial and venous \( O_2 \) and \( CO_2 \) partial-pressure expressions

We now need to express \( P_{O_2}^{AB} \) and \( P_{CO_2}^{VB} \) in terms of \( C^{AB}_{O_2} \) and \( C^{VB}_{CO_2}. \)
So that let us look at the $O_2$ disassociation curve, as shown in Fig. 5.

$$C_{O_2} = C_{O_2}^{max} \left[1 - e^{-k_5 \frac{P_{O_2}}{P_{O_2}^{max}}} \right],$$

or,

$$C_{O_2}^e = 1 - e^{-k_5 P_{O_2}^e},$$

where $C_{O_2} = \frac{C_{O_2}}{C_{O_2}^{max}}$, $P_{O_2}^e = \frac{P_{O_2}}{P_{O_2}^{max}}$.

(20)

From Fig. 5, at $P_{O_2}^e = \frac{40 \text{ mmHg}}{140 \text{ mmHg}} = 0.29$ (for normal venous blood), and

$$C_{O_2}^e = \frac{15}{20} = 0.75.$$

Hence from eqn. (20):

$$0.75 = 1 - e^{-0.29k_5}$$

$$\therefore k_5 = 4.78.$$  (21)

Also, $P_{O_2}^e = \frac{95 \text{ mmHg}}{140 \text{ mmHg}} = 0.68$ (for normal arterial blood), and

$$C_{O_2}^e = \frac{19}{20} = 0.95.$$

Hence from eqn. (20):

$$0.95 = 1 - e^{-0.68k_5}$$

So, we take the average value of $k_5$:

$$\therefore k_5 = \frac{4.78 + 4.4}{2} = 4.59.$$  (23)

Then the $O_2$ disassociation curve is given by:

$$C_{O_2} = C_{O_2}^B = 0.2 \left[1 - e^{-4.59 \frac{P_{O_2}^e}{P_{O_2}^{max}}} \right],$$

and

$$P_{O_2} = \frac{140}{4.59} \ln \left[ \frac{0.2}{0.2 - C_{O_2}^B} \right] = 30.5 \ln \left[ \frac{0.2}{0.2 - C_{O_2}^B} \right].$$  (25)

Finally, we look at the $CO_2$ disassociation curve

$$C_{CO_2} = C_{CO_2}^{max} \left(1 - e^{-k_6 \frac{P_{CO_2}}{P_{CO_2}^{max}}} \right),$$

or,

$$C_{CO_2}^e = 1 - e^{-k_6 \frac{P_{CO_2}^e}{P_{CO_2}^{max}}} = 1 - e^{-k_6 P_{CO_2}^e}.$$  (26)
Based on Fig. 6, when \( P_{\text{CO}_2}^* = \frac{20 \text{ mmHg}}{140 \text{ mmHg}} = 0.14 \), \( C_{\text{CO}_2}^* = \frac{38}{80} = 0.475 \), so that
\[
0.475 = 1 - e^{-0.14k_6}, \quad k_6 = 4.60, \tag{27}
\]
when \( P_{\text{CO}_2}^* = \frac{70 \text{ mmHg}}{140 \text{ mmHg}} = 0.5 \), \( C_{\text{CO}_2}^* = \frac{60}{80} = 0.75 \), so that
\[
0.75 = 1 - e^{-0.5k_6}, \quad k_6 = 2.77. \tag{28}
\]
So, we take the average value of \( k_6 \):
\[
k_6 = \frac{(4.60 + 2.77)}{2} = 3.69. \tag{29}
\]
Then the CO\(_2\) concentration is given (from eqns. (26–29)) by:
\[
C_{\text{CO}_2} = C_{\text{CO}_2}^B = 0.8 \left[ 1 - e^{-4.71 \left( \frac{P_{\text{CO}_2}}{140} \right)} \right] \tag{30}
\]
and
\[
P_{\text{CO}_2} = 29.72 \ln \left( \frac{0.8}{0.8 - C_{\text{CO}_2}^B} \right). \tag{31}
\]

3.4 Sequential procedure to compute \( D_{\text{O}_2} \) and \( D_{\text{CO}_2} \):

1. We first monitor: \( V(t) \), \( \dot{V}(t) \), SV (stroke volume), EP (cardiac ejection period), \( C_{\text{O}_2}^{\text{VB}} \cdot C_{\text{O}_2}^{\text{AB}} \cdot C_{\text{CO}_2}^{\text{VB}} \) and \( C_{\text{CO}_2}^{\text{AB}} \) (\( \text{O}_2 \) and \( \text{CO}_2 \) concentrations in pre oxygenated and post oxygenated blood).
2. We substitute the values of \( C_{\text{O}_2}^{\text{AB}} (=C_{\text{O}_2}^{\text{VE}}) \) and \( C_{\text{CO}_2}^{\text{VB}} (=C_{\text{CO}_2}^{\text{AE}}) \) into eqn. (3), and the values of \( C_{\text{CO}_2}^{\text{AB}} (=C_{\text{CO}_2}^{\text{VE}}) \) and \( C_{\text{CO}_2}^{\text{VB}} (=C_{\text{CO}_2}^{\text{AE}}) \) into eqn. (4).
3. We next determine:
   \[
   Q = SV/\text{ejection period}, \tag{32}
   \]
   \[
   \dot{V}_{\text{O}_2}(t) = Q(C_{\text{O}_2}^{\text{AB}} - C_{\text{O}_2}^{\text{VB}}), \tag{33}
   \]
   \[
   \dot{V}_{\text{CO}_2}(t) = Q(C_{\text{CO}_2}^{\text{AB}} - C_{\text{CO}_2}^{\text{VB}}). \tag{34}
   \]
4. We then substitute the expressions for \( \dot{V}_{\text{O}_2}(t) \) and \( \dot{V}_{\text{CO}_2}(t) \) into the equations for \( P_{\text{O}_2}^{\text{pl}} \) (eqn. (14)) and \( P_{\text{CO}_2}^{\text{pl}} \) (eqn. (19)).
5. We substitute the monitored values of \( C_{\text{O}_2}^{\text{VB}} (=C_{\text{O}_2}^{\text{AE}}) \) and \( C_{\text{CO}_2}^{\text{VB}} (=C_{\text{CO}_2}^{\text{AE}}) \) into eqns. (25) and (31), to obtain the values of \( P_{\text{O}_2}^{\text{AE}} \) and \( P_{\text{CO}_2}^{\text{AE}} \).
6. Now, in order to determine the values of the lung gas-exchange parameters \( D_{\text{O}_2} \) and \( D_{\text{CO}_2} \), we substitute into eqns. (3) and (4) for \( Q \) from eqn. (32), \( P_{\text{O}_2}^{\text{pl}} \) from eqn. (14), \( P_{\text{CO}_2}^{\text{pl}} \) from eqn. (19), \( P_{\text{O}_2}^{\text{AE}} \) from eqn. (26), and \( P_{\text{CO}_2}^{\text{AE}} \) from eqn. (31).
3.5 Determining $D_{O_2}$ and $D_{CO_2}$

Figure 7 illustrates the variation of $\Delta P^{O_2} (= P^{al}_{O_2} - P^{cap}_{O_2} = P^{al}_{O_2} - P^{AB}_{O_2})$ along the length ($l$) of the capillary bed.

Let $l^* = l / l_m$.

Then we can express:

$$\Delta P^{O_2} = \Delta P^{O_2}_{\text{max}} f_{O_2}(l^*).$$

(35)

Then,

$$\Delta P^{O_2}_{\text{av}} = \Delta P^{O_2}_{\text{max}} \left( \int_0^1 f_{O_2}(l^*) \, dl^* \right) = \Delta P^{O_2}_{\text{max}} \left( F_{O_2} \right).$$

(36)

Based on data [3], since $\Delta P^{O_2}_{\text{av}} = 12 \text{ mmHg}$ for $\Delta P^{O_2}_{\text{max}} = 65 \text{ mmHg}$, we have $F_{O_2} = 0.185$.

We can similarly determine the average value of $\Delta P^{CO_2}_{\text{av}}$ from Fig. 8 as:

Let $l^* = l / l_m$.

Then, we can represent Fig. 8 as:

$$\Delta P^{CO_2} = \Delta P^{CO_2}_{\text{max}} f_{CO_2}(l^*).$$

(37)

Then,

$$\Delta P^{CO_2}_{\text{av}} = \Delta P^{CO_2}_{\text{max}} \left( \int_0^1 f_{CO_2}(l^*) \, dl^* \right) = \Delta P^{CO_2}_{\text{max}} \left( F_{CO_2} \right).$$

(38)

Figure 7: Uptake of oxygen by the pulmonary capillary blood. (The curve in this figure was constructed from data in Mhorn and Pulley: Biophys. J., 8: 337, 1968). [from Guyton (1971), p. 434.]
Based on data [3], since $\Delta P_{av}^{CO_2} = 0.5$ mmHg for $\Delta P_{max}^{CO_2} = 5$ mmHg, we have $F_{CO_2} = 0.1$.

From the $\Delta P_{av}^{O_2}$ and $\Delta P_{av}^{CO_2}$ expressions, we can determine the $O_2$ consumption and the $CO_2$ production rates, as follows:

$$D_{O_2} = \frac{\text{Total } O_2 \text{ consumed}}{\Delta P_{av}^{O_2}} = \frac{\dot{V}_{O_2}}{\Delta P_{av}^{O_2}} = \frac{Q \left( c^{AB}_{O_2} - c^{VB}_{O_2} \right)}{\Delta P_{av}^{O_2}}$$

$$D_{CO_2} = \frac{\text{Total } CO_2 \text{ produced}}{\Delta P_{av}^{CO_2}} = \frac{\dot{V}_{CO_2}}{\Delta P_{av}^{CO_2}} = \frac{Q \left( c^{VB}_{CO_2} - c^{AB}_{CO_2} \right)}{\Delta P_{av}^{CO_2}}.$$  

4 Case studies

(A) We monitor the partial pressures blood concentrations of $O_2$ and $CO_2$ as:

$$C^{AE}_{O_2} = C^{VB}_{O_2} = 0.13, \quad C^{VE}_{O_2} = C^{AB}_{O_2} = 0.18, \quad C^{AE}_{CO_2} = C^{VB}_{CO_2} = 0.525,$$

$$C^{VE}_{CO_2} = C^{AB}_{CO_2} = 0.485.$$  

From eqn. (26), we obtain:

$$P_{O_2}^{VB} = 30.5 \ln \left( \frac{0.2}{0.2 - C^{VB}_{O_2}} \right) = 29.72 \ln \left( \frac{0.2}{0.2 - 0.13} \right)$$

$$= 32.02 \text{ mmHg}. \quad (41)$$
From eqn. (31), we obtain:

\[
\begin{align*}
P_{\text{CO}_2}^{\text{VB}} &= 37.94 \ln \left( \frac{0.8}{0.8 - C_{\text{VB}}^{\text{CO}_2}} \right) = 37.94 \ln \left( \frac{0.8}{0.8 - 0.525} \right) \\
&= 40.51 \text{ mmHg.} \quad (42)
\end{align*}
\]

We now also monitor \( Q = 51 \text{ l/min}, \ \dot{V}^* = 0.1 \) and \( \dot{V} = 51 \text{ l/min}. \)

Then, from eqn. (33):

\[\hat{V}_O(t) = Q \left( C_{\text{O}_2}^{\text{AB}} - C_{\text{O}_2}^{\text{VB}} \right),\]

so that from the above data,

\[\hat{V}_O(t) = 5000 \times 0.05 = 250 \text{ ml O}_2/\text{min Consumption rate} \quad (43)\]

From eqn. (34):

\[\hat{V}_{\text{CO}_2}(t) = Q \left( C_{\text{CO}_2}^{\text{VB}} - C_{\text{CO}_2}^{\text{AB}} \right) = 5000(0.04) \]

\[= 200 \text{ ml CO}_2/\text{min production rate.} \quad (44)\]

Now, from eqn. (14).

For \( \dot{V}^* = 0.1 \) and \( \hat{V}_O = 0.25 \), we obtain \( P_{\text{O}_2}^{\text{al}}: \)

\[\begin{align*}
P_{\text{O}_2}^{\text{al}} &= 140 \left[ 1 - e^{-4.18 \left( \frac{\dot{V}^*}{\hat{V}_O} \right)} \right] \\
&= 140 \left[ 1 - e^{-4.18[0.1/0.25]} \right] = 113.7 \text{ mmHg.} \quad (45)
\end{align*}\]

From eqn. (19), for \( \dot{V}^* = 0.1 \) and \( \dot{V}_{\text{CO}_2} = 0.20 \), we obtain \( P_{\text{CO}_2}^{\text{al}}: \)

\[\begin{align*}
P_{\text{O}_2}^{\text{al}} &= 107.18e^{-2.19 \left( \frac{\dot{V}^*}{\dot{V}_{\text{CO}_2}} \right)} = 107.18e^{-2.19[0.1/0.2]} \\
&= 35.86 \text{ mmHg.} \quad (46)
\end{align*}\]

Now, we can evaluate the diffusion coefficients:

From eqns. (3), (36), (41), and (45):

\[\begin{align*}
D_{\text{O}_2} &= \frac{Q(C_{\text{O}_2}^{\text{AB}} - C_{\text{O}_2}^{\text{VB}})}{\Delta P_{\text{O}_2}^{\text{al}}} \\
&= \frac{5000(0.18 - 0.13)}{(113.7 - 31.2) \times 0.18} = 16.84 \text{ ml O}_2/\text{min/mmHg}. \quad (47)
\end{align*}\]
From eqn. (4):
\[
D_{CO_2} = \frac{Q(C_{CO_2}^{VB} - C_{CO_2}^{AB})}{\Delta P_{av}^{CO_2}} \times 5000(0.04) = \frac{(40.51 - 35.86) \times 0.1}{(40.51 - 35.86) \times 0.1} = 430.11 \text{ ml CO}_2/\text{min/mmHg}. \tag{48}
\]

(B) Alternately, we derive data from:
(i) the inspired and expired air analysis (such as that carried out in Section 2.3):
\[
\begin{align*}
\text{O}_2 \text{ consumption rate} &= 283.2 \text{ ml/min}, \\
\text{CO}_2 \text{ production rate} &= 226.8 \text{ ml/min}, \\
P_{\text{O}_2}^{\text{al}} &= 103.03 \text{ mmHg and } P_{\text{CO}_2}^{\text{al}} = 38.41 \text{ mmHg}
\end{align*}
\]
and (ii) venous blood gas analysis:
\[
C_{O_2}^{VB} = 0.13, \ C_{CO_2}^{VB} = 0.548.
\]

Then, as per eqn. (41),
\[
P_{O_2}^{VB} = 31.2 \text{ mmHg}, \tag{49}
\]
corresponding to \(C_{O_2}^{VB} = 0.13\) and, as per eqn. (42):
\[
\begin{align*}
P_{CO_2}^{VB} &= 37.94 \ln \left[ \frac{0.8}{0.8 - C_{CO_2}^{VB}} \right] = 37.94 \ln \left[ \frac{0.8}{0.8 - 0.548} \right] \\
&= 43.84 \text{ mmHg}. \tag{50}
\end{align*}
\]

We obtain, from air-composition analysis, that \(\dot{V}_{O_2}(t) = 283.3 \text{ ml/min} \tag{51}\)

and \(\dot{V}_{CO_2}(t) = 226.8 \text{ ml/min}. \tag{52}\)

Hence,
\[
D_{O_2} = \frac{\dot{V}_{O_2}}{\Delta P_{av}^{O_2}} \times \frac{283.2}{(103.03 - 31.2) \times 0.18} = 21.90 \text{ mlO}_2/\text{min/mmHg}, \tag{53}
\]
and
\[
D_{CO_2} = \frac{\dot{V}_{CO_2}}{\Delta P_{av}^{CO_2}} \times \frac{226.8}{(43.84 - 38.41) \times 0.1} = 417.68 \text{ mlCO}_2/\text{min/mmHg}. \tag{54}
\]

The advantage of this method (B) over (A) is that it does not require monitoring of the cardiac output, and is hence simpler to implement clinically.
References


$O_2$ consumption
rate
$CO_2$ production
rate
Concentration
$C_{O_2}$
$C_{CO_2}$
Lung Air Composition
Dead Space Air
$D_{O_2}$
$D_{CO_2}$
Partial Pressure
$P_{O_2}^{alt}$
$P_{CO_2}^{alt}$
## TABLE 1: Nomenclature

<table>
<thead>
<tr>
<th>SYMBOL</th>
<th>MEANING</th>
<th>UNITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C$</td>
<td>Lung Complance</td>
<td>$(cmH_2O)^{-1}$</td>
</tr>
<tr>
<td>$C_a$</td>
<td>Average Lung Complance</td>
<td>$(cmH_2O)^{-1}$</td>
</tr>
<tr>
<td>$R$</td>
<td>Lung air-flow resistance</td>
<td>$cmH_2Osl^{-1}$</td>
</tr>
<tr>
<td>$R_a$</td>
<td>Average Lung air-flow resistance</td>
<td>$cmH_2Osl^{-1}$</td>
</tr>
</tbody>
</table>

## TABLE 2: ABBREVIATIONS

<table>
<thead>
<tr>
<th>ABBREVIATION</th>
<th>MEANING</th>
</tr>
</thead>
<tbody>
<tr>
<td>$VTI$</td>
<td>Lung-Ventilatory Index</td>
</tr>
<tr>
<td>WOB</td>
<td>Work of Breathing</td>
</tr>
</tbody>
</table>
Human Respiration

Anatomy and Physiology, Mathematical Modeling, Numerical Simulation and Applications

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Human Respiration

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Series: Advances in Bioengineering Volume 3

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ISSN: 1464-9292
Chapter 3
Lung-gas composition and transfer analysis: O₂ and CO₂ diffusion coefficients and metabolic rates ........................................ 77
D.N. Ghista, K.M. Loh & D. Ng

1 Introduction ........................................................................ 77
2 Lung-air composition analysis (and O₂ consumption and CO₂ production rates) ....................................................... 78
   2.1 Calculation of O₂ consumption rate and CO₂ production rate .... 78
   2.2 Dead-space air composition ........................................... 79
   2.3 Alveolar air composition and partial pressures ................. 80
3 Lung gas-exchange model and parametric analysis ............... 81
   3.1 Expressions for \( D_{O_2} \) and \( D_{CO_2} \) ............................ 81
   3.2 Alveolar \( O_2 \) and \( CO_2 \) partial-pressure expressions ........ 85
   3.3 Arterial and venous \( O_2 \) and \( CO_2 \) partial-pressure expressions .................................................. 86
   3.4 Sequential procedure to compute \( D_{O_2} \) and \( D_{CO_2} \) .......... 88
   3.5 Determining \( D_{O_2} \) and \( D_{CO_2} \) .................................... 89
4 Case studies ....................................................................... 90

Chapter 4
Lung ventilation modeling and assessment ................................. 95
D.N. Ghista, K.M. Loh & M. Damodaran

1 Introduction ........................................................................ 95
   1.1 Role of lung ventilation .................................................. 95
2 Lung ventilation performance using a linear first-order model .......... 96
3 Ventilatory Index .............................................................. 101
   3.1 Noninvasively determinable ventilatory index ................... 101
4 Variations in \( R \) and \( C \) during a respiratory cycle (towards nonlinear) ................................................................. 103
   4.1 Nonlinear compliance ................................................... 104
5 Work of breathing (WOB) .................................................... 106
6 Second-order model for single-compartment lung model .......... 108
7 Two-compartmental linear model ......................................... 110
   7.1 Two compartmental model using first order ventilatory model ................................................................. 112
   7.1.1 Stiff right lung (with compliance problems) ............... 115
   7.1.2 Right lung with \( R \) problems ..................................... 115

Chapter 5
Modeling of two-phase flow in the human respiratory system ............ 117
V.V. Kulish, B. Wijayanto & C.S. Lim

1 Introduction ........................................................................ 117
2 Methodology ...................................................................... 118
   2.1 Geometry of the human respiratory duct ......................... 118
CHAPTER 4

Lung ventilation modeling and assessment

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Abstract

We have developed a lung-ventilation model by modeling the lung-volume response to mouth minus pleural driving pressure (by means of first- and second-order differential equations) in terms of resistance to airflow ($R$) and the lung compliance ($C$). The lung-volume solution of the differential equation is matched with the clinical-volume data, to evaluate the parameters, $R$ and $C$. These parameter values can help us to distinguish an obstructive lung and a lung with stiffened parenchyma from a normal lung, and hence diagnose lung diseases such as asthma and emphysema. We have also formulated a nonlinear compliance lung model, and demonstrated deceased lung compliance with filling volume. We then formulated a nondimensional lung-ventilatory index ($\textit{VIT}$), incorporating the parameters $R$ and $C$ as well as the lung-breathing rate. When the $\textit{VIT}$ is evaluated for various lung diseases, it will conveniently enable us to diagnose lung diseases in terms of just one $\textit{VIT}$ number. Finally, we have shown how to model a two-lobed lung, and differentiate between normal and diseased lobes.

1 Introduction

1.1 Role of lung ventilation

Lung ventilation constitutes inhalation of an appropriate air volume under driving pressure (mouth pressure − pleural pressure), so as to: (i) provide an adequate alveolar $O_2$ amount at an appropriate partial pressure, (ii) oxygenate the pulmonary blood, and (iii) thereby provide adequate metabolic oxygen to the cells.
Hence, ventilatory function and performance assessment entails determining how much air volume is provided to the alveoli, to make available adequate alveolar oxygen for blood oxygenation and cellular respiration.

Based on Fig. 1, we get:

(i) \((P_a - P_p) - P_{el} = 0\)
(ii) \(P_{el} = (2aV)/R = 2T/r = V/C + P_{el0}\)
(iii) \((P_m - P_a) = R(dV/dt)\)
(iv) \(P_L = P_m - P_p\)
(v) \(R(dV/dt) + VIC = P_L - P_{el0}\) (lungen elastic recoil pressure at end of expiration)

2 Lung-ventilation performance using a linear first-order model

We first analyze the lung-ventilation function by means of a very simple model represented by a first-order differential equation \((D_{eq})\) in lung-volume \((V)\) dynamics in response to the driving pressure \((P_0 = \text{atmospheric pressure} - \text{pleural pressure})\), as displayed in Fig. 1. The clinical pressure-volume data is in Fig. 2.

The model-governing equation (shown derived in Fig. 1) is as follows:

\[
R\dot{V} + \frac{V}{C} = P_L(t) - P_{el0} = P_N(t),
\]

wherein:

(i) the values of pressure are obtained from the given \(P_L(=P_m - P_p)\) data
(ii) the parameters of this governing \(D_{eq}\) are lung compliance \((C)\) and airflow resistance \((R)\); in the equation both \(R\) and \(C\) are instantaneous values
(iii) \(V = V(t) - V_0\) (the lung volume at the end of expiration
(iv) \(P_{el0}\) is the lung elastic-recoil pressure at the end of expiration, and

\[
P_{el0} = P_{el} - \frac{V}{C}.
\]
At the end of expiration when \( \omega t = \omega T, P_L = P_{el0} = P_N(t) \), which is represented by

\[
P_N(t) = \sum_{i=1}^{3} p_i \sin(\omega_i t + \phi_i).
\]

and the governing eqn. (1a) becomes:

\[
R \dot{V} + \frac{V}{C} = P_N(t) = \sum_{i=1}^{3} p_i \sin(\omega_i t + \phi_i),
\]

(2a)

where the right-hand side represents the net driving pressure minus pleural pressure, \( P_N = (P_m - P_P) - P_{el0} \). This \( P_N \) is, in fact, the driving pressure \( (P_m - P_P) \) normalized with respect to its value at end of expiration. Equation (2a) can be rewritten as follows:

\[
\dot{V} + \frac{V}{RC} = \frac{1}{R} \sum_{i=1}^{3} p_i \sin(\omega_i t + \phi_i).
\]

(2b)
wherein the $P(t)$ clinical data (displayed in Fig. 2) is assumed to be represented by:

$$P(t) = \sum_{i=1}^{3} P_i \sin (\omega_i t + c_i),$$

(3)

$$P_1 = 1.581 \text{ cmH}_2\text{O} \quad P_2 = -5.534 \text{ cmH}_2\text{O} \quad P_3 = 0.5523 \text{ cmH}_2\text{O}$$

$$\omega_1 = 1.214 \text{ rad/s} \quad \omega_2 = 0.001414 \text{ rad/s} \quad \omega_3 = 2.401 \text{ rad/s}$$

$$c_1 = -0.3132 \text{ rad} \quad c_2 = 3.297 \text{ rad} \quad c_3 = -2.381 \text{ rad}.$$

The pressure curve (in Fig. 3A) represented by the above eqn. (3) closely matches the pressure data of Fig. 2. If, in eqn. (1), we designate $R_a$ and $C_a$ as the average values ($R$ and $C$) for the ventilatory cycle, then the solution of eqn. (1) is given by:

$$V(t) = \sum_{i=1}^{3} \frac{P_i C_a [\sin (\omega_i t + c_i) - b_i R_a C_a \cos (\omega_i t + c_i)]}{(1 + \omega_i^2 (R_a C_a)^2)} - H e^{-\frac{t}{\tau_a}},$$

(4)

wherein the term $(R_a C_a)$ is denoted by $	au_a$. We need to have $V = 0$ at $t = 0$. Hence, putting $V$ (at $t = 0) = 0$, gives us:

$$H = \sum_{i=1}^{3} \frac{P_i C_a [\sin (\omega_i t + c_i) - b_i R_a C_a \cos (\omega_i t + c_i)]}{(1 + \omega_i^2 (R_a C_a)^2)}.$$

(5)

Then from eqns. (4) and (5), the overall expressions for $V(t)$ becomes

$$V(t) = \sum_{i=1}^{3} \frac{P_i C_a [\sin (\omega_i t + c_i) - \omega_i \tau_a^2 \cos (\omega_i t + c_i)]}{(1 + \omega_i^2 \tau_a^2)}$$

$$- \sum_{i=1}^{3} \frac{P_i C_a [\sin (\omega_i t + c_i) - \omega_i \tau_a^2 \cos (\omega_i t + c_i)]}{(1 + \omega_i^2 \tau_a^2)} e^{-\frac{t}{\tau_a}}$$

$$= \sum_{i=1}^{3} \frac{P_i C_a [\sin (\omega_i t + c_i) - \omega_i \tau_a^2 \cos (\omega_i t + c_i)]}{(1 + \omega_i^2 \tau_a^2)} [1 - e^{-\frac{t}{\tau_a}}].$$

(6)

We also want that $dV/dt = 0$ at $t = 0$, implying no air-flow at the start of inspiration. So, by differentiating eqn. (6), we get:

$$\ddot{V} = \sum_{i=1}^{3} \frac{P_i C_a [\omega_i \cos (\omega_i t + c_i) + \omega_i^2 \tau_a \sin (\omega_i t + c_i)]}{(1 + \omega_i^2 \tau_a^2)} [1 - e^{-\frac{t}{\tau_a}}]$$

$$+ \sum_{i=1}^{3} \frac{P_i C_a [\sin (\omega_i t + c_i) - \omega_i \tau_a \cos (\omega_i t + c_i)]}{(1 + \omega_i^2 \tau_a^2)} e^{-\frac{t}{\tau_a}}.$$

(7)

From eqn. (7), we get $\ddot{V} \neq 0$ at $t = 0$, thereby also satisfying this initial condition.
Figure 3: A The pressure curve represented by eqn. (3) matched against the pressure data (represented by dots). B The volume curve represented by eqn. (6), for from $C_a = 0.2132 \text{ (cmH}_2\text{O)}^{-1}$ and $R_a = 2.275 \text{ cmH}_2\text{O s}^{-1}$ pp. 3 matched against the volume data represented by dots.
Now, by matching the above \( V(t) \) expression (6) with the given \( V(t) \) data in Fig. 2, and carrying out parameter identification, we can determine the in vivo values of \( R_\alpha \) and \( C_\alpha \), to be

\[
C_\alpha = 0.2132 \text{ (cmH}_2\text{O})^{-1}, \quad R_\alpha = 2.275 \text{ cmH}_2\text{O}l^{-1}
\]

The computed \( V(t) \) curve, represented by eqn. (6) for the above values of \( C_\alpha \) and \( R_\alpha \), is shown in Fig. 3B. We can however analytically evaluate \( R_\alpha \) and \( C_\alpha \) by satisfying some conditions. For this purpose, we first note that \( V \) is maximum (= tidal volume, TV) at about \( t = t_V = 2.02 \text{ s}. \) At \( t = t_V \), the exponential term \( e^{-\frac{t}{\tau_\alpha}} \) in (6) becomes of the order of \( e^{-10} \), and hence negligible. Then by putting \( \dot{V}(t=2.02) = 0 \) in eqn. (7), without the exponential term we obtain:

\[
\dot{V}_{l=2.02} = \sum_{i=1}^{3} P_i C_\alpha \left[ \omega_i \cos(\omega_i x 2.02 + c_i) + \omega_i^2 \tau_\alpha \sin(\omega_i x 2.02 + c_i) \right] \left( 1 + \omega_i^2 \tau_\alpha^2 \right) = 0,
\]

in which the values of \( P_i, \omega_i, \) and \( c_i \) are given by eqn. (3). Then by solving eqn. (8), we get \( \tau_\alpha = 0.522 \text{ s}. \) We can also put \( \dot{V} = 0 \) at \( t \approx 1.81/2.87 \text{ s} \) and obtain a similar value for \( \tau. \)

Then, we also note that at \( t_\alpha = 2.02 \text{ s} \) (at which \( dV/dt = 0 \)) and \( V = 0.551. \) Hence upon substituting into eqn. (6), and neglecting the exponential term, we get the following algebraic equation:

\[
V(t)|_{l=2.02} = \sum_{i=1}^{3} P_i C_\alpha \frac{\sin(\omega_i t + c_i) - \omega_i \tau_\alpha^2 \cos(\omega_i t + c_i)}{1 + \omega_i^2 \tau_\alpha^2} = 2.55 C_\alpha,
\]

by employing the values of \( P_i, \omega_i \) and \( c_i \) from eqn. (3). Now since \( V(t=2.02 \text{ s}) = 0.551, \) we get

\[
2.55 C_\alpha = 0.55
\]

\[
C_\alpha = 0.221 \text{ (cmH}_2\text{O})^{-1}.
\]

We can substitute, therein, the values of \( P_1 \) and \( P_2 \) from eqn. (3), and obtain the value of \( C_\alpha \) as: \( C_\alpha = 0.221 \text{ (cmH}_2\text{O})^{-1}. \) Since we have computed \( \tau_\alpha = 0.485 \text{ s}, \) therefore \( R_\alpha = 2.275 \text{ (cmH}_2\text{O})l^{-1}. \) These are the average values of resistance to airflow and lung compliance during the ventilatory cycle shown in Fig. 2.

Since lung disease will influence the values of \( R \) and \( C \), these parameters can be employed to diagnose lung diseases. For instance in the case of emphysema, the destruction of lung tissue between the alveoli produces a more compliant lung, and hence results in a larger value of \( C. \) In asthma, there is increased airway resistance (\( R \)) due to contraction of the smooth muscle around the airways. In fibrosis of the lung, the membranes between the alveoli thicken and hence lung compliance (\( C \)) decreases. Thus, by determining the normal and diseased ranges of the parameters \( R \) and \( C \), we can employ this simple lung-ventilation model for differential diagnosis.
3 Ventilatory index

Let us, however, formulate just one non dimensional number to serve as a ventilatory-performance index $VTI_1$ (to characterize ventilatory function), as:

$$VTI_1 = [(R_a C_a)(\text{Ventilatory rate in s}^{-1}) 60]^2 = \tau_a^2 (BR)^2 60^2,$$

where $BR$ is the breathing rate.

Now, let us obtain its order of magnitude by adopting representative values of $R_a$ and $C_a$ in normal and disease states. Let us take the above computed values of $R_a = 2.275$ (cmH$_2$O)sl$^{-1}$ and $C_a = 0.21321$ (cmH$_2$O)$^{-1}$ and $BR = 12$ m$^{-1}$ or 0.2 s$^{-1}$, computed for the data of Fig. 2 and eqn. (3). Then, in a supposed normal situation, the value of $VTI_1$ is of the order of 33.88. In the case of obstructive lung disease, (with increased $R_a$), let us take $R_a = 5$ (cmH$_2$O)sl$^{-1}$, $C_a = 0.121$ (cmH$_2$O)$^{-1}$ and $BR = 0.3$ s$^{-1}$; then we get $VTI_1 = 116.6$. For the case of emphysema (with enhanced $C_a$), let us take $R_a = 2.0$ cmH$_2$Osl$^{-1}$, $C_a = 0.51$ (cmH$_2$O)$^{-1}$ and $BR = 0.2$ s$^{-1}$; then we obtain $VTI_1 = 144$. In the case of lung fibrosis (with decreased $C_a$), we take $R_a = 2.0$ cmH$_2$Osl$^{-1}$, $C_a = 0.081$ (cmH$_2$O)$^{-1}$ and $BR = 0.2$ s$^{-1}$; then we obtain $VTI_1 = 3.7$. We can hence summarize that $VTI_1$ would be in the range of 2–5 in the case of fibrotic lung disease, 5–50 in normal persons, 50–150 in the case of obstructive lung disease and 150–200 for the case of emphysema. This would of course need verification by analyzing a big patient population.

Now, all of this analysis requires pleural-pressure data, for which the patient has to be intubated. If now we evaluate the patient in an outpatient clinic, in which we can only monitor lung volume and not the pleural pressure, then can we develop a non invasively obtainable ventilatory index?

3.1 Noninvasively determinable ventilatory index

In order to formulate a non-invasively determinable ventilatory index from eqn. (1), we need to recognize that in this case $P_N(t)$ (and hence $P_i$, $\omega_i$ and $C_i$) will be unknown and we need to redesignate the model parameters and indicate their identification procedure. So we make use of the following features from the volume–time data to facilitate evaluation of the following three parameters:

$$\left(P_i, C_i, \omega_i + c_i, \tau_s \right).$$

At $t = \tau_v = 2.02$ s, $V$ is max and $dV/dt = 0$; hence we rewrite eqn. (9) as:

$$\dot{V}|_{t=2.02} = \sum_{i=1}^{3} \left( P_i C_i \left[ \frac{\omega_i \cos (2.02 \times \omega_i + c_i) + \omega_i^2 \tau_s \sin (2.02 \times \omega_i + c_i)}{1 + \omega_i^2 \tau_s^2} \right] \right) = 0.$$  

(12)
Also, at \( t = t_m = 1.82/2.87 \text{ s} \), \( \dot{V} = 0 \). Hence by differentiating eqn. (7), without the exponential term, we obtain:

\[
\dot{V}(t) = \sum_{i=1}^{3} (P_i C_a) \left[ - \sin(\omega_1 t_m + c_i) \omega_1^2 + \omega_1^3 \tau_a^2 \cos(\omega_1 t_m + c_i) \right] \left[ 1 - e^{-\frac{t_m}{\tau_a}} \right] \\
+ 2 \sum_{i=1}^{3} (P_i C_a) \left[ \omega_1 \cos(\omega_1 t_m + c_i) - \omega_1^2 \tau_a \sin(\omega_1 t_m + c_i) \right] e^{-\frac{t_m}{\tau_a}} \\
- \sum_{i=1}^{3} (P_i C_a) \left[ \sin(\omega_1 t_m + c_i) - \omega_1^2 \tau_a \cos(\omega_1 t_m + c_i) \right] e^{-\frac{t_m}{\tau_a}} = 0. \tag{13}
\]

Then, at \( t = 1 \text{ s} \), \( V_1 = 2.02l \). From eqn. (6), without the exponential term, this condition yields:

\[
V_1 = \sum_{i=1}^{3} (P_i C_a) \left[ - \sin(\omega_1 + c_i) \omega_1^2 + \omega_1^3 \tau_a^2 \cos(\omega_1 + c_i) \right] \left( 1 + \omega_1^2 \tau_a^2 \right) = 2.02.
\]

In addition, we can utilize data information concerning \( V_j \) at \( t_j \) (\( j = 1 \) to 8), and put down:

\[
V_j = \sum_{i=1}^{3} (P_i C_a) \left[ - \sin(\omega_1 t_j + c_i) \omega_1^2 + \omega_1^3 \tau_a^2 \cos(\omega_1 t_j + c_i) \right] \left( 1 + \omega_1^2 \tau_a^2 \right) ; \quad j = 1 \quad \text{to} \quad 8. \tag{14}
\]

From eqns. (12)–(14), we can obtain the values of \( P_1 C_a \) (but not of \( P_1, P_2 \) and \( P_3 \) by themselves), \( \omega_1, c_1 \) and \( \tau_a \). On the other hand, by also fitting eqn. (6), (without the exponential term) to the \( V(t) \) data, we obtain:

\[
P_1 C = 0.3223 \quad P_2 C = 0.3143 \quad P_3 C = -0.02269 \tag{15}
\]

\[
\omega_1 = -1.178 \quad \omega_2 = 0.5067 \quad \omega_3 = 1.855 \tag{16}
\]

\[
c_1 = 90223 \quad c_2 = 0.2242 \quad c_3 = -3.961 \tag{17}
\]

\[
\tau_a = 0.5535.
\]

We can now also formulate another noninvasively determinable nondimensional ventilatory index \( VTI_2 \) in terms of these parameters as follows:

\[
VTI_2 = \frac{(BR)r[TV]^2}{|P_1 C||P_2 C||P_3 C|} = \frac{(BR)r[TV]^2}{|P_1 P_2 P_3 C^2|}. \tag{18}
\]

It is seen that \( VTI_2 \) can in fact be expressed in terms of \( P_1, P_2, P_3 \) and \( R, C \). This \( VTI_2 \) index can be evaluated by computing the values of \( (BR) \) and \( r \), along with \( (P_i C) \), as given by eqn. (17). Then, after evaluating \( VTI_2 \) for a number of patients, its distribution can enable us to categorize and differentially diagnose patients with various lung disorders and diseases.
4 Variations in $R$ and $C$ during a respiratory cycle (towards nonlinear)

Thus far, we have adopted the average cyclic values $C_a$ and $R_a$ for our $DE_q$ model parameters. However, we expect that $C$ will vary with lung volume ($V$), and that $R$ will perhaps vary with the airflow rate or ($\dot{V}$) or even $\omega$. Hence, for a true representation of the lung properties $C$ and $R$, let us determine their values for different times during the ventilatory cycle, and compare them with their average values $C_a$ and $R_a$, so as to make a case for a nonlinear ventilatory-function model.

Let us hence compute the instantaneous value of compliance ($C$) at time ($t = t_m$), when $\ddot{V} = 0$. Let us differentiate eqn. (2a), giving:

$$R\ddot{V} + \frac{\dot{V}}{C} = \sum_{i=1}^{3} P_i C \omega_i \cos (\omega_i t + c_i). \tag{19}$$

Now at about mid-inspiration, when $t = t_m = 1.18$ and $\dot{V} = 0.48$ l/s, $\ddot{V} = 0$ l/s and $V = 0.291$ (based on Fig. 2). By substituting for $\ddot{V}$, $\dot{V}$ and $V$ in eqn. (19), we obtain, $C = 0.486 \text{ l/cmH}_2\text{O}$ (compared to its $C_a$ value of 0.21). Now, in order to compute $R$, we utilize the data information that at $t_V = 2.02$ s we substitute $\dot{V} = 0$ l/s, $\ddot{V} = -0.89$ l/s and $V = 0.541$ (from the Fig. 2 data) into eqn. (2a), to obtain:

$$R\ddot{V} = \sum_{i=1}^{3} P_i \omega_i \cos (\omega_i t + c_i)$$

$$R = \frac{\sum_{i=1}^{3} P_i \omega_i \cos (\omega_i t + c_i)}{\ddot{V}}. \tag{20}$$

Substitute $C$ (at $t_m = 1.18$ s) = 0.486 l/cmH$_2$O in either eqns. (6) or (2b), and obtain $R = 1.122$ (cmH$_2$O)sl$^{-1}$. This gives us some idea of the order of magnitude of $R$ and $C$, in comparison to their average values $C_a$ and $R_a$. We could naturally expect $C$ at $t = t_m$ (which is about mid-inspiration) to be higher than its value at the end of inspiration, when the lung is fully inflated. Also, we could expect the flow resistance to be minimum at the peak of inspiration, when $\ddot{V} = 0$.

Because $C$ and $R$ are not constant, but a function of $V$ and $\dot{V}$, we can hence represent lung compliance ($C$) and resistance ($R$) as follows:

$$C = C_0 e^{-k e} \dot{V} \quad \text{or} \quad E = \frac{1}{C} = E_0 e^{k e} \dot{V} \tag{21a}$$

$$R = R_0 e^{k e} \ddot{V}, \tag{21b}$$

wherein $\dot{V}$ can also be varied by having the subjects breathe at different ventilation frequencies ($\omega$).
4.1 Nonlinear compliance

We note as per the conventional formulation of compliance, given by eqn. (2) in Fig. 1 as:

$$P_{el} = \frac{V}{C} + P_{e0} = VE + P_{e0}. \tag{22}$$

In the above formulation, we assume that $C$ and $E(=1/C)$ remains constant throughout the ventilation cycle. However, at the start of inspiration, $C = C_0$ at $t = 0$, and it decreases as the lung volume increases, based on the lung (static) volume vs pressure curve. So let us improve upon this (22) model, by making $P_{el}$ a nonlinear function of volume, as follows:

$$P_{el} = P_{e0} + VE_0e^{kV}. \tag{23a}$$

We can alternatively write eqn. (23) as:

$$P_{el} = P_{e0} + V(E_0 + E_1t + E_3t^2). \tag{23b}$$

Employing the above format of compliance, the governing $DE_0$ (1) becomes

$$R\dot{V} + VE_0e^{kV} = P_l(t) - P_{e0} = PN(t) = \sum_{i=1}^{3} P_i \sin (\omega_it + c_i). \tag{24}$$

Again at the end of expiration, $P_{e0}$ = intrapulmonary pressure = $(P_0 + P_1)$.

Hence eqn. (24) becomes:

$$R\dot{V} + VE_0e^{kV} = \sum_{i=1}^{3} P_i \sin (\omega_it + c_i) \tag{25a}$$

whose RHS is similar to that of eqn. (2a), and the values of $P_1, P_2$, and $P_3$ are given by eqn. (3) for the Fig. 2 data.

Solving eqn. (25a):

$$R\dot{V} + VE_0e^{kV} = \sum_{i=1}^{3} P_i \sin (\omega_it + c_i),$$

or,

$$\dot{V} + \frac{VE_0}{R}e^{kV} = \sum_{i=1}^{3} \frac{P_i}{R} \sin (\omega_it + c_i),$$

or, based on eqn. (23b),

$$\dot{V} + \frac{V}{R} (E_0 + E_1t + E_2t^2) = \sum_{i=1}^{3} \frac{P_i}{R} \sin (\omega_it + c_i).$$
This yields:

\[
V(t) = e^{-\frac{\sigma (E_0 + 3E_1 + 2E_2 t^2)}{6k}} \int_0^t e^{-\frac{\sigma (E_0 + 3E_1 + 2E_2 u^2)}{6k}} \sum_{i=1}^{3} \frac{P_i}{R} \sin (\omega_i u + c_i) \, du. \tag{25b}
\]

We could employ this expression for \(V(t)\) to fit the clinical \(V(t)\) data. However, let us try a simpler approach to evaluate these parameters \(k\) and \(E_0\). For this purpose, we again bring to bear the situation that at the end of inspiration, for \(t = t_e = 2.02\, s\), we have \(\bar{V} = 0\) and \(V = V_{\text{max}} = TV = 0.55\, l\). Hence, from Fig. 2 data, and eqns. (3) and (25a), we obtain:

\[
0.55 E_0 e^{0.55k} = 2.55. \tag{26}
\]

Let us now employ the volume data point at which \(\ddot{V} = 0\). For this purpose, we differentiate eqn. (25a), to obtain:

\[
\ddot{V} + \frac{E_0}{R} e^{kV} (1 + kV) = \sum_{i=1}^{3} \frac{P_i C_2 \omega_i}{R} \cos (\omega_i t + c_i)
\]

\[
\ddot{V} + \frac{(1 + kV)}{R} \left[ E_0 + E_1 t + E_2 t^2 \right] = \sum_{i=1}^{3} \frac{P_i C_2 \omega_i}{R} \cos (\omega_i t + c_i). \tag{27}
\]

From the Fig. 2 data at about mid-inspiration, for which at \(t = t_m = 1.18\, s\), \(\ddot{V} = 0\), \(V = 0.29\) and \(P = 2.53\), from Fig. 2 data. Substituting these values into eqn. (27), we get:

\[
(1 + 0.29k)(E_0 + 1.18E_1 + 1.39E_2) = 2.53. \tag{28}
\]

Now, in eqns. (26) and (28), we have four unknowns to be identified: \(k\), \(E_0\), \(E_1\), and \(E_2\). Hence we need two more equations, corresponding to two additional time instants. From the values in the following table,

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</tbody>
</table>

we can determine the unknowns:

\[
k = -0.13, \ E_0 = 4.98, \ E_1 = -2.24 \text{ and } E_2 = 0.21. \tag{29}
\]

Hence, by employing the nonlinear formulation,

\[
P_{el} = P_{el0} + E_0 e^{-kV}, \tag{30}
\]
we obtain the following expression for nonlinear lung compliance (or elastance):

\[
\frac{dP_{el}}{dV} = E = \frac{1}{C} = E_0 ke^{kV} = 0.65 e^{0.13V}.
\]

(31)

Based on this expression, we obtain, for \( t = t_m \) and \( V = 0.29 \text{l} \):

\[
E = \frac{1}{C} = 0.67 \text{ cmH}_2\text{O/l and } C = 1.48 \text{ cmH}_2\text{O/l.}
\]

(32)

Equation (31) can now provide us a more realistic characterization of lung compliance as follows:

\[
\begin{align*}
\text{At } t = 0 \text{ and } V = 0, \text{ we compute } E &= \frac{1}{C} = 0.65 \text{ and } C = 1.53 \text{ cmH}_2\text{O/l;} \\
\text{At } t = t_m = 1.18 \text{s and } V = 0.29 \text{l, } E &= \frac{1}{C} = 0.67 \text{ and } C = 1.48 \text{ cmH}_2\text{O/l;} \\
\text{At } t = t_3 = 2.02 \text{s and } V = 0.55 \text{l and } E &= \frac{1}{C} = 0.70 \text{ and } C = 1.43 \text{ cmH}_2\text{O/l.}
\end{align*}
\]

(33)

which corresponds to the value of \( C_n \).

Our nonlinear formulation of lung compliance, as depicted by eqns. (31) and (33), indicates that compliance decreases from 1.53 cm H2O/l at the start of inspiration to 1.48 cm H2O/l at about mid-inspiration, and then to 1.43 cm H2O/l at the end of inspiration. What this also tells us is that the ventilatory model (1) gives the correct reading of the compliance at \( V_{\text{max}} \), i.e., at the end of inspiration. At other times of inspiration and expiration, the \( C_n \) parameter underestimates the instantaneous value of lung compliance. Now, we could also obtain an analytical solution of eqn. (25) for \( V(t) \), and fit the expression for \( V(t) \) to the lung-volume data, to evaluate the parameters:

1. \( R, E_0 \) and \( k \) for an intubated patient
2. \( R, E_0, k \) and \( P_1, P_2 \) and \( P_3 \) for a non-intubated patient in the out-patient clinic.

However, this is outside the scope of this chapter.

5 Work of breathing (WOB)

This is an important diagnostic index, especially if it can be obtained without intubating the patient and even without using the ventilator. The premise for determining WOB is that the respiratory muscles expand the chest wall during inspiration, thereby lowering the pleural pressure (i.e., making it more negative) below the atmospheric pressure to create a pressure differential from the mouth to the alveoli during inspiration. Then, during expiration, the lung recoils passively.

Hence, the work done during a respiratory life cycle, is given by the area of the loop generated by plotting lung volume (\( V \)) versus net driving pressure (\( P_p \)).
Figure 4: Plot of pressure versus volume. The area under the curve provides the work done.

This plot is shown in Fig. 4. Its area can by obtained graphically, as well as analytically as shown below:

\[
WOB = \int_0^{t=T} VdP_p(t) = \int_0^{T} V \frac{dP_p(t)}{dt} dt
\]  

\[
= \int_0^{t=T} \left( \sum_{i=1}^{3} P_i C_a \left[ \sin (\omega_i t + c_i) - \frac{\omega_3 \tau_a^2 \cos (\omega_i t + c_i)}{1 + \omega_1^2 \tau_a^2} \right] \right) \left( \sum_{i=1}^{3} \omega_i \cos (\omega_i t + c_i) \right) dt
\]

\[
= \sum_{i=1}^{3} -P_i C_a \left. \left[ \frac{\cos (\omega_i T + c_i) + \omega_3 \tau_a \sin (\omega_i T + c_i) - \cos c_i - \omega_3 \tau_a \sin c_i}{\omega_i (1 + \omega_1^2 \tau_a^2)} \right] \right|_0^T
\]

The above expression for WOB can be evaluated, once the values of \( C_i \) and \( \tau \) (or \( \omega \tau \)) and \( P_1 \), \( P_2 \) and \( P_3 \) and have been computed (as shown in the previous section). So let us substitute into this equation, the following values associated with eqn. (3).

\[
P_1 = 1.581 \text{ cmH}_2\text{O} \quad P_2 = -5.534 \text{ cmH}_2\text{O} \quad P_3 = 0.5523 \text{ cmH}_2\text{O}
\]

\[
\omega_1 = 1.214 \text{ rad/s} \quad \omega_2 = 0.001414 \text{ rad/s} \quad \omega_3 = 2.401 \text{ rad/s}
\]

\[
c_1 = -0.3132 \text{ rad} \quad c_2 = 3.297 \text{ rad} \quad c_3 = -2.381 \text{ rad}
\]
We compute the value of WOB to be 0.9446 (cmH₂O) in 5 s, or 0.19 cmH₂O 1 s⁻¹ or 0.14 mmHg 1 s⁻¹ or 0.02 W, which is equivalent to an oxygen consumption of about 0.51 ml/min or about 0.18% of the resting \( \bar{V}_{O₂} \) of 28.87 ml/min. This value can be verified by calculating the value of the area of the pressure-volume loop in Fig. 4 which is equal to 0.8 cmH₂O.

6 Second-order model for single-compartment lung model

Let us now consider the dynamic (instead of static) equilibrium of a spherical segment of the lung model in Fig. 1, obtained as (by dividing throughout by the elemental lung area):

\[
m_s \dddot{u} + (P_p - P_a) + P_{elas} = 0, \tag{36a}
\]

wherein: \( P_a \) and \( P_p \) are the alveolar and pleural pressures, \( u \) is the alveolar-wall displacement, \( m_s = \text{lung mass (M) per unit surface area} = M/4\pi R^2 \), (1b) and

\[
P_{elas} = \frac{2\sigma h}{R} = \frac{V}{C} + P_{eb}, \tag{36b}
\]

where:

(i) \( C \) is in l (cmH₂O)⁻¹
(ii) \( m_s \) (wall mass per unit surface area or surface density) = \( \rho h \), \( \rho \) is the density (mass per unit volume)
(iii) \( \sigma \) is the wall stress
(iv) \( h \) and \( R \) are the wall thickness and radius of the equivalent-lung model.

Now, the displaced alveolar volume, \( V = \frac{4}{3} \pi (R + u)^3 \),

from which we get \( \dddot{u} \approx 4\pi R^2 \dot{u} \). \tag{37}

Now, from eqn. (1), by putting

(i) \( P_p - P_a = (P_0 - P_a) + (P_p - P_0) \) and \( P_L = P_0 - P_p \),

so that \( P_p - P_a = P_0 - P_a - P_L = R\dot{V} - P_L \), \tag{38}

(ii) \[
m_s \ddot{u} = \left( \frac{M}{4\pi R^2} \right) \left( \frac{\dddot{V}}{4\pi R^2} \right) = \frac{M \ddot{V}}{16\pi^2 R^4} = M^* \ddot{\dot{V}}; \quad M^* = \frac{M}{16\pi^2 R^4} \]

\[
= \frac{m_s}{4\pi R^2}, \tag{39}
\]
we obtain, from eqns. (1), (2) and (3):

\[ M^* \ddot{V} + (P_0 - P_a) + \frac{V}{C} = P_L - P_e \delta \;
M^* = \frac{M}{16\pi^2 R^4} \left( = \frac{m_s}{4\pi R^2} \right). \quad (40) \]

Now, putting \( P_0 - P_a = R \dot{V} \), we obtain:

\[ M^* \ddot{V} + R \dot{V} + \frac{V}{C} = P_L - P_e \delta = \sum_{i=1}^{3} P_1 \sin (\omega_i t + c_i) - P_e \delta = P_N. \quad (41) \]

Since at the end of expiration when \( \omega_i t = \omega_i T \) for \( i = 1 \) to 3 and \( P_L = P_e \delta \) so that \( P_e \delta = 0 \). In eqn. (6), we have:

wherein:

(i) \( M^* = \frac{m_s}{4\pi R^2} = \rho_s R \); \( \rho_s \) is the lung volume-density per unit surface area (in Kgm\(^{-2}\)) and \( M^* \) is in Kgm\(^{-4}\);

(ii) the clinical data in Fig. 2 is assumed to be represented by

\[ P_N(t) = \sum_{i=1}^{3} P_1 \sin (\omega_i t + c_i) \quad \text{with} \]

\[
\begin{align*}
P_1 &= 1.581 \text{ cmH}_2\text{O} & P_2 &= -5.534 \text{ cmH}_2\text{O} & P_3 &= 0.5523 \text{ cmH}_2\text{O} \\
\omega_1 &= 1.214 \text{ rad/s} & \omega_2 &= 0.001414 \text{ rad/s} & \omega_3 &= 2.401 \text{ rad/s} \\
c_1 &= -0.3132 \text{ rad} & c_2 &= 3.297 \text{ rad} & c_3 &= -2.381 \text{ rad}.
\end{align*}
\]

Then we can rewrite eqn. (6) as:

\[ \ddot{V} + \left( \frac{R}{M^*} \right) \dot{V} + \frac{V}{CM^*} = \sum_{i=1}^{3} \frac{P_1}{M^*} \sin (\omega_i t + c_i), \quad (43a) \]

or as:

\[ \ddot{V} + 2n \dot{V} + p^2 V = \sum_{i=1}^{3} Q_i \sin (\omega_i t + c_i). \quad (43b) \]

In the above equation:

(i) the damping coefficient, \( 2n = \frac{R}{M^*} \)

(ii) the natural frequency of the lung-ventilatory cycle, \( p^2 = \frac{1}{CM^*} \)

(iii) \( Q_i = \frac{P_i}{M^*} \). \quad (43c)

So the governing eqn. (8) of the lung-ventilatory response to the inhalation pressure has three parameters: \( M^*, R \) and \( C \) (if the lung pressure is also monitored by
intubating the patient). The solution of this equation is given by:

\[
V(t) = \sum_{i=1}^{3} \left\{ \left[ \frac{\Theta_i (-2\omega_i \cos (\omega_i t + c_i) + \sin (\omega_i t + c_i) p^2 - \sin (\omega_i t + c_i) \omega_i^2)}{4\omega_i^2 + p^4 - 2p^2\omega_i^2} \\
- \frac{1}{2} \left[ (n^2 - p^2)^{\frac{1}{2}} \omega_i^2 + p^2 (n^2 - p^2)^{\frac{1}{2}} \sin c_i - 2\omega_i n^2 \cos c_i \\
+ p^2 n \sin c_i - 2\omega_i n (n^2 - p^2)^{\frac{1}{2}} \cos c_i - \omega_i^3 \cos c_i + \omega_i n \sin c_i \\
+ \omega_i p^2 \cos c_i \right] e^{\left(-\left(\frac{\omega_i}{p^2 + \omega_i n}\right)^{\frac{1}{2}} \right)} \right\} \left( (n^2 - p^2)^{\frac{1}{2}} (4\omega_i^2 + p^4 - 2p^2\omega_i^2 + \omega_i^4) \right) \right\} \\
+ \frac{1}{2} \sum_{i=1}^{3} \left[ \left[ (n^2 - p^2)^{\frac{1}{2}} \sin c_i + n p^2 \sin c_i + \omega_i \cos c_i p^2 \\
+ \omega_i^2 n \sin c_i - 2\omega_i n^2 \cos c_i + 2\omega_i n (n^2 - p^2)^{\frac{1}{2}} \cos c_i \\
+ \omega_i^2 (n^2 - p^2)^{\frac{1}{2}} \sin c_i - \omega_i^3 \cos c_i \right] e^{\left(-\left(\frac{\omega_i}{p^2 + \omega_i n}\right)^{\frac{1}{2}} \right)} \left( (n^2 - p^2)^{\frac{1}{2}} (4\omega_i^2 + p^4 - 2p^2\omega_i^2 + \omega_i^4) \right) \right]. \quad (44)
\]

We will ignore the exponential terms and perform parameters identification by matching the above expression for \(V(t)\) to the clinical data, shown in Fig. 2. The matching is illustrated in Fig. 5, wherein the first- and second-order differential equation solutions for \(V(t)\) are depicted. The computed values of the model parameters are also shown in the table below the figure. Further, the first- and second-order model values of \(R\) and \(C\) are compared in the table.

Let us compare these values with those obtained by simulating the first-order model to the clinical data.

7 Two-compartmental linear model

Now, it is possible that only one of the two lungs (or lung lobes) may be diseased. So, let us develop a procedure to distinguish between the normal lung and the pathological lung? We hence employ the 2-compartment model (based on our first-order differential equation of lung ventilatory function) to solve the problem of a two-lung model (schematized in Fig. 6).

For this purpose we make the subject breath at different values of frequency (\(\omega\)), and monitor the total lung pressure \(P^L_i(t)\) (i.e., \(P_{1i}^L\) and \(P_{2i}^L\)) and total lung volume \(V_i^L(t)\). Correspondingly, we have \(P^R_i(t)\) and \(V^R_i(t)\) for the left and right lungs, respectively. The governing equations will be as follows
First order model  Second order model

\[
\begin{align*}
R \text{ [cm H}_2\text{O l}^{-1} \text{s}] & \quad 2.28 & \quad 3.44 \\
C \text{ [l/cm H}_2\text{O]} & \quad 0.21 & \quad 0.85 \\
M^* \text{ [cm H}_2\text{O l}^{-1} \text{s}^2] & \quad 3.02 \\
\alpha \left( = \frac{R}{M^*} \right) \text{ [s}^{-1}] & \quad 1.14 \\
p^2 \left( = \frac{1}{CM^*} \right) \text{ [s}^{-2}] & \quad 0.39
\end{align*}
\]

Figure 5: Results of single compartmental model based on differentiate equation formulation, compared with the first-order differential equation model.

(refer to Fig. 3)

\[
\begin{align*}
p^T = p^l = p^R, \quad \text{i.e. } p^T_1 = p^l_1 = p^R_1 & \quad \& \quad p^T_2 = p^l_2 = p^R_2 \\
V^T = V^l + V^r
\end{align*}
\]

(45) (46)

corresponding to \( \omega \); wherein

(i) \( V^l(t) = f(\omega, R^l, C^l, p^T(t)) \) \hspace{1cm} (47)

(ii) \( V^R(t) = f(\omega, R^R, C^R, p^T(t)) \). \hspace{1cm} (48)

In these equations (20),

(i) the variables \( \omega, p^T(t), V^T(t) \) are deemed to be known, i.e. monitored.

(ii) the parameters \( R^l, C^l, \text{ and } R^R, C^R \) are to be evaluated.
Using the first-order differential equation model, (presented in sect. 2, as given by eqn. (6) or (14):

$$V(t) = \sum_{i=1}^{3} \frac{(P_1 C_a) \left[ -\sin(\omega t + c_i) - \omega t^2 \cos(\omega t + c_i) \right]}{(1 + \omega t^2)}.$$  \( (49) \)

We put down the expression for \( V^T(t) = V^L(C_L, \tau_L) + V^R(C_R, \tau_R) \), match it with the volume data (using a parameter-identification technique (software), to obtain the values of \( (C_L, \tau_L) \) and \( (C_R, \tau_R) \) by means of which we can differentially diagnose left and right lung lobes' ventilatory capacities and associated disorders (or diseases).

### 7.1 Two compartmental model using first-order ventilatory model

Using eqn. (6) without the exponential term, we put down the expression for the total lung volume equal to the sum of left and right lung volumes, as follows:

$$V(t) = \sum_{i=1}^{3} \frac{P_i C_L \left[ \sin(\omega t + c_i) - \omega t^2 \cos(\omega t + c_i) \right]}{(1 + \omega t^2)}$$

$$+ \sum_{i=1}^{3} \frac{P_i C_R \left[ \sin(\omega t + c_i) - \omega t^2 \cos(\omega t + c_i) \right]}{(1 + \omega t^2)}.$$  \( (50) \)
Two compartmental model

First order model

<table>
<thead>
<tr>
<th></th>
<th>Left lung</th>
<th>Right lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R$ [cmH$_2$O l$^{-1}$ s]</td>
<td>1.137</td>
<td>1.137</td>
</tr>
<tr>
<td>$C$ [l/cmH$_2$O]</td>
<td>0.1066</td>
<td>0.0533</td>
</tr>
<tr>
<td>$VTL_1$</td>
<td>2.115</td>
<td>0.5289</td>
</tr>
<tr>
<td>$VTL_2$</td>
<td>0.2198</td>
<td>1.0320</td>
</tr>
</tbody>
</table>

Figure 7: Results of the two-compartment model, based on the first-order differential equation model. Based on our assumption of $TV^L/TV^R = 0.92$ we have $TV^L = 0.48 \times 0.48 = 0.2304$ l and $TV^R = 0.52 \times 0.48 = 0.2496$ l.

wherein, for the clinical data, we have:

\[
\begin{align*}
    P_1 &= 1.581 \ \text{cmH}_2\text{O} & P_2 &= -5.534 \ \text{cmH}_2\text{O} & P_3 &= 0.5523 \ \text{cmH}_2\text{O} \\
    \omega_1 &= 1.214 \ \text{rad/s} & \omega_2 &= 0.001414 \ \text{rad/s} & \omega_3 &= 2.401 \ \text{rad/s} \\
    c_1 &= -0.3132 \ \text{rad} & c_2 &= 3.297 \ \text{rad} & c_3 &= -2.381 \ \text{rad}.
\end{align*}
\]

We further assume that the ratio of $TV$ of the left lung to that of the right lung is 0.92.

Now, in order to develop a measure of confidence in our analysis, we first generate the total lung-volume data by assuming different values of $C$ and $R$ for left
Two compartmental model

First order model

<table>
<thead>
<tr>
<th></th>
<th>Left lung</th>
<th>Right lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R$ [cmH$_2$O/l/s]</td>
<td>1.138</td>
<td>2.276</td>
</tr>
<tr>
<td>$C$ [l/cmH$_2$O]</td>
<td>0.1066</td>
<td>0.1066</td>
</tr>
<tr>
<td>$VTL_1$</td>
<td>2.1192</td>
<td>8.4766</td>
</tr>
<tr>
<td>$VTL_2$</td>
<td>0.3553</td>
<td>0.8341</td>
</tr>
</tbody>
</table>

Figure 8: Results of the two-compartment model, based on the first-order differential equation model. Based on our assumption of $TV^L/TV^R = 0.92$ we have $TV^L = 0.48 \times 0.61 = 0.2928$ l and $TV^R = 0.52 \times 0.61 = 0.3172$ l.

and right lung lobes. We then use eqn. (50) along with the above data on pressure and frequency, to generate the total lung-volume data. We adopt this generated lung volume data as the clinical-volume data.

We now make our volume-solution expression (eqn. (50)) match this generated clinical-volume data, by means of the parameter-identification procedures, to evaluate $C$ and $R$ for the left and right lung-lobes and hence $VTL_1$ and $VTL_2$ (eqns. (11) and (18)) for these lobes. Based on the values of $VTL_1$ and $VTL_2$, we can differentially diagnose the left and right lung lobes.
7.1.1 Stiff right lung (with compliance problems)
We now simulate a normal left lung and stiff right lung, represented by:

\[ R^L = R^R = 1.14 \text{ cmH}_2\text{O} \text{ l}^{-1} \text{ s} \text{ and } C^L = 0.11, \ C^R = 0.051/\text{cmH}_2\text{O}. \]  (51)

Substituting these parametric values into eqn. (50), we generate the total lung-volume data, as illustrated in Fig. 7.

Now our clinical data for this two-compartment model comprises of the pressure data of Fig. 2 and the generated volume data of Fig. 6. For this clinical data, we match the volume solution given by eqn. (50) with the generated volume data, illustrated in Fig. 7, and carry our parameter identification. The computed values of \( R \) and \( C \), listed in the table of Fig. 7, are in close agreement with the initially assumed parametric values of eqn. (51). This lends credibility to our model and to our use of parameter-identification method.

Now for differential diagnosis, we compute the lung-ventilatory indices, as shown in the table in Fig. 7.

7.1.2 Right lung with \( R \) problems
Now, we simulate a lung with an obstructive right lung, as represented by:

\[ R^L = 1.14 \text{ and } R^R = 2.28 \text{ cmH}_2\text{O l}^{-1} \text{ s} \text{ and } C_L = C_R = 0.11 \text{ l/cmH}_2\text{O}. \]  (52)

As in the case of the stiff right lung, we first generate the lung-volume data for the above values of compliance and resistances. We then match the total lung-volume solution given by eqn. (50) with the generated lung-volume data, and compute the compliance and flow resistance values of the right and left lung. These are tabulated in Fig. 8, and found to have good correspondence with the assumed values of eqn. (52).
Compliance (C) 1, 4, 6, 9, 10, 23, 26
  nonlinear compliance 12, 14
  \( C_u \) 4
Resistance (R) 4, 6, 10, 26
  resistance-to-airflow 1, 6
  \( R_a \) 4
lung-ventilatory index (VTI) 1, 7
second order differential equation 1
Second-Order model for Single-compartment Lung Model 16
Two-compartmental Linear Model 21
  Using First Order Ventilatory Model 22
  Stiff Right Lung (with compliance problems) 23
  Right Lung with R problems 25
ventilation model 1, 2, 22
Work of Breathing (WOB) 15
### TABLE 1: Nomenclature

<table>
<thead>
<tr>
<th>SYMBOL</th>
<th>MEANING</th>
<th>UNITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C$</td>
<td>Lung Compliance</td>
<td>$(cmH_2O)^{-1}$</td>
</tr>
<tr>
<td>$C_a$</td>
<td>Average Lung Compliance</td>
<td>$(cmH_2O)^{-1}$</td>
</tr>
<tr>
<td>$R$</td>
<td>Lung air-flow resistance</td>
<td>$cmH_2Osl^{-1}$</td>
</tr>
<tr>
<td>$R_a$</td>
<td>Average Lung air-flow resistance</td>
<td>$cmH_2Osl^{-1}$</td>
</tr>
</tbody>
</table>

### TABLE 2: ABBREVIATIONS

<table>
<thead>
<tr>
<th>ABBREVIATION</th>
<th>MEANING</th>
</tr>
</thead>
<tbody>
<tr>
<td>$VTI$</td>
<td>Lung-Ventilatory Index</td>
</tr>
<tr>
<td>$WOB$</td>
<td>Work of Breathing</td>
</tr>
</tbody>
</table>
Abstract — The primary function of the lung is to (i) oxygenate the blood and thereby provide oxygen to the cells for metabolization purposes, and (ii) to remove the $CO_2$ produced by the tissues from the pulmonary blood. Herein, we provide a noninvasive methodology to asses the capacity of the lung to oxygenate the pulmonary capillary blood and to reduce its $CO_2$ concentration. For this purpose, we analyze the compositions of the inspired and expired air per breath, and therefrom compute the metabolic $O_2$ consumption rate ($\dot{V}_{O_2}$) and $CO_2$ production rate ($\dot{V}_{CO_2}$). Next we compute the cardiac out (CO) as 

$$CO = \dot{V}_{O_2}(C_{O_2}^{AB} - C_{O_2}^{VB})$$.

We have derived the expressions for diffusion coefficients (i) $D_{O_2}$ in terms of $\dot{V}_{O_2}$ and the alveolar and venous partial pressures, $P_{O_2}^{al}$ and $P_{O_2}^{vb}$ and (ii) $D_{CO_2}$ in terms of $\dot{V}_{CO_2}$, $P_{CO_2}^{al}$ and $P_{CO_2}^{vb}$. The coefficients $D_{O_2}$ and $D_{CO_2}$ represent the gas transfer capacity of the lung.

The paper provides a case study for the determination of $Q$, $D_{O_2}$ and $D_{CO_2}$. The derived information of $D_{O_2}$ and $D_{CO_2}$ as well as of $O_2$ and $CO_2$ metabolic rates can be of considerable clinical use including for SARS assessment.

Keywords — gas exchange, $O_2$ metabolic-rates, $CO_2$ metabolic-rates, diffusion coefficients $D_{O_2}$, diffusion coefficients $D_{CO_2}$, blood flow rate

I. INTRODUCTION

The lung functional performance is characterized by (i) its ventilatory capacity, to bring air (and hence $O_2$) into the alveoli, and (ii) its capacity to transfer $O_2$ and $CO_2$ into and from the pulmonary capillary bed. Hence, the $O_2$ and $CO_2$ diffusion coefficients $D_{O_2}$ and $D_{CO_2}$ as well as the $O_2$ consumption-rate and the $CO_2$ production rate represent the lung performance indices. In this paper, we are demonstrating their evaluations.

II. LUNG GAS-EXCHANGED MODEL

Fig. 1 schematically illustrates the gas-exchange between the lung alveolus and the pulmonary capillary-vasculature. Based on our earlier work [1, 2] the gas exchange between the alveolar air and pulmonary capillary blood is represented by the following $O_2$ and $CO_2$ conservation equations and Fig. 2.

$$\dot{Q}^{VE}C_{O_2}^{VE} = \dot{Q}^{AE}C_{O_2}^{AE} + \dot{V}_{O_2}$$ (from the alveolar air to capillary blood)

$$\dot{Q}^{VE}C_{CO_2}^{VE} = \dot{Q}^{AE}C_{CO_2}^{AE} - \dot{V}_{CO_2}$$

wherein

(i) $\dot{Q}^{AB}$ and $\dot{Q}^{VB}$ are arterial and venous blood flow-rates;

(ii) $P_{O_2}^{al}$ and $P_{O_2}^{cap}$ are the alveolar and capillary $O_2$ partial pressures

(iii) $P_{CO_2}^{al}$ and $P_{CO_2}^{cap}$ are the alveolar and capillary $CO_2$ partial pressure.

(iv) $D_{O_2}$ and $D_{CO_2}$ are the $O_2$ and $CO_2$ diffusion coefficients

(v) $\Delta P_{O_2}^{al}$ = average of $(P_{O_2}^{al} - P_{O_2}^{OP})$ over the capillary length;

$\Delta P_{CO_2}^{al}$ = average of $(P_{CO_2}^{al} - P_{CO_2}^{OP})$ over the capillary length.

Determination of Pulmonary Gases ($O_2$ & $CO_2$) Metabolic-Rates and Lung Diffusion Coefficients Based on the Inspired and Expired Air Compositions and Venous Blood and Gas Concentration

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0-7803-8740-6/05/$20.00 ©2005 IEEE.
(vi) \( P_{O_2}^{cap} = P_{O_2}^{PRB} \) (\( O_2 \) concentration of the pre-oxygenated blood) = \( P_{O_2} \)

(vii) \( P_{CO_2}^{cap} = P_{CO_2}^{PRB} \) (\( CO_2 \) concentration of the pre-oxygenated blood) = \( P_{CO_2}^{VE} \)

(viii) \( V_{O_2}^\circ \) is the \( O_2 \) transfer rate from alveolar air to capillary blood (= \( O_2 \) consumption rate), \( V_{CO_2}^\circ \) is the \( CO_2 \) transfer-rate from capillary blood to alveolar air (= \( CO_2 \) production rate).

Now we can equate the arterial and venous blood flow rates, as
\[
Q^{AE} = Q^{AB} = Q^{VE} = Q^{AV} = \frac{(SV)/(EP)}{60}
\]
SV, EP and CO being the stroke-volume, ejection-period and cardiac-output respectively.

\[
D_{O_2} = \frac{Q(O_{2av}^{VE} - O_{2av}^{AE})}{\Delta P_{O_2}^{av}} = \frac{Q(O_{2av}^{AB} - O_{2av}^{VB})}{\Delta P_{O_2}^{av}} = \frac{\circ V_{O_2}}{\Delta P_{O_2}^{av}} (3)
\]

\[
D_{CO_2} = \frac{Q(CO_{2av}^{VE} - CO_{2av}^{AB})}{\Delta P_{CO_2}^{av}} = \frac{\circ V_{CO_2}}{\Delta P_{CO_2}^{av}} (4)
\]

Fig. 1: Process of oxygenating the venous blood. The low oxygen (\( O_2 \)) concentration Red Blood Cell (RBC) is shown in dark blue. As it travels down the artery towards the venous end, the \( O_2 \) concentration increases. After the distance \( L \), its \( O_2 \) has increased to 0.18 from the initial concentration of 0.13.

From equations (1) and (2):

Fig. 2: Schematic of blood gas concentration in the Pulmonary Capillary. (Adapted from references [3] & [4])

III. CLINICAL DATA

The monitored data consists of inspired and expired air gas compositions (TABLE 1) and \( O_2 \) and \( CO_2 \) concentrations of arterial blood and venous blood (TABLE 2).

TABLE 1: Air Composition Analysis. Inspired and expired air composition and partial pressures are monitored. Assumed Breathing Rate (BR) = 12 breaths/min. Assumed \( P_{H_2O} \) at 37°C = 47 mmHg.

<table>
<thead>
<tr>
<th>Respiratory gases</th>
<th>Atmospheric Air</th>
<th>ml/%</th>
<th>Expired Air</th>
<th>ml/%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmHg</td>
<td></td>
<td>mmHg</td>
<td></td>
</tr>
<tr>
<td>( N_2 )</td>
<td>597</td>
<td>78.55%</td>
<td>566</td>
<td>74.5%</td>
</tr>
<tr>
<td>( O_2 )</td>
<td>159</td>
<td>104.2</td>
<td>120</td>
<td>80.6</td>
</tr>
<tr>
<td>( CO_2 )</td>
<td>0.3</td>
<td>0.04%</td>
<td>27</td>
<td>3.6%</td>
</tr>
<tr>
<td>( H_2O )</td>
<td>3.7</td>
<td>2.5%</td>
<td>47</td>
<td>32.6</td>
</tr>
<tr>
<td></td>
<td>760</td>
<td>100%</td>
<td>760</td>
<td>100%</td>
</tr>
</tbody>
</table>

TABLE 2: Blood Gas Analysis. The monitored blood \( O_2 \) and \( CO_2 \) concentration.

\( C_{O_2} \) of venous blood \( (C_{O_2}^{vb}) \) = 0.13
\( C_{O_2} \) of arterial blood \( (C_{O_2}^{ab}) \) = 0.18
\( C_{CO_2} \) of venous blood \( (C_{CO_2}^{vb}) \) = 0.56
\( C_{CO_2} \) of arterial blood \( (C_{CO_2}^{ab}) \) = 0.52
IV. EXPRESSIONS FOR $D_O^O$ AND $D_C^{CO_2}$

If we want to evaluate the diffusion coefficients $D_O^O$ and $D_C^{CO_2}$, we need to also express $P_{O^2}^{al}$, $P_{O^2}^{cap}$ and $P_{CO_2}^{al}$, $P_{CO_2}^{cap}$ in terms of monitorable quantities [1 & 2].

(i) Alveolar $P_{O^2}^{al}$ can be expressed in terms of $V$ (the ventilation rate) and $V_{O^2}$ (the $O^2$ consumption rate).

$$P_{O^2}^{al} = 140 \left[ 1 - e^{-4.18 V/V_{O^2}} \right]$$

wherein the normalized ventilation rate

$$V^* = \frac{V}{V_m} = \frac{V}{60}$$

litres/min, is the consumption rate (in litres/min).

(ii) Alveolar $P_{CO_2}^{al}$ can be expressed in terms of $V$ and $V_{O^2}$.

$$P_{CO_2}^{al} = 107.18e^{-2.19 V/V_{CO_2}}$$

wherein $V_{CO_2}$ is the $CO_2$ production rate (in liters/min).

(iii) Blood $P_{O^2}^{al}$ can be obtained in terms of blood $C_{O^2}$, from the $O^2$ disassociation curve.

$$P_{O^2}^{al} = 30.5 \ln \left[ \frac{0.2}{0.2 - C_{O^2}^{al}} \right]$$

(iv) Blood $P_{CO_2}^{al}$ can be obtained in terms of $C_{CO_2}^{B}$, from the $CO_2$ disassociation curve.

$$P_{CO_2}^{al} = 37.94 \ln \left[ \frac{0.8}{0.8 - C_{CO_2}^{al}} \right]$$

Now, $\Delta P_{O^2} = (P_{O^2}^{al} - P_{O^2}^{Cap}) = P_{O^2}^{al} - P_{O^2}^{al}$ and $\Delta P_{CO_2} = (P_{CO_2}^{B} - P_{CO_2}^{al})$ vary along the capillary bed. Based on [3], we have:

$$\Delta P_{O^2}^{al} = 0.185 \Delta P_{O^2}^{max}$$

$$\Delta P_{CO_2}^{al} = 0.1 \Delta P_{CO_2}^{max}$$

V. EVALUATING OF $O^2$ AND $CO_2$ METABOLIC RATES AND CARDIAC OUTPUT

From monitored data of inspired-exhaled gas compositions, in TABLE 1:

$$O^2$$ consumption rate, $\dot{V}_{O^2} = BR(\text{Inspired } O^2 - \text{Expired } O^2) = 12(104.2 - 80.6) = 283.2 \text{ ml/min}$$

$$CO_2$$ consumption rate, $\dot{V}_{CO_2} = BR(\text{Expired } CO_2 - \text{Inspired } CO_2) = 12(19.1 - 0.2) = 226.8 \text{ ml/min}$$

From monitored $O^2$ and $CO_2$ concentrations of arterial and venous blood, in TABLE 2:

$$\dot{V}_{O^2} = Q(C_{O^2}^{al} - C_{O^2}^{Cap}) = 283.2 \text{ ml/min}$$

where $Q$=blood flow rate=cardiac output

VI. EVALUATING OF THE LUNG DIFFUSION COEFFICIENTS $D_O^O$ AND $D_C^{CO_2}$

From equation (7) and TABLE 2 ($C_{O^2}^{Cap} = 0.13$), we get for venous blood @ arterial end of the pulmonary capillary

$$D_O^O = \frac{V_{O^2}^{al}}{0.185\Delta P_{O^2}^{al} - P_{O^2}^{al}}$$

$$D_C^{CO_2} = \frac{V_{CO_2}^{al}}{0.14\Delta P_{CO_2}^{al} - P_{CO_2}^{al}}$$

From equation (8) and TABLE 2 ($C_{CO_2}^{B} = 0.56$), we get for $P_{CO_2}^{al}$ (venous blood @ arterial end of the pulmonary capillary)

$$P_{CO_2}^{al} = 30.5 \ln \left[ \frac{0.2}{0.2 - C_{CO_2}^{B}} \right]$$

$$= 30.5 \ln \left[ \frac{0.2}{0.2 - 0.13} \right]$$

$$= 32.02 \text{ mmHg}$$

From equation (7) and TABLE 2 ($C_{O^2}^{Cap} = 0.13$), we get for $P_{O^2}^{al}$ (venous blood @ arterial end of the pulmonary capillary)

$$P_{O^2}^{al} = 30.5 \ln \left[ \frac{0.2}{0.2 - C_{O^2}^{B}} \right]$$

$$= 30.5 \ln \left[ \frac{0.2}{0.2 - 0.13} \right]$$

$$= 32.02 \text{ mmHg}$$
\[ P_{CO_2}^{al} = 37.94 \ln \left( \frac{0.8}{0.8 - C_T^{TB}} \right) \]
\[ = 37.94 \ln \left( \frac{0.8}{0.8 - 0.56} \right) \]
\[ = 45.68 \text{ mmHg} \quad (16) \]

Also, from equation (5) and TABLE 1 \( (V^* = 0.1) \), we get:

\[ P_{O_2}^{al} = 140 \left[ 1 - e^{-4.18 \frac{V^*/V_{O_2}}{}^* \left[ 0.1 / 0.2832 \right]} \right] \]
\[ = 140 \left[ 1 - e^{-4.18 \left[ 0.1 / 0.2832 \right]} \right] = 108 \text{ mmHg} \quad (17) \]

Hence, from equations (9, 15 & 17), we get:

\[ \Delta P_{av}^{O_2} = 0.185 \times (108 - 32.02) = 14.06 \text{ mmHg} \quad (18) \]

Finally, from equations (11) and (18), we get:

\[ D_{O_2} = \frac{V_{O_2}^{o}}{\Delta P_{av}^{O_2}} = \frac{283.2 \text{ ml/min}}{14.06 \text{ mmHg}} \]
\[ = 20.14 \text{ ml/min}^{-1} \text{ mmHg}^{-1} \quad (19) \]

Then from equation (6), TABLE 1 \( (V = 0.1) \), and equation (12) we get:

\[ P_{CO_2}^{al} = 107.18 e^{-2.19 \frac{V^*/V_{CO_2}}{}} \]
\[ = 107.18 e^{-2.19 \left[ 0.1 / 0.2268 \right]} = 40.81 \text{ mmHg} \quad (20) \]

Hence, from equations (10, 16 & 20), we get:

\[ \Delta P_{av}^{CO_2} = 0.1 \times (45.68 - 40.81) = 0.487 \text{ mmHg} \quad (21) \]

Finally, from equations (12 & 21), we get:

\[ D_{CO_2} = \frac{V_{CO_2}^{o}}{\Delta P_{av}^{CO_2}} = \frac{226.8 \text{ ml/min}}{0.487 \text{ mmHg}} \]
\[ = 465.71 \text{ ml/min}^{-1} \text{ mmHg}^{-1} \quad (22) \]

VII. CONCLUSION

We have demonstrated a noninvasive clinical procedure

- for obtaining (i) \( O_2 \) consumption rate and \( CO_2 \) production rate, (ii) cardiac output, \( Q \), (iii) and lung diffusion capacities for \( O_2 \) and \( CO_2 \).
- from inhaled and exhaled air composition analysis and blood-gas analysis.

This work could have application to SARS testing and evaluation.

REFERENCES

Quantitation of Renal Function Based on Two-Compartmental Modeling of Renal Pelvis

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⁴Department of Software and Networks, RMIT, Australia

Abstract— The primary functions of the kidney are: (i) to get rid of the body waste materials that are either ingested or produced by metabolism, and (ii) to control the volume and composition of the body fluids. Herein, we provide a noninvasive methodology to assess physiological function of the kidneys. For this purpose, we analyze the renograms with 2-compartmental modelling of the kidney-renal outflow system, and therefrom compute the amount of flow of renal radionuclide into and out of the renal pelvis compartment.

The derived information of uptake \(\frac{\mu C}{A}\) and washout \(\left(e^{-\frac{t}{2\nu^2}} \sinh \alpha t\right)\) rates can be of considerable use. The paper provides a number of case studies for the verification of the derived system governing equations against clinical renograms.

Keywords— Renal outflow obstruction, renal function, glomerular filtration rate, GFR

I. INTRODUCTION

The kidney functional performance is characterized by (i) its filtering capacity, getting rid the body waste materials that are either ingested or produced by metabolism, and (ii) control the volume and composition of the body fluids. Renogram studies have been used for the assessment of renal function for many years [1, 2]. Mathematical modelling has been performed for the kidneys, such as one-compartment model of clearance of tracer [3,4]. However, modeling of the tracer transport between renal parenchyma pool compartment and renal pelvis compartment; derivation of the governing equations for renogram curves has not been reported. Here, we note that the tracer uptake and washout rates can represent the performance indices. In this paper, we evaluate these rates and demonstrate their clinical relevance renogram data.

II. RENAL PELVIS TWO-COMPARTMENTAL MODEL

Fig. 1: illustrates the region of interest (ROI) and we have derived the compartmental model for renal pelvis and shown in Fig. 2.

\[ G_1 \]: Tracer mass in the chamber 1 (renal parenchyma) in Counts.
\[ G_2 \]: Tracer mass in the chamber 2 (renal pelvis) in Counts.
\[ C_1 \]: Concentration of tracer in the chamber 1 in Counts/dL.
\[ C_2 \]: Concentration of tracer in the chamber 2 in Counts/dL.
\[ V_1 \]: Volume of chamber 1, renal parenchyma in dL.
\[ V_2 \]: Volume of chamber 2, renal pelvis in dL.
\[ I(t) \]: Tracer input function in Counts/sec.
\[ F(t) \]: Blood Flow from chamber 1 to chamber 2 in dL/sec.
\[ U(t) \]: Urine outflow in dL/sec.

Fig. 1: Control volume around the renal pelvis area.

Fig. 2: The derived two-compartmental renal model.
III. DERIVATION and PHYSIOLOGICAL SIGNIFICANCE of MODELING SOLUTIONS

From Fig. 2, we derive the following:

$$\frac{dG_1}{dt} = -FC_1 + I(t), \text{ for chamber 1} \quad (1)$$

$$\frac{dG_2}{dt} = FC_1 - C_2 U(t), \text{ for chamber 2} \quad (2)$$

where (i) $G_1 = C_1V_1$ represents the tracer amount in chamber 1, and (ii) $G_2 = C_2V_2$ represents the tracer amount in chamber 2.

In physiological studies of kidney function and urine outflow status (renography), the input function is a tracer bolus administered over a short period of time. Compared to the entire duration of the renal dynamics, this bolus injection of tracer can be approximated by an impulse function (Dirac’s delta function). In the following derivation, whenever $I(t)$ appears it will be assumed equal to $I\delta(t)$.

We assume that the compartmental volumes $V_1$ and $V_2$ are constants (which they generally are), and the urinary flow rate $U$ as unknown constant (urine flowing out of the kidney into the ureters is physiologically continuous and constant with time, unless there are changes in body fluid status). Here, we are only performing an intra-renal analysis for obstruction to the outflow, we have from (1) and (2):

$$\frac{V_1 dC_1}{dt} = -FC_1 + I(t) \quad (3)$$

$$\frac{V_2 dC_2}{dt} = FC_1 - C_2 U \quad (4)$$

By differentiating and combining (3) and (4), we arrive at:

$$V_2 \dot{C}_2 = \left(\frac{F}{V_1}\right) I(t) - \beta \dot{C}_2 - \gamma C_2$$

or,

$$V_2 \dot{C}_2 + \beta \dot{C}_2 + \gamma C_2 = \left(\frac{F}{V_1}\right) I\delta(t) \quad (5)$$

where:

$$\frac{FV_2}{V_1} + U = \beta, \quad \left(\frac{FU}{V_1}\right) = \gamma \quad (6)$$

The equation (5) is a standard form of a linear second-order ordinary differential equation, with $I(t)$ as the unit impulse function. This is the governing differential equation for the behavior of tracer within the renal pelvicalyceal compartment.

Solution by Laplace transform method yields the following equations, given the initial conditions of $C(0)$ and $C'(0) = 0$.

$$L\{V_2 \dot{C} + \beta \dot{C} + \gamma C\} = L\left(\frac{F}{V_1}\right) I\delta(t)$$

$$\therefore \left(V_2 s^2 + \beta s + \gamma\right)C(s) = \left(\frac{F}{V_1}\right)$$

$$C_i(t) = C(t) = \left(\frac{F}{V_1}\right) \left(\frac{1}{s^2 + \frac{\beta}{V_2} s + \frac{\gamma}{V_2}}\right) = \left(\frac{F}{V_1}\right) \left(\frac{1}{\frac{\gamma - \beta^2}{V_2} + \frac{\beta^2}{4V_2^2}}\right)$$

Solving the above Laplace transform and taking care of the characteristics of the roots (which is now in standard form, by looking up standard tables), we obtain the results for the dynamic behavior of the tracer concentration in the renal pelvis for this physiological system. The term underneath the square root is the determinant of the behavior of the system with regards to whether there is underdamped, critical-damped or overdamped behaviour.

This term can be expressed as $\beta^2 - 4V_2\gamma$ and it yields a significant functional index for assessing the outflow status of the kidney. We will classify the observed physiological behaviours of renogram systems into underdamped, overdamped or critically damped systems based on the index, as follows:

**Case 1:**

If $\beta^2 - 4V_2\gamma < 0$, the condition is underdamping, and (7) yields the solution:

$$C(t) = \left(\frac{F}{V_1}\right) \left(\frac{1}{\frac{\gamma - \beta^2}{V_2} + \frac{\beta^2}{4V_2^2}}\right) e^{\frac{\beta}{2V_2^2}} \sin \left(\frac{\gamma - \beta^2}{V_2} \frac{t}{4V_2^2}\right) \quad (8)$$

As can be seen from equation (8), the terms which describe urine outflow and determine the shape of the tracer-concentration curve of the renogram during the tracer washout phase are the $e^{\frac{\beta}{2V_2^2}}$ and $\sin \left(\frac{\gamma - \beta^2}{V_2} \frac{t}{4V_2^2}\right)$. The important dynamic information captured in these two terms can be succinctly found in the physiological index that we have described. We will demonstrate the discriminatory nature of this index (which will be extracted as $A$) in section.
when we analyse correlation with actual renogram studies.

Equation (8) is a linear second-order ordinary differential equation, very similar to that of the linear oscillator with damping. In a functioning renal system, the characteristic oscillating-underdamped conditions do not exist.

Case 2:
Whenever there is outflow obstruction, the key term
\[ \beta^2 - 4V_2 \gamma = \left( \frac{FV_2}{V_1} + U \right)^2 - 4V_2 \left( \frac{FU}{V_1} \right) = \left( \frac{FV_2}{V_1} - U \right)^2 > 0 \]
and the condition is overdamping. Then,
\[ C(t) = \left( \frac{F}{V_1V_2} \right) \left( \frac{1}{\gamma} \right) e^{\frac{\beta}{2V_2^2} t} \sinh \left( \frac{\gamma - \beta^2}{4V_2^2} t \right) \] (9)

We can express output segment of the tracer curve of compartment 2 looks different from that of the tracer input
\[ \beta^2 - 4V_2 \gamma = \left( \frac{FV_2}{V_1} + U \right)^2 - 4V_2 \left( \frac{FU}{V_1} \right) = \left( \frac{FV_2}{V_1} - U \right)^2 \]
so the key term actually reflects the rate of tracer input \((FC_i)\) minus the rate of tracer output \((UC_j)\).

Case 3:
In the normal case, most physiological systems are well-compensated, and hence the output are fairly similar, hence,
\[ \beta^2 - 4V_2 \gamma = \left( \frac{FV_2}{V_1} + U \right)^2 - 4V_2 \left( \frac{FU}{V_1} \right) = \left( \frac{FV_2}{V_1} - U \right)^2 = 0 \]
In other words, the renal system is critically damped.

The governing equations for this will be
\[ C(t) = \left( \frac{F}{V_1V_2} \right) t e^{\frac{\beta}{2V_2} t} \] (10)

IV. CLINICAL DATA & EVALUATION

We will demonstrate and verify the application of our models using the renograms obtained from the Nuclear Medicine and PET Department. The radionuclide used are 99mTc-DTPA and 99mTc-MAG3. The degree of match with the governing equations is based on the area under the left and right kidney curves against the clinical curves between 60 and 120 seconds.

Model Application:
We will first digitalize and normalized the renograms. Next, we will perform parameters identification and obtain the system parameters: \(k, A, \beta\) and \(V_2\). We will only accept the results of the best fit.

![Fig. 3: Clinical renograms of volunteer coded Patient 7. Note that the \((Q_R-R_R)\) segment of the tracer curve for the right kidney is similar to the \((P_R-Q_R)\) segment and demonstrates good outflow-rate compared to the \((Q_L-R_L)\) segment of the obstructive curve for the left kidney.](image)

<table>
<thead>
<tr>
<th>Identity</th>
<th>% Clinical Area Under the curves between 60 to 120 sec.</th>
<th>% Calculated Area Under the curves between 60 to 120 sec</th>
<th>% Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>Patient 7</td>
<td>44</td>
<td>56</td>
<td>43.87</td>
</tr>
<tr>
<td>Patient 8</td>
<td>50</td>
<td>50</td>
<td>49.69</td>
</tr>
</tbody>
</table>
V. RESULTS

We have performed parametric identification for equations (9) and (10) using MatLab 7. The following are the best fitted results for patients 7 & 8.

TABLE 1 shows that the area under the curves from the simulation matches that of the clinical with an error less than 1%.

VI. CONCLUSION

We have demonstrated modeling of kidney-renal outflow tract compartments with derivation of the governing equations from second-order differential equations and assessed the clinical relevance with comparison with clinical renogram studies.

REFERENCES


Biofeedback as validated by EEG/QEEG

ERAS 2002
22 Nov 2002

By
Loh Kah Meng and Prof Ghista

Introduction

- Biofeedback entails providing a person with information about his own on-going physiological processes through parameters such as EEG or QEEG, ECG, EMG, etc.
Types of Biofeedback

- There are two types of biofeedback systems: Volitional Feedback Systems (VBFS) and Non-Volitional Feedback Systems (NVFS).

The VBFS require conscious effort to attain a desired physiological state. They hence cannot be used in the case of subjects who have mental dysfunction or mentally depressed.

- The NVFS do not require subjects to be conscious.
Objectives

- The NVFS presented in this paper is designed for rehabilitation purpose. We will also present to you some results that we have gathered in our experiments with subjects with eyes opened with aids and eyes closed with and without aids.

International 10-20-2. EEGs are taken at 19 different channels to give us spatial & temporal information.
The Lexicor system that our experiments were conducted with.

Screen snapshot of the EEG display
Screen shot of the QEEG

Experimental Results

<table>
<thead>
<tr>
<th>Subject</th>
<th>EEG 1</th>
<th>EEG 2</th>
<th>EEG 3</th>
<th>EEG 4</th>
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<tr>
<td>F7</td>
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<td>1.5</td>
<td>1.8</td>
<td>2.1</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Objective: Similar to experiment 1. This time for open-eyes, we have the psychological board. Each session is 10 minutes.

Location of experiment: INT RM 07-02-10

Name of subjects:

W [normal subject]

Notes:

1. Eyes Open: Subject does not focus on the psychological board.
2. Eyes Closed: Unattended
3. Eyes Closed, Warm Goggles with LCDs flashing at a constant frequency.
4. Alpha waves in units of μV^2 (mean power).
Experimental results of subjects. Note that alpha energies are greatest when eyes closed with the goggles active. The goggles are designed to flash at 10 Hz. It has been found that the Red super-bright LEDs are most efficient.

Results of V and W

Application of the Concept
Conclusions

- The above results have significant influence to the system we are designing for rehab purpose.
- The details will be elaborated later in our next coming presentation.

Thank You
Virtual Reality in Rehabilitation

ERAS 2002
22 Nov 2002
By
Loh Kah Meng and Prof Ghista

Introduction

- The use of Virtual Reality (VR) to enhance rehabilitation is a relatively new concept.
- The novel aspect of using VR as an evoked-psychological therapy for rehabilitation will cause a revolution in rehab technology.
Objectives

- In this paper we will discuss some of these concepts. There may be some ideas that could be obscure to some of the audience, so we elicit an open mind.

Concepts/Applications

- Firstly we would like to share with you the concept about stressed and relaxed mind. Next we would like to share with you how this concept can be incorporated into a rehabilitation system for spinal-cord injured patients.
Deformed Mind’s Transcendence into a high-conscious environment.

Evoked-Psychological Response to Initiate Rehabilitation Process

- When a person is under stress her/his mind is compressed and deformed as compared to a relaxed mind under a high consciousness level.
- This is especially so when the patients are undergoing long monotonous physical therapies without experiencing some definitive progress.
Then this self-induced frustration acts as a positive feedback, further bringing down the consciousness level.

Application of VR

- Our objective is to use VR to help conjure a curative and healthy environment, which can also bring her/him into a relaxed and higher consciousness level, which can be verified by examining the EEG alpha-wave energy-content. The amount of improvement is proportional to the increase in alpha wave density.
Spinal-Cord Injury Rehabilitation

- For Spinal Cord Injury (SCI) patients, the VR system will be designed to psychologically make the patient feel that the resected spinal cord reconnected, and thereby the associated physiologically disordered (such as bladder control, temperature regulation, etc) are also remedied.

- For sitting and lying-down, we can design a mattress, of skin-breathing synthetic material.
Spinal-Cord Injury Rehabilitation

- The mattress will be designed as a controllable pneumatic bed with turbulence generators.
- The waves will act as physiotherapists’ fingers, giving massage. The warm fluid with the massage can facilitate blood flow to the patient and reduce sustained-pressure bed-ridden related skin diseases.
SSREFS

- Additionally, a Sympathetic Signal-Reinforcing EEG Feedback System (SSREFS) will be designed to extract alpha signals and filter beta signals from the EEG. The extracted alpha signals can be fed into patient’s spinal cord, to stimulate cerebral-neuronal growth.

Conclusions

- For paraplegic patients, the VR would be employed to make the patient feel that she/he is ambulatory, and that autonomic system is reconnected and working, so that the patient can void independently and feel the outside temperature so the VR will help the patient develop a strong will power to be cured and adopt independent living mood.
Thank You
## Authors’ Index

<table>
<thead>
<tr>
<th>Name</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal A.</td>
<td>345, 361</td>
</tr>
<tr>
<td>Agarwal H.K.</td>
<td>125</td>
</tr>
<tr>
<td>Alini M.</td>
<td>33</td>
</tr>
<tr>
<td>Amis A.</td>
<td>185</td>
</tr>
<tr>
<td>Anand R. S.</td>
<td>369</td>
</tr>
<tr>
<td>Anantharaman V.</td>
<td>89, 440</td>
</tr>
<tr>
<td>Ang K.C.</td>
<td>385</td>
</tr>
<tr>
<td>Aziz A.</td>
<td>85</td>
</tr>
<tr>
<td>Aziz A.R.</td>
<td>328</td>
</tr>
<tr>
<td>Bockholt U.</td>
<td>25</td>
</tr>
<tr>
<td>Boey F.Y.C.</td>
<td>77</td>
</tr>
<tr>
<td>Cai Y.Y.</td>
<td>232</td>
</tr>
<tr>
<td>Cao J</td>
<td>373</td>
</tr>
<tr>
<td>Chai G.B.</td>
<td>278, 428</td>
</tr>
<tr>
<td>Chan K.L.</td>
<td>89, 217</td>
</tr>
<tr>
<td>Chan V.</td>
<td>42</td>
</tr>
<tr>
<td>Chan W.A.</td>
<td>77, 150</td>
</tr>
<tr>
<td>Chan Y.W.</td>
<td>217, 271</td>
</tr>
<tr>
<td>Chaudhari N.S.</td>
<td>228</td>
</tr>
<tr>
<td>Chen C.</td>
<td>209</td>
</tr>
<tr>
<td>Chen H.J.</td>
<td>93</td>
</tr>
<tr>
<td>Chen Q.</td>
<td>412</td>
</tr>
<tr>
<td>Cheng J.</td>
<td>420</td>
</tr>
<tr>
<td>Chew W.</td>
<td>213</td>
</tr>
<tr>
<td>Chia E.</td>
<td>469</td>
</tr>
<tr>
<td>Chia S.L.</td>
<td>33</td>
</tr>
<tr>
<td>Chian K.S.</td>
<td>51, 154</td>
</tr>
<tr>
<td>Chong A.</td>
<td>196</td>
</tr>
<tr>
<td>Chong C.</td>
<td>117</td>
</tr>
<tr>
<td>Chong C.K.</td>
<td>51</td>
</tr>
<tr>
<td>Chong V.</td>
<td>61</td>
</tr>
<tr>
<td>Chou S.M.</td>
<td>192, 196</td>
</tr>
<tr>
<td>Chu F.</td>
<td>244</td>
</tr>
<tr>
<td>Chua A.W.C.</td>
<td>213</td>
</tr>
<tr>
<td>Chua L.P.</td>
<td>154, 259, 263, 274, 278, 286, 289, 293</td>
</tr>
<tr>
<td>Chua T.</td>
<td>30, 49</td>
</tr>
<tr>
<td>Chuy Y.L.</td>
<td>30</td>
</tr>
<tr>
<td>Chutatape O.</td>
<td>424, 121</td>
</tr>
<tr>
<td>Dandapat S.</td>
<td>424</td>
</tr>
<tr>
<td>Dhar P.K.</td>
<td>221</td>
</tr>
<tr>
<td>Diao X.N.</td>
<td>240</td>
</tr>
<tr>
<td>Doraiswami R.</td>
<td>129</td>
</tr>
<tr>
<td>Drerup B.</td>
<td>202</td>
</tr>
<tr>
<td>Dutton A.Q.</td>
<td>27</td>
</tr>
<tr>
<td>Fan S.C.</td>
<td>412</td>
</tr>
<tr>
<td>Fang W.</td>
<td>89</td>
</tr>
<tr>
<td>Feng M.</td>
<td>77</td>
</tr>
<tr>
<td>Feng Z. Q.</td>
<td>42</td>
</tr>
<tr>
<td>Foo S.W.</td>
<td>54, 420</td>
</tr>
<tr>
<td>Fu C.Y.</td>
<td>141</td>
</tr>
<tr>
<td>Fung T.C.</td>
<td>51</td>
</tr>
<tr>
<td>Fuss F.K.</td>
<td>181, 312, 392, 397</td>
</tr>
<tr>
<td>Gao C.</td>
<td>224</td>
</tr>
<tr>
<td>Gao C.Q.</td>
<td>365</td>
</tr>
<tr>
<td>Garcia E.</td>
<td>145</td>
</tr>
<tr>
<td>Gogolewski K.</td>
<td>33</td>
</tr>
<tr>
<td>Goh J.</td>
<td>27</td>
</tr>
<tr>
<td>Goh J.C.H.</td>
<td>408</td>
</tr>
<tr>
<td>Goh K.W.</td>
<td>473</td>
</tr>
<tr>
<td>Gorna K.</td>
<td>33</td>
</tr>
<tr>
<td>Grant M.H.</td>
<td>38</td>
</tr>
<tr>
<td>Gu H.</td>
<td>213</td>
</tr>
<tr>
<td>Guo N. Q.</td>
<td>357</td>
</tr>
<tr>
<td>Gupta J.</td>
<td>125</td>
</tr>
<tr>
<td>Harris M.</td>
<td>81</td>
</tr>
<tr>
<td>Henderson C.</td>
<td>38</td>
</tr>
<tr>
<td>Heng P.A.</td>
<td>105</td>
</tr>
<tr>
<td>Hibbs A.</td>
<td>81</td>
</tr>
<tr>
<td>Ho K.L.I.</td>
<td>199</td>
</tr>
<tr>
<td>Hu Q</td>
<td>109</td>
</tr>
<tr>
<td>Hu Y.</td>
<td>170</td>
</tr>
<tr>
<td>Huang Z.</td>
<td>58</td>
</tr>
<tr>
<td>Hui J.P.P.</td>
<td>27</td>
</tr>
<tr>
<td>Indhumathil C.</td>
<td>232</td>
</tr>
<tr>
<td>Irawan R.</td>
<td>137, 141, 457</td>
</tr>
<tr>
<td>Ji W.F.</td>
<td>293</td>
</tr>
<tr>
<td>Joshi M.</td>
<td>133</td>
</tr>
<tr>
<td>Kannathal N.</td>
<td>444</td>
</tr>
<tr>
<td>Kho K.W.</td>
<td>81</td>
</tr>
<tr>
<td>Khong K.S.</td>
<td>416</td>
</tr>
<tr>
<td>Khong P.W.</td>
<td>469</td>
</tr>
<tr>
<td>Khoo J.</td>
<td>21</td>
</tr>
<tr>
<td>Kim E.H.</td>
<td>461</td>
</tr>
<tr>
<td>Kim J.J.</td>
<td>461</td>
</tr>
<tr>
<td>Kim M.T.</td>
<td>251</td>
</tr>
<tr>
<td>Kim W.</td>
<td>202, 301, 305, 324</td>
</tr>
<tr>
<td>Kim Y.</td>
<td>19, 339, 345, 361, 461</td>
</tr>
<tr>
<td>Koh E.C.Y.</td>
<td>389</td>
</tr>
<tr>
<td>Koh L.M.</td>
<td>353, 373</td>
</tr>
<tr>
<td>Krishna K.R.</td>
<td>416</td>
</tr>
<tr>
<td>Krishna V.</td>
<td>192</td>
</tr>
<tr>
<td>Kugean C.</td>
<td>473</td>
</tr>
<tr>
<td>Kurniawati T.</td>
<td>158</td>
</tr>
</tbody>
</table>

Proceedings of IBEC 2004 477
The papers presented in this Proceedings of the 1st International BioEngineering Conference 2004 in conjunction with 6th Annual NTU-SGH Biomedical Engineering Symposium 2004 “BioEngineering: Challenges and Innovations”, comprises of contributions made by the authors participating in the Conference. Therefore, the opinions expressed and contents provided herein reflect those of the authors and does not necessarily constitute endorsement by editors, organizers and sponsors of the Conference. All the papers have been peer-reviewed for the contents and their suitability for presentation at the Conference. The final papers sent by authors as Camera Ready Paper might have been modified and altered a bit to suit presentation and print style. The editors, organizers and sponsors are not liable to any claim whatsoever, arising out of the publication of these proceedings.

Editors: F. K. Fuss, S. L. Chia, S. S. Venkatraman, S. M. Krishnan, and B. Schmidt
# Conference Papers

## Invited Speakers

<table>
<thead>
<tr>
<th>Session</th>
<th>Title</th>
<th>Author(s)</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nanostructure Processing of Advanced Biomaterials (Ying J.)</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>Bioengineering, Technology Commercialization and Entrepreneurship (Kim Y.)</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>Esophageal Tissue Engineering (Ratner B.)</td>
<td></td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>A Case Study of Integrated Biomedical Engineering: A Novel Method for Creating an Automated Sutureless Anastomosis (Sharkawy A.)</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>Advances in Cancer Imaging (Khoo J.)</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>6</td>
<td>Tissue Engineering Heart Constructs using Bone Marrow Stem Cell (Wong P.)</td>
<td></td>
<td>--</td>
</tr>
<tr>
<td>7</td>
<td>Computational Technologies to Accelerate Biotech Innovation (Meier U.)</td>
<td></td>
<td>--</td>
</tr>
<tr>
<td>8</td>
<td>A new Approach to Protein Structure Prediction (Schroder H.)</td>
<td></td>
<td>22</td>
</tr>
<tr>
<td>9</td>
<td>Development of Microfluidic-Based Point-of-Care Diagnostic Systems (Yager P.)</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>10</td>
<td>Innovation in The Medical Device Industry: Development of Cypher - the first Drug-Eluting Stent (Mishra A.)</td>
<td></td>
<td>--</td>
</tr>
<tr>
<td>11</td>
<td>Heart Tissue Engineering (Ratner B.)</td>
<td></td>
<td>--</td>
</tr>
<tr>
<td>12</td>
<td>Biological Resurfacing of Articular Cartilage - from Bench to Bedside (Lee E.H.)</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>13</td>
<td>Virtual Reality, Augmented Reality and its Medical Application (Bockholt U.)</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>14</td>
<td>Vital Signs in the Real World (Wilson S.)</td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>15</td>
<td>Clinical Endoscopy System: Present and Future (Hidaka T.)</td>
<td></td>
<td>--</td>
</tr>
</tbody>
</table>

## Session: 01 Tissue Engineering  
**Day 1 1515- 1715 hrs**

<table>
<thead>
<tr>
<th>Session</th>
<th>Title</th>
<th>Author(s)</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Polyurethane Membranes for Chondroctye Transplantation and Cartilage Engineering (Chia S.L., Gorna K., Gogolewski K., Alini M.)</td>
<td></td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>Theoretical and Experimental Determination of State of Two Dimensional Strain in a Bioreactor (Ong W.F., Wijaya S., Ritchie A.C.)</td>
<td></td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>Culture of Rodent Hepatocytes on Microgrooved Surfaces: Application for a Flat-Plate Bioartificial Liver Device (Ting K.S., Wang N.D., Grant M.H., Henderson C.)</td>
<td></td>
<td>38</td>
</tr>
<tr>
<td>6</td>
<td>Simultaneous Probing of Morphology, Cytoskeleton, and Adhesion Dynamics of HepG2 Cells (Feng Z. Q., Liao K., Chan V.)</td>
<td></td>
<td>42</td>
</tr>
<tr>
<td>7</td>
<td>ECM-Dependent Proliferation of Adult Bone Marrow Mesenchymal Stem Cells (Tan G.M.Y., Shim W.S.N., Chua T., Liu T.C., Teh M., Sim E.K.W., Wong P.)</td>
<td></td>
<td>49</td>
</tr>
<tr>
<td>8</td>
<td>Parameters for Scaffold Design of Esophageal Tissue from a Structural Constitutive Model (Yang W., Fung T.C., Chian K.S., Chong C.K.)</td>
<td></td>
<td>51</td>
</tr>
</tbody>
</table>

## Session 02: Cancer Detection & Therapy  
**Day 1 1515-1700 hrs**

<table>
<thead>
<tr>
<th>Session</th>
<th>Title</th>
<th>Author(s)</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Automated Segmentation of Breast Masses in Mammograms (Zhang H., Foo S.W., Thng C.H.)</td>
<td></td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>Diagnosis of Lung Cancer Using NIR Raman Spectroscopy (Huang Z., McWilliams A., Lam S., McLean D.I., Lui H., Zeng H.)</td>
<td></td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>Extraction of head and neck tumors using deformation models from MR images (Zhou J., Chong V.)</td>
<td></td>
<td>61</td>
</tr>
<tr>
<td>Session 03A: Medical Image Processing</td>
<td>Day 1 1515-1745 hrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>---------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. An Improved Active Contour Method for Heart Wall Boundary Detection in Echocardiographic Image Sequence (Fang W., Chan K.L., Anantharaman V.)</td>
<td>89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Augmented Reality Assisted Sinus Surgery (Shi D. M., Ng W. S., Ling K. V., Shao W., Chen H.J., Kwoh C. K.)</td>
<td>93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Removing Blocking Artifacts in Compressed Medical Images (Singh S., Vinod K., Verma H.K.)</td>
<td>101</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Extraction of the Two Modified Talairach Cortical LandMarks (I and S) from MR T1-Weighted Images (Hu Q., Qian G., Nowinski W.L.)</td>
<td>109</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Mapping Human Skin and Aural Temperature with ANNs and IR Imager (Ng E.Y.K., Chong C.)</td>
<td>117</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session 03B: Medical Image Processing</th>
<th>Day 3 1130-1215 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Automatic 3-D optic Disk Image Reconstruction from Low-Resolution Fundus Image for Glaucoma Analysis (Xu J., Chutatape O.)</td>
<td>121</td>
</tr>
</tbody>
</table>

Proceedings of IBEC 2004 13
### Session 05: Biomaterials & Drug Delivery  
**Day 2 1015-1230 hrs**

<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
<th>Authors</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Smart Polymer Nanocarriers for Targeted Delivery</td>
<td>Yang Y.Y.</td>
<td>149</td>
</tr>
<tr>
<td>2</td>
<td>Release of Lipoplexes from a Biodegradable Polymer Film: Preliminary Study</td>
<td>Chan W.A., Ramgopal Y.</td>
<td>150</td>
</tr>
<tr>
<td>3</td>
<td>Cross linking of Bovine Serum Albumin with Genipin: Investigation of Mechanical Properties</td>
<td>Sathapan K., Chian K.S., Chua L.P.</td>
<td>154</td>
</tr>
<tr>
<td>4</td>
<td>Porous Beta-TCP and Its Modification with PLGA Coating for Bone Regeneration</td>
<td>Miao X., Kurniawati T.</td>
<td>158</td>
</tr>
<tr>
<td>5</td>
<td>In vitro Study on the Release Kinetics of Bovine Serum Albumin (BSA) from Injectable PLGA/BB Depot</td>
<td>Wang L.W., Venkatraman S.</td>
<td>162</td>
</tr>
<tr>
<td>8</td>
<td>Clinical Applications of Magnetic Nanomaterials</td>
<td>Ramanujan R.V.</td>
<td>174</td>
</tr>
</tbody>
</table>

### Session 06: Biomechanics  
**Day 2 1015-1230 hrs**

<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
<th>Authors</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Biomechanics Highlights in Sports, Physiology and Medicine</td>
<td>Ghista D.N.</td>
<td>178</td>
</tr>
<tr>
<td>2</td>
<td>Evolution and Biomechanics of the Cruciate Ligaments</td>
<td>Fuss F.K.</td>
<td>181</td>
</tr>
<tr>
<td>3</td>
<td>The Double-Bundle ACL Graft Reconstruction: A superior technique to restore knee kinematics</td>
<td>Lie D.T.T., Amis A.</td>
<td>185</td>
</tr>
<tr>
<td>4</td>
<td>Finger Pulley Injuries are Self-Propagating: A Mathematical Analysis of the A2-Pulley</td>
<td>Tan M.A., Fuss F.K., Niegl G.</td>
<td>188</td>
</tr>
<tr>
<td>5</td>
<td>A Comparative Study of Different Gripping Methods for Tendons</td>
<td>Ng B.H., Chou S.M., Krishna V.</td>
<td>192</td>
</tr>
<tr>
<td>6</td>
<td>Statistical Analysis of Human Metacarpal Morphology using CT Scan Data</td>
<td>Zhai L.Y., Chou S.M., Lim B.H., Chong A., Tsou I., Ng S.Y.</td>
<td>196</td>
</tr>
<tr>
<td>7</td>
<td>Mechanics and Finite Element Analysis of the Auditory Ossicles</td>
<td>Ho K.L.I., Fuss F.K.</td>
<td>199</td>
</tr>
<tr>
<td>8</td>
<td>Foot Characterization and Anatomical Landmarks Localization</td>
<td>Liu X., Kim W., Drerup B.</td>
<td>202</td>
</tr>
</tbody>
</table>

### Session 07A: Computational Bioengineering 1  
**Day 2 1015-1230 hrs**

<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
<th>Authors</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A Case Study on Pattern-based Systems for Computational Biology</td>
<td>Liu W., Schmidt B.</td>
<td>205</td>
</tr>
<tr>
<td>2</td>
<td>A Grid Implementation of Database Searching</td>
<td>Chen C., Schmidt B.</td>
<td>209</td>
</tr>
<tr>
<td>3</td>
<td>The Use of Computer Modelling to elucidate the Efficacy of Slit Arteriortomy for End-to-side Arterial Anastomosis in Microsurgery</td>
<td>Chua A.W.C., Gu H., Tan B.K., Chew W., Li J.Z., Song C.</td>
<td>213</td>
</tr>
<tr>
<td>4</td>
<td>A Mixed SVM-Based Hierarchical Learning Approach for Abnormal ECG Beat Recognition</td>
<td>Li P., Chan K.L., Chan Y.W.</td>
<td>217</td>
</tr>
<tr>
<td>5</td>
<td>Capturing Cellular Life In-Silico</td>
<td>Dhar P.K.</td>
<td>221</td>
</tr>
<tr>
<td>7</td>
<td>Fuzzy c-Means and Neural Network Framework for Arrhythmia Classification</td>
<td>Chaudhari N.S., Siang L.C.</td>
<td>228</td>
</tr>
<tr>
<td>8</td>
<td>VRML Modeling for Bio-Molecular Structures</td>
<td>Indhumathi C., Lu B.F., Cai Y.Y.</td>
<td>232</td>
</tr>
<tr>
<td>9</td>
<td>BioSequence Comparison for Large Database on Reconfigurable Platforms</td>
<td>Wong M.T., Schmidt B.</td>
<td>237</td>
</tr>
</tbody>
</table>
### Session 07B: Computational Bioengineering 2  
**Day 2 1330-1415 hrs**

1. **Clustering Based Watershed Segmentation for Two-Dimensional Gel Electrophoresis Image**  
   (Diao X.N., Mao K.Z.)  
   - Page: 240

2. **Estimating error-dimensionality relationship for gene expression based cancer classification**  
   (Chu F., Wang L.)  
   - Page: 244

3. **Finite Element Analysis of Brain for Neurosurgical Procedure**  
   (Roy A., Nowinski W.L., Tay F.E.H.)  
   - Page: 247

### Session 08A: Cardiovascular Engineering 1  
**Day 2 1330-1530 hrs**

1. **A Decoupled Control Method for the Magnetic Bearings of a Blood Pump**  
   (Lim T.M., Zhang D., Kim M.T.)  
   - Page: 251

   (Xia G.H., Zhao Y., Yeo J.H., Tai C.H.)  
   - Page: 255

3. **Computation of Gap Flow Field in a Bio-Centrifugal Blood Pump**  
   (Chua L.P., Song G.L., Yu S.C.M.)  
   - Page: 259

4. **Computational Studies of Steady Flows In Designed Sleeve Models At Distal Anastomoses**  
   (Chua L.P., Tong J.H.)  
   - Page: 263

5. **Contractility of the Left Ventricle in Terms of its Sacromere Power Generation**  
   (Zhong L., Ghista D.N., Ng E.Y.K.)  
   - Page: 267

6. **Detection of Cardiac Arrhythmia using Phase Space Analysis**  
   (Wong M.T., Srinivasan N., Chan Y.W.)  
   - Page: 271

7. **Flow Studies in Aorto-Right Coronary Bypass Graft System**  
   (Meena S., Chua L.P., Ghista D.N., Tan Y.S.)  
   - Page: 274

8. **LV Twisting Analyzed for Pressure-Increase During Iso-Volumic Contraction**  
   (Liu L., Yeo S.Y., Ghista D.N., Chua L.P., Chai G.B., Tan Y.S., Tan R.S.)  
   - Page: 278

### Session 08B: Cardiovascular Engineering 2  
**Day 2 1545-1645 hrs**

1. **Multiple-Model Adaptive Control by Means of a Fuzzy Controller-based Control System**  
   (Zheng H., Zhu K.Y., Tan Y.S.)  
   - Page: 282

2. **Numerical Investigation of Hemodynamics for the Coronary Artery Bypass Graft Model**  
   - Page: 286

3. **Numerical Investigation of Stress Field in Distal End-to-side Anastomoses**  
   (Liu L., Chua L.P., Ghista D.N., Tan Y.S.)  
   - Page: 289

4. **PIV Measurements on the Pulsatile Flow Characteristics in 45-degree Backward Proximal Anastomosis**  
   - Page: 293

### Session 09A: Sports Engineering 1  
**Day 2 1330-1530 hrs**

1. **Quantitative analysis of Singapore Golfers**  
   (Lim S.L., Xie X., Ong V., Teh K.C.)  
   - Page: 297

2. **Three-Dimensional Kinematics Study of Left Hand During Golf Swing**  
   (Teu K.K., Kim W., Fuss F.K., Tan J.)  
   - Page: 301

3. **Investigation of Weight Transfer during Golf Swing**  
   (Teu K.K., Kim W., Fuss F.K., Tan J.)  
   - Page: 305

4. **Biomechanics of Push-up Exercise and Triceps Contractility**  
   (Tan M.A., Zhong L., Fuss F.K., Ghista D.N.)  
   - Page: 308

5. **Comparison of Pinch- and Open Hand Grip during Sport Climbing**  
   (Yap Y.H., Fuss F.K., Niegl G., Tan M.A.)  
   - Page: 312

6. **Friction at the Climbing Handhold under Different Conditions and its Implications for Sport Climbing**  
   (Tan M.A., Fuss F.K., Niegl G.)  
   - Page: 316

---

Proceedings of IBEC 2004  
15
7 Finger Load Distribution During Sport Climbing (See W.N.W., Fuss F.K., Niegl G., Yap Y.H.) 320
8 Analysis of Badminton Smash Using Dual Euler Angles Algorithm (Liu X., Teu K.K., Kim W., Tan J., Fuss F.K.) 324

Session 09B: Sports Engineering 2
Day 2 1545-1630 hrs
2 Comparative Study on the techniques of Singapore and Thailand Table Tennis players during SEA Games 2001 (Lee K.T., Xie W., Teh K.C.) 333
3 Experimental Study on Different Types of Service Spins for Singapore National Table Tennis players (Lee K.T., Xie W.) 336

Session 10A: Ultrasonic Imaging 1
Day 2 1415-1530 hrs
1 Medical Ultrasound Imaging: Current Status and Future Trends (Yoo Y.M., Kim Y.) 339
2 Reconfigurable and Programmable Architecture for Digital Receive Beamformer (Schneider F.K., Yoo Y.M., Agarwal A., Kim Y.) 345
3 Adaptive Speckle Reduction Based on Nakagami Distribution in Medical Ultrasound Imaging (Zhang L.C., Wong E.M.C.) 349
4 Specific Homomorphic Nonlinear Diffusion for Speckle Reduction in Ultrasound B-mode Images (Zhang F., Koh L.M.) 353
5 Design and Optimization of Broadband Ultrasonic Sparse Array Transducers for Medical Imaging Applications (Wang Q. B., Guo N. Q.) 357

Session 10B: Ultrasonic Imaging 2
Day 2 1545-1645 hrs
1 Field of View-based Imaging for Efficient Beamforming in Low-end Portable Ultrasound Systems (Agarwal A., Schneider F.K., Yoo Y.M., Kim Y.) 361
2 Low Sampling Frequency Digital Beamformer for Ultrasonic Imaging without Interpolation (Gao C.Q., Zhang L.C., Wong E.M.C.) 365
3 Comparative Evaluation of Wavelet Filters for Speckle Reduction in Ultrasound Medical Images (Thakur A., Anand R. S.) 369
4 Window Function Optimization by Genetic Algorithm for Ultrasound Imaging System (Cao J., Koh L.M.) 373

Session 11: Respiratory Biomechanics
Day 2 1645-1730 hrs
1 Determination of O2 and CO2 Metabolic Rates and Lung O2 and CO2 Diffusion Coefficients (Loh K.M., Ghista D.N.) 377
2 Oxygen Saturation Profiles in a Hollow Fibre Oxygenator (Ritchie A.C., Thimm G.) 381
3 Graphical Technique for Assessing Pulmonary Disease (Loo C.M., Ang K.C., Ong J.H., Ghista D.N., Lim G.H.) 385

Session 12A: Orthopaedic Engineering 1
Day 2 1630-1745 hrs
1 Design Optimisation in BioMedical Engineering (Koh E.C.Y., Fuss F.K.) 389
2 Design Classification and Mechanics of Artificial Discs (Fuss F.K.) 392
3 Extraforaminal Lumbar Interbody Fusion: Simulation of the Fusion Process Based on Different Implant Materials (Fuss F.K., Sabitzer R.J.) 397
4 FE Investigation on Spinal Interbody Fusion (Lee K.K., Teo E.C., Fuss F.K., Sabitzer R.J.) 401
5 Optimization of Cervical Ring Cage by Taguchi Philosophy (Yang K., Teo E.C., Fuss F.K.) 405
### Session 12B: Orthopaedic Engineering 2  
**Day 3 1130-1215 hrs**

1. Integration of CAD to FEA for Prosthetic Socket Design (Goh J.C.H., Lee P.V.S., Toh S.L., Ooi C.K.)
2. Analyses of Fractured Bone (Femur) with Plate and Intra-Medullary Rod Fixations (Chen Q., Fan S.C., Ghista D. N.)

### Session 13A: Biosignal Processing 1  
**Day 2 1645-1745 hrs**

1. A Novel Approach to Automatic Left Ventricular Contour Tracking (Cheng J., Foo S.W.)
2. A Novel Wavelet Based ECG Compression with X-tree Coding (Swain S., Chutatape O., Dandapat S.)
3. Left Ventricular Surface Kinematics During Isovolumic Contraction (Yeo S.Y., Tan R.S., Liu L., Chai G.B., Ghista D.N.)
4. Evaluation of Slice Sensitivity Profiles for TPRF Algorithm (Yan M., Zhang C.)

### Session 13B: Biosignal Processing 2  
**Day 3 1045-1130 hrs**

1. Uni-channel PCA for noise reduction from ECG signals (Palaninippan R., Tan E.K.)
2. Wavelet-Based Denoising and Analysis of Phonocardiogram (Wang P., Anantharaman V.)
3. Dynamical Analysis of Heart Rate Variability Signals (Rajendra A.U., Kannathal N., Lim C.M.)

### Session 14: Biosensors/ Diagnostic Tools  
**Day 3 1045-1145 hrs**

1. Multi-Parameter Clinical Diagnosis Using Neural Networks (Tan E.K.)
2. An Otoacoustic Emissions Detecting System using USB AD/DA Board (Qian X., Ye D.)
4. Feasibility of biosensing based on two-dimensional square photonic lattice (Zhang D.W., Irawan R., Tjin S.C., Yuan X.C.)

### Session 15: Distributed Diagnosis & Home Healthcare  
**Day 3 1045-1130 hrs**

1. Distributed Diagnosis and Home Healthcare (D2H2) and Patient-Centered Electronic Medical Record (Kim E.H., Kim J.J., Matsen F.A., Kim Y.)
2. Application of Artificial Neural Network Technique in Healthcare Expenditure Analysis (Chia E., Khong P.W., Ghista D.N.)
3. Advanced System Architecture for Telecardiology (Goh K.W., Kugean C., Tan E.K., Prabaharan K.)

Proceedings of IBEC 2004
Abstract — The primary function of the lung is to (i) oxygenate the blood and thereby provide oxygen to the cells for metabolism purposes, and (ii) to remove the collected CO₂ from the pulmonary blood. Herein, we provide a noninvasive methodology to assess physiological metabolic rates as well as blood-oxygenation capacity of the lung. For this purpose, we analyze the compositions of the inspired and expired air per breath, and therefrom compute the metabolic O₂ consumption and CO₂ production rates.

Next, we derive expressions for diffusion coefficients \(D_{O₂}\) and \(D_{CO₂}\), in terms of the evaluated cardiac-output \(CO\), \(O₂\) and \(CO₂\) concentrations in arterial and venous blood as well as alveolar and blood \(O₂\) and \(CO₂\) partial-presures. The coefficients \(D_{O₂}\) and \(D_{CO₂}\) represent the lung capability to oxygenate the blood. We can then also determine the cardiac output, from knowing the concentrations of oxygen and carbon dioxide in the arterial and venous bloods.

The derived information of \(D_{O₂}\) and \(D_{CO₂}\) as well as of \(O₂\) and \(CO₂\) metabolic rates can be of considerable use (including for SARS assessment). The paper provides a case study for the determination of \(Q\), \(D_{O₂}\) and \(D_{CO₂}\).

Keywords — gas exchange, \(O₂\) metabolic-rates, \(CO₂\) metabolic-rates, diffusion coefficients \(D_{O₂}\), diffusion coefficients \(D_{CO₂}\), blood flow rate

I. SCOPE

The lung functional performance is characterized by (i) its ventilatory capacity, to bring air (and hence \(O₂\)) into the alveoli, and (ii) its capacity to transfer \(O₂\) and \(CO₂\) into and from the pulmonary capillary bed. Hence, the \(O₂\) and \(CO₂\) diffusion coefficients \(D_{O₂}\) and \(D_{CO₂}\) as well as the \(O₂\) consumption-rate and the \(CO₂\) production rate represent the lung performance indices. In this paper, we are demonstrating their evaluations.

II LUNG GAS-EXCHANGED MODEL

Figure 1 schematically illustrates the gas-exchange between the lung alveolus and the pulmonary capillary-vasculature. Based on our earlier work [2] the gas exchange between the alveolar air and pulmonary capillary blood is represented by the following \(O₂\) and \(CO₂\) conservation equations and Figure 2.

\[
Q^{VE} C_{O₂}^{VE} = Q^{AE} C_{O₂}^{AE} + V O₂ \quad \text{(from the alveolar air to capillary blood)}
\]
\[
= Q^{AE} C_{O₂}^{AE} + (\Delta p_{av}^{O₂}) D_{O₂} \quad (1)
\]
\[
Q^{VE} C_{CO₂}^{VE} = Q^{AE} C_{CO₂}^{AE} - V CO₂ \quad \text{(2)}
\]

wherein

(i) \(Q^{AB}\) and \(Q^{VB}\) are arterial and venous blood flow-rates;
(ii) \(P_{O₂}^{al}\) and \(P_{O₂}^{cap}\) are the alveolar and capillary \(O₂\) partial pressures
(iii) \(P_{CO₂}^{al}\) and \(P_{CO₂}^{cap}\) are the alveolar and capillary \(CO₂\) partial pressure
(iv) \(D_{O₂}\) and \(D_{CO₂}\) are the \(O₂\) and \(CO₂\) diffusion coefficients
(v) \(\Delta p_{av}^{O₂}\) = average of \((P_{O₂}^{al} - P_{O₂}^{cap})\) over the capillary length;
(vi) \(\Delta p_{av}^{CO₂}\) = average of \((P_{CO₂}^{al} - P_{CO₂}^{cap})\) over the capillary length
(vii) \(P_{O₂}^{cap} = P_{O₂}^{PRB}\) (\(O₂\) concentration of the pre-oxygenated blood) = \(P_{O₂}^{AE}\)
(viii) \(P_{CO₂}^{cap} = P_{CO₂}^{PRB}\) (\(CO₂\) concentration of the pre-oxygenated blood) = \(P_{CO₂}^{VE}\)

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(viii) $V_{O_2}$ is the $O_2$ transfer rate from alveolar air to capillary blood (= $O_2$ consumption rate), $V_{CO_2}$ is the $CO_2$ transfer rate from capillary blood to alveolar air.

Now we can equate the arterial and venous blood flow rates, as $Q_A^{BE} = Q_B^{AB} = Q_V^{VE} = Q = (SV)/(EP) = CO / 60$

SV, EP and CO being the stroke-volume, ejection-period and cardiac-output respectively.

![Figure 1: Process of oxygenating the venous blood. The low oxygen ($O_2$) concentration Red Blood Cell (RBC) is shown in dark blue. As it travels down the artery towards the venous end, the $O_2$ concentration increases. After the distance $L$, its $O_2$ has increased to 0.18 from the initial concentration of 0.13.]

![Figure 2: Schematic of blood gas concentration in the Pulmonary Capillary.]

### III. CLINICAL DATA

The monitored data consists of inspired and expired air gas compositions (Table 1) and $O_2$ and $CO_2$ concentrations of arterial blood and venous blood (Table 2).

<table>
<thead>
<tr>
<th>Respiratory gases</th>
<th>Atmospheric Air</th>
<th>Expired Air</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmHg</td>
<td>ml/%</td>
</tr>
<tr>
<td>N$_2$</td>
<td>597</td>
<td>78.55%</td>
</tr>
<tr>
<td>O$_2$</td>
<td>159</td>
<td>20.84%</td>
</tr>
<tr>
<td>CO$_2$</td>
<td>0.3</td>
<td>0.04%</td>
</tr>
<tr>
<td>H$_2$O</td>
<td>3.7</td>
<td>0.49%</td>
</tr>
<tr>
<td>Total</td>
<td>760</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 2: Blood Gas Analysis. The monitored blood $O_2$ and $CO_2$ concentration.

- $C_{O_2}$ of venous blood ($C_{O_2}^{VE}$) = 0.13
- $C_{O_2}$ of arterial blood ($C_{O_2}^{VE}$) = 0.18
- $C_{CO_2}$ of venous blood ($C_{CO_2}^{VE}$) = 0.5
- $C_{CO_2}$ of arterial blood ($C_{CO_2}^{AB}$) = 0.46

### IV. EXPRESSIONS FOR $D_{O_2}$ AND $D_{CO_2}$

If we want to evaluate the diffusion coefficients $D_{O_2}$ and $D_{CO_2}$, we need to also express $P_{O_2}^{al}$, $P_{O_2}^{cap}$ and $P_{CO_2}^{al}$, $P_{CO_2}^{cap}$ in terms of monitorable quantities [1 & 2].

- **(i)** Alveolar $P_{O_2}^{al}$ can be expressed in terms of $V$ (the ventilation rate) and $V_{O_2}$ (the $O_2$ consumption rate).
\[ P_{O_2}^{al} = 140 \left[ 1 - e^{-4.18 \left[ \frac{\nu}{V_{O_2}} \right]} \right] \] ; \quad (3)

wherein the normalised ventilation rate, \( \nu = \frac{V}{V_m} = \frac{V}{60} \) litres/min, is the consumption rate (in liters/min).

(ii) Alveolar \( P_{CO_2}^{al} \) can be expressed in terms of \( V \) and \( V_{O_2} \).

\[ P_{CO_2}^{al} = 114.68 e^{-2.46 \left[ \frac{\nu}{V_{CO_2}} \right]} \] \quad (4)

wherein \( V_{CO_2} \) is the CO2 production rate (in liters/min).

(iii) Blood \( P_{O_2} \) can be obtained in terms of blood \( C_{O_2} \), from the \( O_2 \) disassociation curve.

\[ P_{O_2}^B = 29.72 \ln \left[ \frac{0.2}{0.2 - \frac{C_{O_2}^B}{O_2}} \right] \] \quad (5)

(iv) Blood \( P_{CO_2} \) can be obtained in terms of \( C_{CO_2}^B \), from the \( CO_2 \) disassociation curve.

\[ P_{CO_2}^B = 29.72 \ln \left[ \frac{0.8}{0.8 - \frac{C_{CO_2}^B}{CO_2}} \right] \] \quad (6)

Now, \( (P_{O_2}^{al} - P_{O_2}^{cap}) = P_{O_2}^{al} - P_{O_2}^B \) both \( \Delta P_{O_2} \) and \( \Delta P_{CO_2} \) \( (P_{CO_2}^{al} - P_{CO_2}^{cap}) \) vary along the capillary bed. Based on [3], we have:

\[ \Delta P_{O_2}^{av} = 0.185 \Delta P_{O_2}^{max} \] \quad (7)

\[ \Delta P_{CO_2}^{av} = 0.1 \Delta P_{CO_2}^{max} \] \quad (8)

From the above expressions, we obtain:

\[ D_{O_2} = \frac{V_{O_2}}{\Delta P_{O_2}^{av}} = \frac{V_{O_2}}{0.185(P_{O_2}^{al} - P_{O_2}^B) / P_{O_2}^{max}} \] \quad (9)

\[ D_{CO_2} = \frac{V_{CO_2}^\circ}{\Delta P_{CO_2}^{av}} = \frac{V_{CO_2}^\circ}{0.1(P_{CO_2}^{al} - P_{CO_2}^B)} \] \quad (10)

V. DETERMINATION OF \( O_2 \) AND \( CO_2 \) METABOLIC RATES AND CARDIAC OUTPUT

From monitored data of inspired-exhaled gas compositions, in Table 1:

\[ O_2 \] consumption rate, \( \dot{V}_{O_2} = BR(\text{Inspired } O_2 - \text{Expired } O_2) \text{ml/min} = 12(104.2 - 83.37) = 250 \text{ ml/min} \] \quad (11)

\[ CO_2 \] consumption rate, \( \dot{V}_{CO_2} = BR(\text{Expired } CO_2 - \text{Inspired } CO_2) \text{ml/min} = 12(16.87 - 02) = 200 \text{ ml/min} \] \quad (12)

From monitored \( O_2 \) and \( CO_2 \) concentrations of arterial and venous blood, in Table 2:

\[ \dot{V}_{O_2} = Q( CO_2 \text{ of arterial blood} - CO_2 \text{ of venous blood}) \]

where \( Q = \text{blood flow rate=cardiac output} \)

\[ Q = \frac{\dot{V}_{O_2}}{(0.18 - 0.13)} = \frac{250}{0.05} = 5000 \text{ ml/min} \]

VI. EVALUATING OF THE LUNG DIFFUSION COEFFICIENTS \( D_{O_2} \) AND \( D_{CO_2} \)

From equation (3) and Table 2 \( C_{O_2}^{AV} = 0.18 \), we get for (arterial blood @ venous end of the pulmonary capillary or \( P_{O_2}^{AV} \))

\[ P_{O_2}^{AV} = 29.72 \ln \left[ \frac{0.2}{0.2 - \frac{C_{O_2}^{AV}}{O_2}} \right] \]

\[ = 29.72 \ln \left[ \frac{0.2}{0.2 - 0.18} \right] \]

\[ = 68.43 \text{ mmHg} \] \quad (13)

From equation (5) and Table 2 \( C_{CO_2}^{VB} = 0.13 \), we get for \( P_{CO_2}^{VB} \) (venous blood @ arterial end of the pulmonary capillary or \( P_{CO_2}^{AV} \))
\[ P_{O_2}^{i/V} = 29.72 \ln \left[ \frac{0.2}{0.2 - C_{O_2}^{V/B}} \right] \]

\[ = 29.72 \ln \left[ \frac{0.2}{0.2 - 0.13} \right] = 31.20 \text{ mmHg} \quad (14) \]

Also, from equation (3) and Table 1 (\( V^* = 0.1 \)), we get:

\[ P_{O_2}^{d/V} = 140 \left[ 1 - e^{-4.18 V^*/V_{O_2}} \right] \]

\[ = 140 \left[ 1 - e^{-4.18[0.1/0.25]} \right] = 113 \text{ mmHg} \quad (15) \]

Hence, from equations (14 & 15), we get:

\[ \Delta P_{O_2}^{V} = 0.185 \times (113 - 31.2) = 14.95 \text{ mmHg} \quad (16) \]

Finally, from equations (11) and (16), we get:

\[ D_{O_2} = \frac{V_{O_2}^\circ}{\Delta P_{O_2}^{V}} = \frac{250 \text{ ml/min}}{14.95 \text{ mmHg}} \]

\[ = 16.72 \text{ ml/min}^{-1} \text{ mmHg}^{-1} \quad (17) \]

From equation (6) and Table 2 (\( C_{CO_2}^{V/B} = 0.5 \)), we get:

\[ P_{CO_2}^{V/B} = P_{CO_2}^{AE} = 29.72 \ln \left[ \frac{0.8}{0.8 - C_{CO_2}^{V/B}} \right] \]

\[ = 29.72 \ln \left[ \frac{0.8}{0.8 - 0.5} \right] = 29.15 \text{ mmHg} \quad (18) \]

Then from equation (4), Table 1 (\( V = 0.1 \)), and equation (12) we get:

\[ P_{CO_2}^{d/V} = 114.68 e^{-2.46 V^*/V_{CO_2}} \]

\[ = 114.68 e^{-2.46[0.1/0.2]} = 33.52 \text{ mmHg} \quad (19) \]

Hence, from equations (8, 18 & 19), we get:

\[ \Delta P_{CO_2}^{V} = 0.1 \times (33.52 - 29.15) = 0.44 \text{ mmHg} \quad (20) \]

Finally, from equations (10 & 20), we get:

\[ D_{CO_2} = \frac{V_{CO_2}^\circ}{\Delta P_{CO_2}^{V}} = \frac{200 \text{ ml/min}}{0.44 \text{ mmHg}} \]

\[ = 454.55 \text{ ml/min}^{-1} \text{ mmHg}^{-1} \quad (21) \]

**VIII. CONCLUSION**

We have demonstrated a noninvasive clinical procedure:

- for obtaining (i) \( O_2 \) consumption rate and \( CO_2 \) production rate, (ii) cardiac outflow-rate or output, \( Q \), (iii) and lung diffusion capacities for \( O_2 \) and \( CO_2 \),
- from inhaled and exhaled air composition analysis, and blood-gas analysis.

This work could have application to SARS testing and evaluation.

**REFERENCES**


Abstract—This paper provides a systems-engineering analysis of the glucose-insulin responses to an ingested bolus of glucose for OGTT (Oral Glucose Tolerance Test). The clinical data of patients is fitted by either under-damped or over-damped or critically-damped solutions of the model’s governing equations for glucose and insulin responses to glucose bolus ingestion. Based on the best fit of the three types of solutions, we designate the patients (and their response) to be normal (and under-damped), diabetic (and over-damped) and either border-line or at-risk of becoming diabetic (and critically-damped). In this way, the model simulation of the clinical data enables more reliable diagnosis relative to the clinical assessment.

Keywords—diabetic, systems-engineering model, under-damp, over-damp, critically-damped, R-square, fitting, clinical diagnosis

I. INTRODUCTION

Oral Glucose Tolerance Testing Protocol

The test subjects need to fast for 12 hours before the test and during the 2-hour test. A blood sample of the subject is taken before the beginning of the test. Then after the subject drinks a 75 g of glucose solution dissolved in 250–300 mL of water, the subject’s blood glucose and insulin concentrations are measured at specified intervals 30 minutes, 60 minutes, 90 minutes and 120 minutes [1, 2, 4].

Qualitative interpretation of the results, for preliminary categorization of the patients [1, 2, 4]:

(a) Blood glucose normal values:
   fasting: 70 to 115 mg/dl
   30 min.: less than 200 mg/dl
   1 hour : less than 200 mg/dl
   2 hour : less than 140 mg/dl

(b) Normal insulin level (reference range): 1-30 mU/L

When a person has a fasting glucose equal to or greater than 110 mg/dl and less than 126 mg/dl, it is considered as impaired fasting glucose. This is considered a risk factor for future diabetes and will likely trigger another test in the future, but, by itself, does not make the diagnosis of diabetes.

A person is said to have impaired glucose tolerance when the 2-hour glucose results from the oral glucose tolerance test are greater than or equal to 140 but less than 200 mg/dl. This is also considered a risk factor for future diabetes. A person has diabetes when oral glucose tolerance tests show that the blood glucose level at 2 hours is equal to or more than 200 mg/dl. This must be confirmed by a second test (any of the three) on another day.

II. SYSTEM SOLUTIONS FOR DIABETIC, NON-DIABETIC AND AT-RISK PATIENTS

The governing differential equation for glucose response to glucose bolus intake is:

\[ y' = q(t) - \gamma x - \delta y \]  

(1)

The governing differential equation for insulin response to glucose bolus intake is:

\[ x' = p(t) - \alpha x + \beta y \]  

(2)

\[ y(t) : \text{Glucose response of the patient to the oral bolus of glucose.} \]

\[ x(t) : \text{Insulin response of the patient due to} \ y(t). \]

Solution For Underdamped Case (non-diabetic):

\[ y(t) = \left( \frac{G}{\omega} \right) e^{\alpha t} \sin \omega t \]  

(3)

\[ \begin{bmatrix} - (\sin(wt) \alpha e^{(-At)}) \\
                   - \sin(wt) \alpha e^{(-At)} \\
                   - e^{(-\alpha t)} w + \cos(wt) e^{(-At)} w \\
                   x\beta \frac{G}{w} \end{bmatrix} \times \frac{A^2 - 2 \alpha A + \alpha^2 + w^2}{(A^2 - 2 \alpha A + \alpha^2 + w^2)} \]  

\[ x(t) = \]  

(4)
Solution For Overdamped Case (diabetic):

\[ y(t) = \frac{G}{\omega} e^{-\alpha t} \sinh(w t) \]  
\[ (5) \]

\[ x(t) = \frac{1}{2} \left( \cosh(w t + \alpha t) A + \sinh(w t + \alpha t) A - \cosh(w t - \alpha t) A - \sinh(w t - \alpha t) A \right) \]  
\[ \omega \]  
\[ \sinh(w t - \alpha t) A \]  
\[ \cosh(w t + \alpha t) A - \cosh(w t - \alpha t) A \]  
\[ + \sinh(w t - \alpha t) w - \cosh(w t - \alpha t) w \]  
\[ - \sinh(w t + \alpha t) \alpha + \sinh(w t - \alpha t) \alpha \]  
\[ - \cosh(w t + \alpha t) \alpha - \cosh(w t - \alpha t) w \]  
\[ + \cosh(w t - \alpha t) \alpha + 2w \]  
\[ + \sinh(w t - \alpha t) w e^{-\alpha t} \beta \frac{G}{w} \]  
\[ \left( -w^2 + \alpha^2 + 2 \alpha \alpha + \alpha^2 \right) \]  
\[ (6) \]

Solution For Critically Damped Case (at the dangerous boundary):

\[ y(t) = G e^{-\alpha t} \]  
\[ (7) \]

\[ x(t) = -\beta G (t A e^{(-\alpha t)} - t \alpha e^{(-\alpha t)} + e^{(-\alpha t)} - e^{-(-\alpha t)}) \]  
\[ \left( A - \alpha \right)^2 \]  
\[ (8) \]

III. CLINICAL APPLICATION AND DISCUSSION

Under-damped Category and Normal Designated Patient

These \( y(t) \) and \( x(t) \) response solutions are fitted to the monitored glucose and insulin data, and the fitness coefficients are determined. Based on the high degree of fit, patient S14 fits best the under-damped category, and hence is designated to be normal. His Glucose and Insulin responses, shown in Figure 1, illustrates the fast recovery of blood glucose and insulin concentrations.

The below table displays the values of the model parameters and the R-Square coefficients of fitness and the model solution to the clinical data.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
<th>Fitting</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>2.007</td>
<td>Glucose SSE 0.0001099</td>
</tr>
<tr>
<td>G</td>
<td>2.795</td>
<td>Fit R-Square 0.9992</td>
</tr>
<tr>
<td>\omega</td>
<td>1.882</td>
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<tr>
<td>\alpha</td>
<td>2.8245</td>
<td>Insulin SSE 0.0003014</td>
</tr>
<tr>
<td>\beta</td>
<td>0.1059</td>
<td>Fit R-Square 0.9871</td>
</tr>
<tr>
<td>\gamma</td>
<td>1.1895</td>
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</tr>
<tr>
<td>\delta</td>
<td>2.6355</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1: Patient S14 is designated to be under-damped and normal. However, this patient is quite hyper-insulinemic; in other words, this patient has elicited considerable insulin response in order to maintain an under-damped glucose response.

Over-damped Category of Patients Designated as Diabetic

For patients D05, our over-damped model solution fits the clinical data best of the 3 solution categories. Hence, this patient is designated to be diabetic. His Glucose and Insulin responses are shown in Figure 2, and the model parameters are given in the Table.
Figure 2: This patient D05 has the higher R-Square value when fitted by the over-damped solution, and is hence classified as diabetic.

Critically-damped Category of Patients

There are some patients clinically diagnosed to be normal for which the critically-damped solution gives a better fit of the data (and a higher value of R-Square) than the under-damped solution. One such patient is S04, whose under-damped and critically-damped model response-curves are shown in Figures 3 and 4. Similarly, patients S06 and S19 are not normal as clinically diagnosed, but at the risk of becoming diabetic. Their response curves are illustrated in Figures 5 and 6.

![Graph showing glucose and insulin responses for S04 patient](image)

Figure 3: This S04 patient’s data is fitted by the under-damped solution. Next, we will compare the results fitted by the critically-damped solution as shown in the following figure.

![Graph showing glucose and insulin responses for S04 patient](image)

Figure 4: This S04 patient’s data is better fitted (i.e. at higher R-Square value) by the critically-damped solution than by the under-damped solution. Because of the critically-damped model solution giving us a better fit (iterations of a higher value of R-Square), we differ from the clinical diagnosis and alert this patient that he is at risk at becoming diabetic.

<table>
<thead>
<tr>
<th>Parameters</th>
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<th>Fitting</th>
<th>Values</th>
<th>Fitting</th>
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</thead>
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<tr>
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<td>SSE</td>
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<td>G</td>
<td>3.21</td>
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<tr>
<td>(\alpha)</td>
<td>2.776e-14</td>
<td>R-Square</td>
<td>0.9834</td>
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<tr>
<td>(\alpha)</td>
<td>1.6693</td>
<td>Insulin Fit</td>
<td>SSE</td>
<td>0.002765</td>
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<tr>
<td>(\beta)</td>
<td>0.1209</td>
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<tr>
<td>(\gamma)</td>
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<td>R-Square</td>
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<tr>
<td>(\delta)</td>
<td>3.3926</td>
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</table>
Figure 5: This S06 patient’s data is better fitted (i.e. at higher R-Square value) by the critically-damped solution than by the under-damped solution. Hence, we will differ from the clinical diagnosis and designate this patient to be at risk of becoming diabetic.

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>R-Square</th>
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<td>G</td>
<td>4.1120</td>
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<td>Insulin Fit</td>
<td>0.003012</td>
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<tr>
<td>$\beta$</td>
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<td>$\gamma$</td>
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<tr>
<td>$\delta$</td>
<td>2.0613</td>
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</table>

Figure 6: This S19 patient’s response curves are best fitted (with a higher value of R-Square) by the critically-damped solution than by the under-damped solution.

V. CONCLUSION

We have shown that we can obtain more accurate assessment of diabetic patients by means of our under-damped, over-damped and critically-damped simulation model solutions. Some patients (diagnosed to be normal) were designated by us to be in the borderline category. However, some patients who were clinically declared to be diabetic turned out to be only border-line. As we continue this work, we will develop a clinically-implementable software for model parameter identification and designation of the subjects as normal or at-risk of becoming diabetic or borderline diabetic or distinctly diabetic.

REFERENCES


# Technical Programme

## Scientific Programme – DAY 1

**Wednesday, September 08 2004**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>0800 – 0920</td>
<td>Registration</td>
</tr>
<tr>
<td>0920 – 0940</td>
<td>Opening Ceremony</td>
</tr>
<tr>
<td>0940 – 1010</td>
<td>Nanostructure Processing of Advanced Biomaterials</td>
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<tr>
<td></td>
<td>Invited Speaker: Dr. Jackie Ying</td>
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<tr>
<td>1010 – 1040</td>
<td>Bioengineering, Technology Commercialization and Entrepreneurship</td>
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<tr>
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<td>Invited Speaker: Dr. Yongmin Kim</td>
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<tr>
<td>1040 - 1100</td>
<td>Tea break</td>
</tr>
<tr>
<td>1100 – 1130</td>
<td>Esophageal Tissue Engineering</td>
</tr>
<tr>
<td></td>
<td>Invited Speaker: Dr. Buddy Ratner</td>
</tr>
<tr>
<td>1130 – 1200</td>
<td>A Case Study of Integrated Biomedical Engineering: A Novel Method</td>
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<tr>
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<td>for Creating an Automated Sutureless Anastomosis</td>
</tr>
<tr>
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<td>Invited Speaker: Dr. Adam Sharkawy</td>
</tr>
<tr>
<td>1200 – 1230</td>
<td>Advances in Cancer Imaging</td>
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<tr>
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<td>Invited Speaker: Dr. James Khoo</td>
</tr>
<tr>
<td>1230 – 1330</td>
<td>Lunch</td>
</tr>
<tr>
<td>1330 – 1400</td>
<td>Tissue Engineering Heart Constructs using Bone Marrow Stem Cells</td>
</tr>
<tr>
<td></td>
<td>Invited Speaker: Dr. Philip Wong</td>
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<tr>
<td>1400 – 1430</td>
<td>Computational Technologies to Accelerate Biotech Innovation</td>
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<tr>
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<td>Invited Speaker: Dr. Ulrich Meier</td>
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<tr>
<td>1430 – 1500</td>
<td>A new Approach to Protein Structure Prediction</td>
</tr>
<tr>
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<td>Invited Speaker: Dr. Heiko Schroder</td>
</tr>
<tr>
<td>1500 – 1515</td>
<td>Tea break</td>
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</tbody>
</table>
## Session 01 Tissue Engineering (Room 1)
1515 – 1730
Chairs: S. Chian, P. Wong

- Enhancement of Meniscus Repair using Mesenchymal Stem Cells in a Porcine Model
  Dutton A., Hui J.P.P., Lee E.H.
- Cardiac Differentiation of Adult Bone Marrow Mesenchymal Stem Cells
- Polyurethane Membranes for Chondrocyte Transplantation and Cartilage Engineering
  Chia S.L., Gorna K., Gogolewski K., Alini M.
- Theoretical and Experimental Determination of State of Two Dimensional Strain in a Bioreactor
  Ong W.F., Wijaya S., Ritchie A.C.
- Culture of Rodent Hepatocytes on Microgrooved Surfaces: Application for a Flat-Plate Bioartificial Liver Device
  Ting K.S., Wang N.D., Grant M.H., Henderson C.
- Simultaneous Probing of Morphology, Cytoskeleton, and Adhesion Dynamics of HepG2 Cells
  Feng Z. Q., Liao K., Chan V.
- ECM-Dependent Proliferation of Adult Bone Marrow Mesenchymal Stem Cells
- Parameters for Scaffold Design of Esophageal Tissue from a Structural Constitutive Model
  Yang W., Fung T.C., Chian K.S., Chong C. K.
- Surface modification of biodegradable poly(L-lactide-co-caprolactone) (PLLC) membrane with proteins to enhance the growth of esophageal smooth muscle cells
  Yabin Z., Chan-Park M.B., Chian K.S.

## Session 02 Cancer Detection & Therapy (Room 2)
1515 – 1715
Chair: J. Khoo

- Automated Segmentation of Breast Masses in Mammograms
  Zhang H., Foo S.W., Thng C.H.
- Diagnosis of Lung Cancer Using NIR Raman Spectroscopy
  Huang Z., McWilliams A., Lam S., McLean D.I., Lui H., Zeng H.
- Extraction of head and neck tumors using deformation models from MR images
  Zhou J., Chong V.
- Breast Cancer Diagnosis using Thermography and complementary learning fuzzy neural network
  Tan T.Z., Quek C., Ng G.S., Ng E.Y.K.
- Magnetic Particles for Hyperthermia Treatment of Cancer
  Ramanujan R.V., Lao L.L.
- Gene Selection for Cancer Classification from Microarray Data using PLS-RLSC
  Shen L., Tan E. C.
- Micelle-like Nanoparticles of Linear and Branched PLA/PEG Block Copolymer as Anti-Cancer Drug Carrier
  Pan J., Feng M., Chan W.A., Venkatraman S., Boey F.Y.C.
- Identify human colorectal cancerous via Laser Induced Autofluorescence spectra confocal image
  Sheng F., Chia T.C., Kwek L.C., Ding C.H., Tang, C.L.

## Session 03A Medical Image Processing (Room 3)
1515 – 1745
Chairs: Z. Kuanyi

- ALA-Induced-PPIX Fluorescence Imaging of Normal and Neoplastic Tongue Tissue using Confocal Endomicroscopy
  Zheng W., Harris M., Kho K.W., Thong P.S.P., Hibbs A., Soo K.C., Olivo M.
- A Simulation System for Remote Interventional Radiology Procedures
  Zhao L., Ma X., Aziz A., Zheng W., Nowinski W.L.
- An Improved Active Contour Method for Heart Wall Boundary Detection in Echocardiographic Image Sequence
  Fang W., Chan K.L., Anantaraman V.
- Augmented Reality Assisted Sinus Surgery
  Shi D. M., Ng W. S., Ling K. V., Shao W., Chen H. J., Kwoh C. K.
- Brain Atlas-assisted Segmentation of the Hippocampus from MR Neuroimages
  Minh P.D., Prakash K.N.B., Nowinski W.L.
- Removing Blocking Artifacts in Compressed Medical Images
  Singh S., Vinod K., Verma H.K.
- Simulated Annealing based Simplified Snakes for Weak Edged Medical Image Segmentation
  You J., Zhou Z., Heng P.A., Xia D.
- Extraction of the Two Modified Talairach Cortical LandMarks (I and S) from MR T1-Weighted Images
  Hu Q., Qian G., Nowinski W.L.
- Knowledge-based Interpolation of the Talairach-Tournoux Brain Atlas
  Liu J., Nowinski W.L.
- Mapping Human Skin and Aural Temperature with ANNs and IR Imager
  Ng E.Y.K., Chong C.

## Session 04 Microfluidics/MEMS (Room 2)
1715-1800
Chair: D. Trau

- Enhancement of Meniscus Repair using Mesenchymal Stem Cells in a Porcine Model
  Dutton A., Hui J.P.P., Lee E.H.
- Cardiac Differentiation of Adult Bone Marrow Mesenchymal Stem Cells
- Polyurethane Membranes for Chondrocyte Transplantation and Cartilage Engineering
  Chia S.L., Gorna K., Gogolewski K., Alini M.
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  Yabin Z., Chan-Park M.B., Chian K.S.

END OF DAY 1
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>0830 – 0900</td>
<td>Development of Microfluidic-Based Point-of-Care Diagnostic Systems</td>
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<td>Invited Speaker: Dr. Paul Yager</td>
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<tr>
<td>0900 – 0930</td>
<td>Innovation in The Medical Device Industry: Development of Cypher - the first Drug-Eluting Stent</td>
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<td>Invited Speaker: Mr. Alok Mishra</td>
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<tr>
<td>0930 – 1000</td>
<td>Heart Tissue Engineering</td>
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<td>Invited Speaker: Dr. Buddy Ratner</td>
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<tr>
<td>1000 – 1015</td>
<td>Tea break</td>
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<tr>
<td>Session 05 Biomaterials &amp; Drug Delivery (Room 1)</td>
<td>Session 06 Biomechanics (Room 2)</td>
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<td>1015 – 1230</td>
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<tr>
<td><strong>Smart Polymer Nanocarriers for Targeted Delivery</strong>&lt;br&gt;Yang Y.Y</td>
<td><strong>Biomechanics Highlights in Sports, Physiology and Medicine</strong>&lt;br&gt;Gihsita D.N.</td>
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<td><strong>Release of Lipoplexes from a Biodegradable Polymer Film: Preliminary Study</strong>&lt;br&gt;Chan W.A., Ramgopal Y.</td>
<td><strong>Evolution and Biomechanics of the Cruciate Ligaments</strong>&lt;br&gt;Fuss F.K.</td>
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<td><strong>Cross linking of Bovine Serum Albumin with Genipin: Investigation of Mechanical Properties</strong>&lt;br&gt;Sathappan K., Chian K.S., Chua L.P.</td>
<td><strong>The Double-Bundle ACL Graft Reconstruction: A superior technique to restore knee kinematics</strong>&lt;br&gt;Lie D.T.T., Amis A.</td>
</tr>
<tr>
<td><strong>Porous Beta-TCP and Its Modification with PLGA Coating for Bone Regeneration</strong>&lt;br&gt;Miao X. and Kurniawati T.</td>
<td><strong>Finger Pulley Injuries are Self-Propagating: A Mathematical Analysis of the A2-Pulley</strong>&lt;br&gt;Tan M.A., Fuss F.K., Niegi G.</td>
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<td><strong>In vitro Study on the Release Kinetics of Bovine Serum Albumin (BSA) from Injectable PLGA/BB Depot</strong>&lt;br&gt;Wang L.W., Venkatraman S.</td>
<td><strong>A Comparative Study of Different Gripping Methods for Tendons</strong>&lt;br&gt;Ng B.H., Chou S.M., Krishna V.</td>
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<tr>
<td><strong>Clinical Applications of Magnetic Nanomaterials</strong>&lt;br&gt;Ramanujan R. V.</td>
<td><strong>Foot Characterization and Anatomical Landmarks Localization</strong>&lt;br&gt;Liu X., Kim W.D., Drerup B.</td>
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<tr>
<td><strong>LUNCH</strong> 1230 - 1330</td>
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<tr>
<td>Session 08A Cardiovascular Engineering 1 (Room 1)</td>
<td>Session 09A Sport Engineering 1 (Room 2)</td>
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<tr>
<td><strong>1330 – 1530</strong></td>
<td><strong>1330 – 1530</strong></td>
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<tr>
<td>Chair: A.C. Ritchie</td>
<td>Chair: W. Kim, F.K. Fuss</td>
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<tr>
<td>• A Decoupled Control Method for the Magnetic Bearings of a Blood Pump</td>
<td>• Quantitative analysis of Singapore Golfers</td>
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<td>Lim T.M., Zhang D., Kim M.T.</td>
<td>Lim S. L., Xie X., Ong V., Teh K. C.</td>
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<tr>
<td>• An Immersed Membrane Method For Simulation of Fluid-Structure Interaction in Bio-Fluid Flows</td>
<td>• Three-Dimensional Kinematics Study of Left Hand During Golf Swing</td>
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<tr>
<td>• Computation of Gap Flow Field in a Bio-Centrifugal Blood Pump</td>
<td>• Investigation of Weight Transfer during Golf Swing</td>
</tr>
<tr>
<td>• Computational Studies of Steady Flows In Designed Sleeve Models At Distal Anastomoses</td>
<td>• Biomechanics of Push-up Exercise and Triceps Contractility</td>
</tr>
<tr>
<td>• Contractility of the Left Ventricle in Terms of its Sacromere Power Generation</td>
<td>• Comparison of Pinch- and Open Hand Grip during Sport Climbing</td>
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<td>• Detection of Cardiac Arrhythmia using Phase Space Analysis</td>
<td>• Friction at the Climbing Handhold under Different Conditions and its Implications for Sport Climbing</td>
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<td>Wong M. T., Srinivasan N., Chan Y.W.</td>
<td>Tan M. A., Fuss F. K., Niegl G.</td>
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<tr>
<td>• Flow Studies in Aorto-Right Coronary Bypass Graft System</td>
<td>• Finger Load Distribution During Sport Climbing</td>
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<td>• LV Twisting Analyzed for Pressure-Increase During Iso-Volumic Contraction</td>
<td>• Analysis of Badminton Smash Using Dual Euler Angles Algorithm</td>
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<tr>
<td>• Medical Ultrasound Imaging: Current Status and Future Trends</td>
<td>• Reconfigurable and Programmable Architecture for Digital Receive Beamformer</td>
</tr>
<tr>
<td>• Reconfigurable and Programmable Architecture for Digital Receive Beamformer</td>
<td>• Adaptive Speckle Reduction Based on Nakagami Distribution in Medical Ultrasound Imaging</td>
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<tr>
<td>• LV Twisting Analyzed for Pressure-Increase During Iso-Volumic Contraction</td>
<td>• Specific Homomorphic Nonlinear Diffusion for Speckle Reduction in Ultrasound B-mode Images</td>
</tr>
<tr>
<td>• Medical Ultrasound Imaging: Current Status and Future Trends</td>
<td>• Design and Optimization of Broadband Ultrasonic Sparse Array Transducers for Medical Imaging Applications</td>
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<td>Yoo Y.M., Kim Y.M.</td>
<td>Wang Q. B., Guo N. Q.</td>
</tr>
</tbody>
</table>

**Session 07B Computational Bioengineering 2 (Room 3)**

**Chair:** B. Schmidt

**Session 10A Ultrasonic Imaging 1 (Room 3)**

**1415 – 1530**

**Chair:** M. Kezhi

**Tea Break**

**1530 – 1545**
| Session 08B Cardiovascular Engineering 2 (Room 1) 1545 – 1645  
Session Chair: A.C. Ritchie | Session 09B Sport Engineering 2 (Room 2) 1545 – 1630  
Chairs: B. Tan, K.C. Teh | Session 10B Ultrasonic Imaging 2 (Room 3) 1545 – 1645  
Chair: M. Kezhi |
|---|---|---|
| • Multiple-Model Adaptive Control by Means of a Fuzzy Controller-based Control System  
Zheng H., Zhu K. Y., Tan Y. S. | • Determinants of Maximal Hiking Performance in Laser Sailors  
Agarwal A., Schneider F.K., Yoo Y.M., Kim Y. |
| • Numerical Investigation of Hemodynamics for the Coronary Artery Bypass Graft Model  
Chua L.P., Zhang J.M., Zhou T.M., Yu S.C.M., Ghista D.N., Tan Y.S. | • Comparative Study on the techniques of Singapore and Thailand Table Tennis players during SEA Games 2001  
Lee K.T., Xie W., Teh K.C. | • Low Sampling Frequency Digital Beamformer for Ultrasonic Imaging without Interpolation  
Gao C.Q., Zhang L.C., Wong E.M.C. |
| • Numerical Investigation of Stress Field in Distal End-to-side Anastomoses  
Liu L., Chua L.P., Ghista D.N., Tan Y.S. | • Experimental Study on Different Types of Service Spins for Singapore National Table Tennis players  
Lee K.T., Xie W. | • Comparative Evaluation of Wavelet Filters for Speckle Reduction in Ultrasound Medical Images  
Thakur A., Anand R.S. |
| • PIV Measurements on the Pulsatile Flow Characteristics in 45-degree Backward Proximal Anastomosis  
Cao J., Koh L.M. |
| **Session 11 Respiratory Biomechanics (Room 1) 1645 – 1730  
Chair: V. V. Kulish** | **Session 12A Orthopaedic Engineering 1 (Room 2) 1630 – 1745  
Chairs: S.M. Chou, D.T.T. Lie** | **Session 13A Biosignal Processing 1 (Room 3) 1645 – 1745  
Chair: O. Chutatape** |
| • Determination of O2 and CO2 Metabolic Rates and Lung O2 and CO2 Diffusion Coefficients  
Loh K.M., Ghista D.N. | • Design Optimisation in BioMedical Engineering  
Koh E.C.Y., Fuss F. K. | • A Novel Approach to Automatic Left Ventricular Contour Tracking  
Cheng J.R., Foo S.W. |
| • Oxygen Saturation Profiles in a Hollow Fibre Oxygenator  
Ritchie A.C., Thimm G. | • Design Classification and Mechanics of Artificial Discs  
Fuss F.K. | • A Novel Wavelet Based ECG Compression with X-tree Coding  
Swain S., Chutatape O., Dandapat S. |
| • Graphical Technique for Assessing Pulmonary Disease  
Loo C. M., Ang K. C., Ong J. H., Ghista D. N., Lim G. H. | • Extraforaminal Lumbar Interbody Fusion: Simulation of the Fusion Process Based on Different Implant Materials  
Fuss F. K., Sabitzer R. J. | • Left Ventricular Surface Kinematics During Isovolumic Contraction  
Yeo S.Y., Tan R.S., Liu L., Chai G.B., Ghista D.N. |
|  | • FE Investigation on Spinal Interbody Fusion  
Lee K. K., Teo E. C., Fuss F. K., Sabitzer R. J. | • Evaluation of Slice Sensitivity Profiles for TPRF Algorithm  
Yan M., Zhang C.S. |
|  | • Optimization of Cervical Ring Cage by Taguchi Philosophy  
Yang K., Teo E. C., Fuss F. K. |  |
## Scientific Programme – DAY 3

**Friday, September 10 2004**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Invited Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>0830-0900</td>
<td>Biological Resurfacing of Articular Cartilage – from Bench to Bedside</td>
<td>Dr. Lee Eng Hin</td>
</tr>
<tr>
<td>0900-0930</td>
<td>Virtual Reality, Augmented Reality and its Medical Application</td>
<td>Dr. Uli Bockholt</td>
</tr>
<tr>
<td>0930-1000</td>
<td>Vital Signs in the Real World</td>
<td>Mr. Stephen Wilson</td>
</tr>
<tr>
<td>1000-1030</td>
<td>Clinical Endoscopy System: Present and Future</td>
<td>Dr. Tsuneo Hidaka</td>
</tr>
<tr>
<td>1030-1045</td>
<td>Tea break</td>
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<tr>
<td>Session 14 Biosensors/Diagnostic Tools (Room 1)</td>
<td>Session 13B Biosignal Processing 2 (Room 2)</td>
<td>Session 15 Distributed Diagnosis &amp; Home Healthcare (Room 3)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>----------------------------------------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>1045-1200 Chair: K. L. Chan</td>
<td>1045-1130 Chair: C. Zhang</td>
<td>1045-1130 Chair: S. C. Tjin</td>
</tr>
<tr>
<td>• Multi-Parameter Clinical Diagnosis using Neural Networks Tan E.K.</td>
<td>• Uni-channel PCA for noise reduction from ECG signals Palaniappan R., Tan E.K.</td>
<td>• Distributed Diagnosis and Home Healthcare (D2H2) and Patient-Centered Electronic Medical Record Kim E.H., Kim J. J., Matsen F.A., Kim Y.M.</td>
</tr>
<tr>
<td>• An Otoacoustic Emissions Detecting System using USB AD/DA Board Qian X., Ye D.</td>
<td>• Wavelet-Based Denoising and Analysis of Phonocardiogram Wang P., Anantharaman V.</td>
<td>• Advanced System Architecture for Telecardiology Goh K. W., Kugean C., Tan E. K., Prabaharan K.</td>
</tr>
<tr>
<td>• Feasibility of biosensing based on two-dimensional square photonic lattice Zhang D. W., Irawan R., Tjin S. C., Yuan X. C.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Application of Artificial Neural Network Technique in Healthcare Expenditure Analysis Chia E., Khong P.W., Ghista D.N.</td>
<td></td>
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</tr>
<tr>
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<td></td>
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</tr>
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<td></td>
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</tr>
</tbody>
</table>
Annual NTU-SGH Symposium 2005
Moving Technology Towards Better Patient Care

11–12 August 2005
Singapore National Eye Centre Auditorium

Programme & Abstracts

Organised by
# Daily Programme

### 11 August 2005

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>0800-0900</td>
<td>Registration</td>
</tr>
<tr>
<td>0900-0910</td>
<td>OPENING CEREMONY</td>
</tr>
<tr>
<td></td>
<td>Welcome Address: Prof. Su Guoming, President, NTU</td>
</tr>
<tr>
<td></td>
<td>Organising Chairperson: Dr. Danny Lim</td>
</tr>
<tr>
<td></td>
<td>Guest of Honour: Prof. Su Guoming</td>
</tr>
<tr>
<td>0910-1010</td>
<td>FELNARY LECTURE 1</td>
</tr>
<tr>
<td></td>
<td>Theme: Integration in Biocomposites and Biomanufacturing</td>
</tr>
<tr>
<td></td>
<td>Chair: Prof. See Khoo-Clax</td>
</tr>
<tr>
<td>1010-1100</td>
<td>Tea Break and Exhibition</td>
</tr>
<tr>
<td>1100-1200</td>
<td>FELNARY LECTURE 2</td>
</tr>
<tr>
<td></td>
<td>Research in Bioengineering and Nanotechnology</td>
</tr>
<tr>
<td></td>
<td>Chair: Prof. Michael Khar</td>
</tr>
<tr>
<td>1200-1315</td>
<td>SHOWCASE OF NTU-SGH JOINT PROJECTS</td>
</tr>
<tr>
<td></td>
<td>Transcutaneous Pumps for Biomedical Applications</td>
</tr>
<tr>
<td></td>
<td>Aortic-Prof. L. Lim</td>
</tr>
<tr>
<td></td>
<td>Adult Human Mesenchymal Stem</td>
</tr>
<tr>
<td></td>
<td>Cells for Cardiac Tissue Engineering</td>
</tr>
<tr>
<td></td>
<td>Dr. Philip, Wong</td>
</tr>
<tr>
<td></td>
<td>Rapid Portable System for Screening Tuberulosis</td>
</tr>
<tr>
<td></td>
<td>A/Prof. Lim, Chng.</td>
</tr>
<tr>
<td></td>
<td>A Displaced Scaffold for the Development of Composite Skin Constructs</td>
</tr>
<tr>
<td></td>
<td>Dr. Vin, Chen &amp; Mr. Leng, Mng, Fung</td>
</tr>
<tr>
<td></td>
<td>Single Living Cell Detection and Sorting</td>
</tr>
<tr>
<td></td>
<td>Using Bioreactor Integrated Chip</td>
</tr>
<tr>
<td></td>
<td>A/Prof. Lim, Chng.</td>
</tr>
<tr>
<td></td>
<td>Chair: A/Prof. Yap, Boons, Kang</td>
</tr>
<tr>
<td>1315-1400</td>
<td>Lunch</td>
</tr>
<tr>
<td></td>
<td>MODERATED POSTER SESSION</td>
</tr>
<tr>
<td></td>
<td>(1315-1340)</td>
</tr>
<tr>
<td></td>
<td>Moderators: A/Prof. Yap, Boons, Kang</td>
</tr>
<tr>
<td></td>
<td>Dr. Vin, Chen</td>
</tr>
</tbody>
</table>
ACTIVITY-BASED DYNAMIC INSULIN INFUSION SYSTEM
Loh Kah Meng1, Chan Ting Kuan2, Dhanjoo N. Ghista1, Heiko Rudolph2
1 School of Engineering (Electronics), Nanyang Polytechnic, Singapore, 2 TechSource Systems Pte Ltd, Singapore
3 Department of Biomedical Engineering, Nanyang Technological University, Singapore, 4 School of Electrical and Computer Engineering, Biomedical, RMIT, Australia

Summary – This paper has demonstrated the operation of an activity-based dynamic insulin infusion system. The amount of insulin infused to bring the blood glucose concentration down is regulated by a closed-loop PD (Proportional-Derivative) control algorithm.

Index Terms – dynamic, clinical diagnosis, insulin release, systems-engineering model

I. MOTIVATION
The current insulin infusion systems are based on the previously known individual’s activities history to estimate the required insulin amount. The techniques adopted do not allow the patients to deviate too much from their normal daily activities [3]. Our work focuses on regular sampling of diabetic patient’s blood glucose concentration through a sensor to compute the required amount of insulin to be released into the blood stream.

II. METHODOLOGY
The closed loop system will continuously monitor the blood glucose concentration at 0.5h interval. Once the system detects that the blood glucose concentration exceeds a predetermined threshold e.g. 120mg/dl [1], the system will be armed and calculate the amount of insulin required [2] to bring the blood glucose concentration below the threshold.

![System Block diagram of the insulin release system. The error is generated from glucose sensor and computed glucose concentration after the release of insulin into the blood stream at 0.5h interval.](image)

III. RESULTS
The figure 2 shows the results of the insulin infusion system. The diabetic subject D18’s unaided glucose clinical data is fed into the system. After the release of insulin at 0.5h, 1h and 1.5h intervals, the final blood glucose concentration drops below the threshold and the controller will stop releasing insulin into the blood stream.

![Figure 2. The subject’s unaided blood glucose concentration at time 0 is above 120mg/dl. The system is armed and re-samples the blood glucose concentration at 0.5h (170mg/dl). The system will send a bolus of insulin 10mU/dl into the blood stream. The system will keep monitoring the resulting blood glucose concentration at 1.0h and 1.5h hour intervals. If the blood glucose concentration is above the threshold, the system will infuse a computed insulin bolus into blood stream.](image)

IV. CONCLUSION
We have demonstrated the capabilities of an activities-adaptive dynamic real-time insulin release system. The system is able to protect the users from hypoglycemia and hyperglycemia. As we continue this work, we will develop a clinically-implementable hardware system for diabetic patients.

REFERENCES
DETERMINATION OF URINE OUTFLOW AND RENAL FUNCTION QUANTITATIVELY

Lah K. Meng, David Ng, Dhanjoo N Ghista, Heiko Rudolph

1 School of Engineering (Electronics), Nanyang Polytechnic, Singapore, 2 Department of Nuclear Medicine and PET, Singapore General Hospital, Singapore, 3 Department of Biomedical Engineering, Nanyang Technological University, Singapore.
4 School of Electrical and Computer Engineering, Biomedical, RMIT, Australia.

Summary – In this paper, we provide a non-invasive methodology to assess physiological function of the kidneys. We analyze the renograms with 2-compartmental modeling of the kidney-renal outflow system, and therefore compute the amount of flow of renal radionuclide into and out of the renal pelvis compartment.

Index Terms – glomerular filtration rate, GFR, renal outflow obstruction, renal function

I. MOTIVATION

Currently there is no mathematical model for renal function and urine outflow rate based on non-invasive renography.

II. METHODOLOGY

We will first digitize and normalize the renograms. The 2-compartmental modeling of the kidney outflow system was performed with derivation of system parameters: $k$, $A$, and $AT$ ($=P_o$) [1]. We will only accept the results of the best fit ($R^2 > 95\%$). From these parameters, we will determine the urine outflow ($U(t)$) $\text{dL/sec}$.

III. RESULTS

![Figure 1. Clinical renograms of volunteer coded Patient 7.](image)

Figure 1. Clinical renograms of volunteer coded Patient 7.

Note that the $(Q_1, R_1)$ segment of the tracer curve for the right kidney is similar to the $(P_o, Q_2)$ segment and demonstrates good outflow-rate compared to the $(Q_1, R_2)$ segment of the obstructive curve for the left kidney.

We have performed parametric identification for equations (9) and (10) using MatLab 7 in the paper [1]. The following are the best fitted results for patients 7.

![Figure 2. Simulated renograms of volunteer coded Patient 7. The clinical data for both kidneys is best fitted by equation (9) in the paper [1]. The identified parameters are: $k_1 = 0.0124; A_1 = 5.48E-05; P_o = 0.0323 & U(t)$ $= 0.0635$ $k_2 = 0.0221; A_1 = 8.08E-05; P_o = 0.0323 & U(t)$ $= 0.0635$](image)

Table 1. Comparison of clinical and calculated results. We can observe that the errors for each kidney is less than 1%.

<table>
<thead>
<tr>
<th>Identity</th>
<th>% Clinical area under the curves between 60 to 120 sec</th>
<th>% Calculated area under the curves between 60 to 120 sec</th>
<th>% Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>Patient 7</td>
<td>44</td>
<td>56</td>
<td>43.87</td>
</tr>
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</table>

IV. CONCLUSION

We have demonstrated the techniques of using the two-compartmental model of kidney-renal outflow tract [1] to assess the clinical relevance with comparison with clinical renogram studies.

REFERENCES

SYSTEM AND METHOD FOR DETECTING OF PULMONARY DISEASES

Field of the Invention

[0001] The present invention generally relates to systems and methods for detecting pulmonary diseases, and more particularly to non-invasive systems and methods for detecting pulmonary diseases by analyzing inhalation and exhalation.

Background of the Invention

[0002] Lung is a vital organ allowing exchanges of O₂ and CO₂ between the alveolar sockets and bloods. When the lung is impaired, e.g., viral or bacterial infections, its physical appearance and/or functions will be altered, resulting in pulmonary diseases. The current detection of pulmonary diseases is mainly done by X-ray. However, the X-ray is not only invasive, but also only able to detect the physical alterations of lungs. Thus, the X-ray is not applicable for detecting pulmonary diseases at early stages. In addition, there are a broad range of so-called pulmonary function tests. For example, spirometry measures how well the lungs exhale. Lung volume measurement permits detection of restrictive lung diseases. Testing the diffusion capacity permits an estimate of how efficiently the lungs are able to transfer oxygen from the air into the bloodstream. However, all the available function tests are mere measures of systemic metabolism rather than of pulmonary functions.

[0003] It is well known that the components of exhalation could be utilized for diagnosis of certain diseases. For example, U.S. Pat. 4,823,803 discloses a device for testing human exhalation for halitosis by using sensors that are sensitive to malodorant gases of predetermined chemical compositions for producing signals variable with the detected concentrations of the malodorant gases. However, this patent is directed to the detection of malodorant gases rather than the lung functions.

[0004] There are situations in which an early detection of viral infection is critical for treatment of the victim and more importantly for the control of the epidemic. For example, the recent epidemic of SARS (Severe Acute Respiratory Syndrome) has raised concerns about effective detection of such relevant diseases, especially at a much earlier
stage of infection in human bodies. Upon early detection, scarce and precious medical resources can be focused on the infected persons. In the early stages of the infections, the X-ray screening may not be useful because the pathogenic damages on the lungs may not be evident enough to be detected by the machine. The current available function tests may not be able to detect the early signs of infections because the functions tests measure the systemic metabolism only. While PCR is powerful in detecting the early infection, it is prone to mutations. Massive mutations will handicap this technique severely.

Therefore, there is an imperative need to develop non-invasive systems and methods for detecting pulmonary diseases, especially ones inflicted by viral or bacterial infections. Furthermore, the detection is independent of the mutations of infectious agents. This invention satisfies this need by disclosing systems and methods of detecting pulmonary diseases by analyzing of the inhalation and exhalation of a test person. Other advantages of this invention will be apparent with reference to the detailed description.

**Summary of the Invention**

The present invention provides a to be completed upon agreement of claims.

The objectives and advantages of the invention will become apparent from the following detailed description of preferred embodiments thereof in connection with the accompanying drawings.

**Brief Description of the Drawings**

Preferred embodiments according to the present invention will now be described with reference to the Figures, in which like reference numerals denote like elements.

FIG 1 is a block diagram of the pulmonary disease detection system (PDDS) in accordance with one embodiment of the present invention.

FIG 2 shows a breath analyzer configured in accordance with one embodiment of the present invention.
FIG 3 shows a flowchart of detecting pulmonary diseases on the basis of altered oxygen consumption and carbon dioxide generation.

FIG 4 shows another functional flowchart of detecting pulmonary diseases in accordance with another embodiment of the present invention.

FIG 5a shows a diagram illustrating the directional relationships among the different pressures that may be detected or induced from the air flow rates detected by the breath analyzer as shown in FIG 2.

FIG 5b shows that different pressures are functions of time.

Detailed Description of the Invention

The present invention may be understood more readily by reference to the following detailed description of certain embodiments of the invention.

Throughout this application, where publications are referenced, the disclosures of these publications are hereby incorporated by reference, in their entireties, into this application in order to more fully describe the state of art to which this invention pertains.

The present invention provides systems and methods for detecting pulmonary diseases. While there are provided more details about the systems and methods hereinafter, it is to be appreciated that the present systems and methods are based on the understanding that anyone developing any pulmonary diseases would demonstrate certain detectable breathing deficiencies. The deficiencies may be manifested by the changes of the oxygen consumption and carbon dioxide generation, or the differences of lung compliance and airflow-resistance.

There is provided a block diagram of the pulmonary disease detection system (PDDS) as shown in FIG 1 in accordance with one embodiment of the present invention. The PDDS 100 comprises a breath analyzer 102, a computer processor 103, and a medical database 104. The breath analyzer 102 will take in the breath from a test person 101 and output the information of components of the breath from the person to the computer processor 103. The computer processor 103 contains algorithms for manipulating the information of the breath and comparing the manipulated results with the medical database 104, so that the computer processor provides the results of diagnosis 105.
The breath analyzer 102 may be any apparatus that can obtain breathing information from a test person that is sufficient for the application of the algorithms embedded in the computer processor 103. For example, for the application of an algorithm based on oxygen consumption and carbon dioxide generation, the breath analyzer 102 basically comprises of gas sensors such as sensors for oxygen, carbon dioxide and water vapor. The compositions of both inhale and exhale gases are analyzed. Then the respective compositions are further processed by the computer processor 103.

FIG 2 shows a breath analyzer 102 configured in accordance with one embodiment of the present invention. The breath analyzer 102 comprises a mask 1, a data acquisition unit 7, and an air tank 11. The mask 1 is configured to cover the nose and mouth of a test person so that maximum fresh air is delivered to the test person and minimum exhaled air is lost before proper measurement is completed. As shown in FIG 2, the mask 1 includes an air outlet membrane 2 as a seal for preventing air within the mask from leaking; an exhaust flip valve 3 that will open to allow all the expired air to flow out 4 of the mask when the test person breathes out; an air inlet membrane 21 as a seal for preventing air within the mask from leaking; an inhale flip valve 22 that will open to allow the fresh air from the air tank 11 to flow in 23 when the test person breathes in; an oxygen electrode 25 for detecting the oxygen in the air composition; a carbon dioxide gas electrode 24 for detecting the carbon dioxide in the air composition; a nitrogen gas electrode 17 for detecting the nitrogen in the air composition; a water vapor electrode 18 for detecting the water vapor in the air composition; an inspired air flow rate electrode 19 for determining the flow rate of exhale air; an expired air flow rate electrode 20 for determining the flow rate of exhale air; and signal conductors 5 that transmit the information from the electrodes to the data acquisition unit 7. The signal conductors may be ultra-low impedance conductor or fiber optic.

The air tank 11 contains pressurized air so as to ensure a measurable and controllable air supply to the test person. An air delivery pipe 16 connects the air tank with the mask so as to deliver a stream of controlled air from the air tank to the mask. The air tank 11 also includes four electrodes 12, 13, 14, 15 for detecting the oxygen, carbon dioxide, nitrogen, and water vapor respectively. The signal conductors 10 transmit the data from the four electrodes to the data acquisition unit 7. The signal conductors may be ultra-low impedance conductor or fiber optic.
The data acquisition unit 7 includes connectors 6, 9 for connecting to the signal conductors 5, 10 so that it will receive all the information from the air tank and the mask. Then the data acquisition unit 7 transmits the received signals to the computer processor 103 which acts as the central processing unit (CPU). The transmitted information may be digitalized packets.

After the CPU receives the data of the air compositions from the data acquisition unit 7, it will process the air composition data. In one aspect of the present invention, the detection of pulmonary diseases is based on the understanding that anyone developing any pulmonary diseases would demonstrate certain detectable breathing deficiencies. The inventors of the present invention further discovered that the breathing deficiencies are manifested by altered oxygen consumption and carbon dioxide generation. FIG 3 shows a flowchart of detecting pulmonary diseases on the basis of altered oxygen consumption and carbon dioxide generation.

Referring now to FIG 3, when the PDDS 100 starts 301, it obtains through the data acquisition unit 7 the information including oxygen composition, carbon dioxide composition, nitrogen composition, water vapor composition, and air flow rate 302. It is to be noted that the air flow rate data will be discussed hereinafter when the air flow rate will be used to calculate the volume compliance and air-flow resistance in another algorithm of the present invention. Then the CPU will calculate the overall relatives of all gases compositions 303. Then the processed data is searched against the stored database to determine whether the test person has pulmonary diseases 304. Then diagnostic results will be outputted 305 and the operation comes to an end 306. It is noted from FIG 3 that the stored database is continuously updated so that the database will become more useful when more data is collected.

Now there is provided a more detailed description of detecting pulmonary diseases on the basis of altered oxygen consumption and carbon dioxide generation. The basic assumption is that the composition of expired air from a patient such as a person with SARS infection is different from that of a normal person. It is further assumed that with an expired air, (a) its O₂ content (or % vol.) will be greater (because of less O₂ consumed from alveoli) and closer to that of inspired air; (b) its CO₂ content will be lesser, and more akin to that of inspired air; and (c) the transfer coefficients for O₂ & CO₂ will be lesser as compared to a medically normal person. Therefore, the mass balance analysis involves (i)
compositions of air breathed in and out; and (ii) consumption or generation of O₂, CO₂ and H₂O.

For calculation of inhale and exhale compositions, there are a few general assumptions: (1) Breathing Rate (BR) = 12 breaths/min; (2) P H₂O at 37°C = 47mmHg; (3) O₂ metabolic consumption rate at (at BTP) = 284 ml/min; and (4) CO₂ production rate (at BTP) = 227 ml/min. Thus, the expected compositions of the expired air can be calculated from the atmospheric air or vice versa. For example, as shown in Table 1, the expected expired air compositions can be calculated from the numbers of the atmospheric air column:

N₂ = 393.1 ml

O₂ = 104.2-(284/12) = 80.53 ml

CO₂ = 0.2+(227/12) = 19.12 ml

Total = 492.75 ml (1)

Ratio of water vapor/dry gas in the expired air = 49.5 mmHg/(760-47) mmHg = 49.5/713 = 6.94% (2)

Volume of water vapor in the Expired air = (1)x(2)=492.75 0.0694=34.21 ml (3)

Total Expired air = [1]+[3]=492.75+34.21=526.96 ml (4)

Thus the percentage of the gases components in the expired air can be calculated as follows:

N₂ = 393.1/526.96 = 74.6%;

O₂ = 80.52/526.96 = 15.28%;

CO₂ = 19.12/526.96 = 3.63%; and

H₂O = 34.21/526.96 = 6.49%.

All the numbers of the atmospheric air and expired air are presented in Table 1.

Table 1. An exemplary air compositions

<table>
<thead>
<tr>
<th>Respiratory gases</th>
<th>Atmospheric Air mmHg</th>
<th>Humidified Air mmHg</th>
<th>Alveolar Air mmHg</th>
<th>Expired Air mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ml/</td>
<td>%</td>
<td>ml/</td>
<td>%</td>
</tr>
<tr>
<td>N₂</td>
<td>597</td>
<td>78.62</td>
<td>563.3</td>
<td>78.5</td>
</tr>
<tr>
<td>O₂</td>
<td>159</td>
<td>20.84</td>
<td>149.3</td>
<td>20.9</td>
</tr>
</tbody>
</table>
So far it has been shown that if the rates of oxygen consumption and carbon dioxide generation are known, the ideal composition of an expired air can be calculated from the original composition of the atmospheric air. This is important for initializing the stored databases because in the early stages, the PDDS may have to generate part of the database by calculating the components of the expired airs from the atmospheric airs based on certain assumptions. With the gradual accumulation of the database, more and more actual data will supplement or substitute the calculated ones. As discussed early, the breath analyzer 102 of the present invention can acquire the data of individual gas components of the expired air from the test person and the CPU can manipulate the data to give the percentages of each gas component as to the expired air. The processed data of each gas components will be compared with the stored medical database. If the test person suffers from any illness that affects pulmonary functions, it is expected that the processed data of the expired air from a test person will be deviated from that of the stored database for a normal person. If this is so, the CPU will output the diagnostic results showing that the test person is probably having pulmonary diseases. Then the test person can seek further examinations to determine which kind of pulmonary diseases he/she is developing.

As shown in Table 1, it is apparent that the rates of oxygen consumption and carbon dioxide generation may be derived from the actual measurements of individual gas components of the atmospheric air and expired air. It is noted that all of the data of individual gas components can be obtained by the breath analyzer as shown in FIG 2. The calculated rates can be compared with the stored database to determine whether the test person is suffering any pulmonary diseases.

As mentioned earlier, the choice of a breath analyzer 102 for the present PDDS is limited by its function only. For example, when the lung compliance and airflow-resistance are used for detecting pulmonary diseases, the breath analyzer 102 may be a commercially available spirometer. Now referring to FIG 4, there is provided another functional flowchart of detecting pulmonary diseases in accordance with another
embodiment of the present invention. When the PDDS starts 400, it obtains data from the breath analyzer 401 (the same as the one shown in FIG 2) to determine the volume breath characteristics of the test person 402, and further extract the parameters of P0, P1, P2, Ra, Ca and W 403. If the extracted parameters are not the best filtered results 404, the program will go back to step 403 to try to get the best parameters. If the extracted parameters are the best filtered results 404, then the VTI1, VTI2 and VTI3 will be determined 405. Then the program will conduct diagnosis 407 by utilizing the medical databases 406, 408, and output the results 409, resulting the end of the program 410.

[0045] FIG 5a shows a diagram illustrating the directional relationships among the different pressures that may be detected or induced from the air flow rates detected by the breath analyzer as shown in FIG 2. FIG 5b shows that different pressures are functions of time. From there are derived a few fundamental equations that are the foundation for the algorithm shown in FIG 4:

[0046]

\[(i) \ (P_a - P_p) - P_{el} = 0\]
\[(ii) \ P_{el} = \frac{(2 \ a \ h)}{R} r = 2 \ T / r = V/C + P_{eb \ 0}\]
\[(iii) \ (P_o - P_d) = R(dV/dt)\]
\[(iv) \ P_L = P_o - P_p\]
\[(v) \ R(dV/dt) + VIC = P_L - P_{el \ 0}\]

[0047] Now there is provided a more detailed description of determination of the volume breath characteristics of the test person 402. In one embodiment of the present invention, the lung ventilation function is analyzed by means of a very simple model represented by a first-order differential equation (Deq) in lung-volume (V) dynamics in response to the driving pressure (P_L = atmospheric pressure - pleural pressure), as shown in FIG 5

[0048] First, the model governing equation derived from the basic equations is as follows:

\[RV + V/C = P_L(t) - P_{el \ 0} = P_o + P_1 \cos \omega t + P_2 \sin \omega t - P_{el \ 0}\]  

[0049] wherein (i) P_o, P_1 and P_2 are obtained from the given P_L (= P_o - P_p) data; (ii) the parameters of this Governing Deq are lung compliance (C) and airflow-resistance (R), wherein in the equation both R and C are instantaneous valves; (iii) V = V(t) - Vo (the
lung volume at the end-expiration); and (iv) \( P_{el,o} \) is the lung elastic recoil pressure at the end of expiration and \( P_{el,o} = P_{el} - V/C \).

At end-expiration when \( \omega t = \omega T \), \( P_L = P_{el,o} \). Hence,

\[
P_{el,o} = P_o + P_1, \quad \text{and the governing equation (1) becomes:}
\]

\[
RV' + V/C = -P_1 + P_1 \cos \omega t + P_2 \sin \omega t = P_n \quad (2-a)
\]

where the right-hand side represents the net pleural pressure. \( (P_n = P_{atm} - P_p - P_{el,o}) \) curve. This \( P_n \) is in fact the driving pressure \( (P_o - P_p) \) normalized with respect to its value at end-expiration. Equation(2-a) can be rewritten as follows:

\[
\dot{V} + V/R C = -P_1 / R + (P_1 / R) \cos \omega t + (P_2 / R) \sin \omega t; \quad RC = \tau \quad (2-b)
\]

wherein the \( P(t) \) clinical data displayed in FIG 5b is assumed to be represented by:

\[
Po = 9.84 \, \text{cm H}_2 \text{O}, \quad P1 = -1.84 \, \text{cm H}_2 \text{O}, \quad \text{and} \quad P2 = 3.16 \, \text{cm H}_2 \text{O} \quad (3)
\]

If, in equation (1), \( R_a \) and \( C_a \) are designated as the average values \( (R \) and \( C) \) for the ventilatory cycle, then the solution of equation (1) is given by:

\[
V(t) = -P_1 C_a + P_1 C_a \left[ \cos \omega t + \omega R_a C_a \sin \omega t \right] / (1 + \omega^2 R_a^2 C_a^2) + P_2 C_a \left[ \sin \omega t - \omega R_a C_a \cos \omega t \right] / (1 + \omega^2 R_a^2 C_a^2) + H e^{-t/R_a} \quad (4)
\]

wherein the term \( (R_a C_a) \) is denoted by \( \tau_a \), and \( \omega = 1.55 \, \text{rad/s} \) (based on the data in FIG 5b). If \( V = 0 \) at \( t = 0 \), then, putting \( V / (at \ t = 0) = 0 \) gives us:

\[
H = \{ C_a \omega \tau_a / (1 + \omega^2 \tau_a^2) \} \left( P_2 + P_1 \omega \tau_a \right) \quad (5)
\]

Then from equations (4) and (5), the overall expression for \( V(t) \) becomes:

\[
V(t) = -P_1 C_a + \{ P_1 C_a (\cos \omega t + \omega \tau_a \sin \omega t) / (1 + \omega^2 \tau_a^2) \} + \{ P_2 C_a (\sin \omega t - \omega \tau_a \cos \omega t) / (1 + \omega^2 \tau_a^2) \} + \{ e^{t/\tau_a} \omega C_a \tau_a (P_2 + P_1 \omega \tau_a) / (1 + \omega^2 \tau_a^2) \} \quad (6)
\]

If \( dV/dt = 0 \) at \( t = 0 \), implying no air-flow at the start of inspiration, then equation (6) can be differentiated into:
\[
\dot{V} = \frac{P_1 C_a}{(1+\omega^2\tau_a^2)} (-\omega \sin \omega t + \omega^2 \tau_a \cos \omega t)
\]

\[+
\frac{P_2 C_a}{(1+\omega^2\tau_a^2)}((\omega \cos \omega t + \omega^2 \tau_a \sin \omega t)
\]

\[+
\frac{- C_a e^{-\tau_a}}{(1+\omega^2\tau_a^2)} (\omega P_2 + P_1 \omega^2 \tau_a)
\]

(7)

[0059] From equation (7), we get: \(\dot{V} = 0\) at \(t = 0\), thereby also satisfying this initial condition. By matching the above \(V(t)\) expression (6) with the given \(V(t)\) data (in FIG 5b), and carrying out parameter-identification, the in vivo values of \(R_a\) and \(C_a\) can be determined. As a check, it can be verified that the substitution of (6) and (7) satisfies equation (2).

[0060] However, we can also analytically evaluate \(R_a\) and \(C_a\) by satisfying some conditions. For this purpose, we first note that \(V\) is maximum (=Tidal Volume, TV) at about \(t (= t_v) = 1.6s\), i.e. at \(\omega t_v = 2.48\) rad. Now, for \(\omega t_v = 2.48\) rad, we get:

\(\sin(\omega t_v) = 0.62\), \(\cos(\omega t_v) = -0.79\) and \(\tan(\omega t_v) = -0.78\).

Also, for \(\omega t_v = 2.48\) rad (and based on the knowledge of the range of \(\tau_a\)), the exponential term \(e^{-\tau_a}\) (in equation 6) becomes of the order of \(e^{-3}\) and less; hence, we decide to neglect it. So then, by and putting \(\dot{V} = 0\) in equation (7), we obtain:

\[\tan(\omega t_v) = (P_2 + \omega \tau_a P_1) / (P_1 - P_2 \omega \tau_a) = -0.78 \] (8)

[0061] Upon substituting the values of \(P_1\) and \(P_2\) from equation (3), and putting \(\omega = 1.55\) rad s\(^{-1}\), we obtain the value of \(\tau_a = 0.26s\). We can also put \(\ddot{V} = 0\) at \(t = 0.58\) or \(\omega t = 93\) and obtain a similar value for \(\tau\). Then, we also note that at \(t_v = 1.6s\) (for which \(dv/dt = 0\)), \(V = 0.6l\). Hence upon substituting for \(\cos(\omega t_v) = -0.79\) and \(\sin(\omega t_v) = 0.62\) in equation(7), and again neglecting the exponential term we get the following algebraic equation:

\[-P_1 C_a - (0.54 P_1 C_a / D) + (0.94 P_2 C_a / D) = 0.6; \] (9)

[0062] wherein \(D = 1 + \omega^2 \tau_a^2\), \(\omega = 1.55\) rad/s, and \(\tau_a = 0.26s\); this equation can hence be rewritten as:

\[C_a (-1.54 P_1 + 0.94 P_2) = 0.7 \] (10)

[0063] We can substitute, therein, the values of \(P_1\) & \(P_2\) from equation (3), and obtain the value of \(C_a = 0.12 L (cm H_2 O)^{-1}\). Since we have computed \(\tau_a = 0.26\) s,
therefore \( R_a = 2.20 \ (cm \ H_2O) \ s \ L^{-1} \). These are the average values of resistance to airflow and lung compliance during the ventilatory cycle shown in FIG 5b.

Since Lung disease will influence the values of \( R \) and \( C \), these parameters can be employed to diagnose lung diseases. For instance in the case of emphysema, the destruction of lung tissue between the alveoli produces a more compliant lung, and hence results in a larger value of \( C \). In asthma, there is increased airway resistance (\( R \)) due to contraction of the smooth muscle around the airways. In fibrosis of the lung, the membranes between the alveoli thicken and hence lung compliance (\( C \)) decreases. Thus by determining the normal and diseased ranges of the parameters \( R \) and \( C \), we can employ this simple Lung-ventilation model for differential diagnosis. Let us, however formulate just one non-dimensional number to serve as a ventilatory performance index \( VTI_1 \) (to characterize ventilatory function), as:

\[
VTI_1 = \int (R_a \ C_a) \ (Ventilatory \ rate \ in \ s^{-1}) \ 60 \ f^2 = \tau^2 \ (BR)^2 \ 60^2
\]  

(11)

where \( BR \) is the breathing rate. Now, let us obtain its order-of-magnitude by adopting representative values of \( R_a \) and \( C_a \) in normal and disease states. Let us take the above computed values of \( R_a = 2.2 \ (cm \ H_2O) \ s \ L^{-1} \) and \( C_a = 0.12 \ L \ (cm \ H_2O)^{-1} \) and \( BR = 12 \ m^{-1} \) or \( 0.2 \ s^{-1} \), computed for the data of Fig(1) and equation(3). Then, in a supposed normal situation, the value of \( VTI_1 \) is of the order of 9.75. In the case of obstructive lung disease, (with increased \( R_a \) ), let us take \( R_a = 3 \ (cm \ H_2O) \ s \ L^{-1} \), \( C_a = 0.12 \ L \ (cm \ H_2O)^{-1} \) and \( BR = 0.3 \ s^{-1} \); then we get \( VTI_1 = 42 \). For the case of emphysema (with enhanced \( C_a \)), let us take \( R_a = 2.0 \ (cm \ H_2O) \ s \ L^{-1} \), \( C_a = 0.2 \ L \ (cm \ H_2O)^{-1} \) and \( BR = 0.2 \ s^{-1} \); then we obtain \( VTI_1 = 23.04 \). In the case of lung fibrosis (with decreased \( C_a \)), we take \( R_a = 2.0 \ (cm \ H_2O) \ s \ L^{-1} \), \( C_a = 0.08 \ L \ (cm \ H_2O)^{-1} \) and \( BR = 0.2 \ s^{-1} \); then we obtain \( VTI_1 = 3.7 \). We can, hence summarize that \( VTI_1 \) would be in the range of 2-5 in the case of fibrotic lung disease, 5-15 in normal persons, 15-25 for the case of emphysema, 25-50 in the case of obstructive lung disease. This would of course be needed to be verified by analyzing a big patient population.

Now, all of this analysis requires pleural pressure data, for which the patient has to be intubated. If now we evaluate the patient in an outpatient clinic, in which we can
only monitor lung volume and not the pleural pressure, then we have to develop a non-invasively obtainable Ventilatory index.

In order to formulate a non-invasively determinable Ventilatory index from equation (1), we need to redesignate the model parameters, and indicate their identification procedure. So we make use of the following features from the volume-time data to facilitate evaluation of the following three parameters: \( (P_1 \, C), \ (P_2 \, C) \) and \( \tau \):

At \( t = t_v = 1.6s \ & \ \omega \, t_v = 2.48 \), \( V \) is max \& \( dV/dt = 0 \); hence we rewrite equation (9) as:

\[
\tan (\omega \, t_v) = -0.78 = (P_2 + \omega \, t \, P_1) / (P_1 - P_2 \omega \, t) \quad (12)
\]

At \( t = t_m \), \( \ddot{V} = 0 \); hence by differentiating equation. (7), without the exponential term ,we obtain:

\[
\ddot{V} = \frac{P_1 C (-\omega^2 \cos \omega \, t_m - \omega^3 \tau \sin \omega \, t_m) + P_2 C (-\omega^2 \sin \omega \, t_m - \omega^3 \tau \sin \omega \, t_m)}{(1 + \omega^2 \tau^2)} \]

i.e. \[
\tan \omega \, t_m = (-P_1 + \omega \tau \, P_2) / (P_1 \omega \tau + P_2)\]

At \( t = 1s \ & \ \omega \, t = \pi/2 \), \( V = V_1 \) (whose value is obtainable from FIG 5b); this condition yields (without the exponential term):

\[
V_1 = -(P_1 C) - \{\omega \, \tau \, (P_1 C)/(1 + \omega^2 \tau^2)\} + \{ (P_2 C) / (1 + \omega^2 \tau^2)\} \quad (14)
\]

At \( t = 2s \ & \ \omega \, t = \pi/2 \), \( V = V_2 \) (whose value is obtainable from FIG 5b); this condition yields (without the exponential term):

\[
V_2 = -(P_1 C) - \{(P_1 C)/(1 + \omega^2 \tau^2)\} + \{\omega \, \tau \, (P_2 C)/(1 + \omega^2 \tau^2)\} \quad (15)
\]

At \( t = 0.3s \ & \ \omega \, t = 270 \), \( V = V_3 \) gives:

\[
V_3 = -(P_1 C) - \{\omega \, \tau \, (P_1 C)/(1 + \omega^2 \tau^2)\} - \{(P_2 C) / (1 + \omega^2 \tau^2)\} \quad (16)
\]

From equations (12) & (13) and any one of the equation(s) (14-16), we can only obtain the values of \( \omega \, \tau \) (or of \( \tau \), since \( \omega = 1.55 \)) and of \( (P_1 \, C) \) & \( (P_2 \, C) \) but not of \( P_1 \) & \( P_2 \) by themselves. On the other hand, by also fitting equation (6), (without the exponential term) to the \( V(t) \) data, we obtain:
\[ \tau = \text{rad s}^{-1} \quad P_1 C = L, \quad P_2 C = L \]  

(17)

We can nevertheless formulate another non-invasively-determinable non-dimensional ventilatory index \((V_T I_2)\) in terms of these parameters, \((\omega \tau, P_1 C, \text{and } P_2 C)\) as follows:

\[ V_T I_2 = 60 \left( \frac{\omega \tau}{TV} \right)^2 / 2\pi \left( P_1 C \right) \left( P_2 C \right) \]

(18)

\[ = 30 \left( \frac{\omega \left( R/C \right)}{TV} \right)^2 / \pi P_1 P_2 \]

It is seen that \(V_T I_2\) can in fact be expressed in terms of \(P_1, P_2\) and \(R, C\). This \(V_T I_2\) index can be evaluated by computing the values of \(\tau\), along with \((P_1 C) \&(P_2 C)\) as given by equation (17). Then, after evaluating \(V_T I_2\) for a number of persons, and patients its distribution can enable us to categorize and differentially diagnose patients with various lung disorders and diseases. Between the two indices \(V_T I_1\) and \(V_T I_2\), we can employ the one that enables more distinct separation of subjects with different ventilatory disorders.

Thus far, we have adopted the average cyclic values \(C_a\) and \(R_a\) for our \(DEq\) model parameters. However, we expect that \(C\) will vary with lung volume \((V)\), and that \(R\) will perhaps vary with the airflow-rate or \((V)\) or even \(\omega\). Hence, for a true representation of the lung properties \(C\) \& \(R\), let us determine their values for different times during the ventilatory cycle, and compare them with their average values \(C_a\) \& \(R_a\), so as to make a case for a non-linear ventilatory-function model.

Let us hence compute the instantaneous value of compliance \((C)\) at mid-inspiration at \((t = t_m)\), and compare it with that of its average cyclic value of \(C_a\). For this purpose let us differentiate equation (2a), giving:

\[ R \ddot{V} + \dot{V} / C = - P_1 \omega \sin \omega t + P_2 \omega \cos \omega t \]

(19)

Now at about mid-inspiration, when \(t \approx 0.87 \text{ s}\) and \(\omega t \approx \omega t_m \approx 1.32 \text{ rad or } 78^\circ, \ddot{V} = 0\) and \(\dot{V} = 0.5 \text{ L/s}\) (based on fig1). By substituting for \(\ddot{V}\) and \(\dot{V}\) in equation (19), we obtain, \(C \approx 0.14 \text{L/cm H}_2\text{O}\) (compared to its \(C_a\) value of 0.118). Now, in order to also...
compute $R$ at $\omega t_m = 1.32$ we substitute $\dot{V} = 0.5 \, \text{L/s}$ and $V = 0.3 \, \text{L}$ (from the fig1 data) into equation (2-a), to obtain:

\[ 0.5 \, R + \frac{0.3}{C} = -P_1 + P_1 \cos 78^\circ + P_2 \sin 78^\circ = 3.8 \quad (20) \]

Now, since $C(at \, \omega t_m = 1.32) \cong 0.14 \, \text{L/cm H}_2\text{O}$, we obtain $R = 4.6 \, \text{cmH}_2\text{O} \, \text{s} \, \text{L}^{-1}$, compared to $R_a = 2.20$. This gives us some idea of the order of magnitude of $R$ & $C$, in comparison to their average values $C_a$ & $R_a$. We could also expect $C$ at mid-inspiration to be higher than its value at end-inspiration, when the lung is fully inflated. Also, we could expect the flow-resistance to be maximum at mid-inspiration, when $\dot{V}$ is maximal.

We can hence represent lung compliance ($C$) and resistance ($R$) as follows:

\[ C = n_1 (V)^{n_2} - C_o \quad \text{or} \quad C = C_o e^{n(V)} \quad \text{(21-a)} \]
\[ R = s_1 \ddot{V}^2 \quad \text{or} \quad R = R_o e^{s \dot{V}} \quad \text{(21-b)} \]

wherein $\dot{V}$ can also be varied by having the subjects breathe at different tidal volumes ($TV_s$) and ventilation frequency ($\omega$).

We note as per the conventional formulation of compliance, given by equation(ii) in FIG 5b as:

\[ P_{el} = \frac{V}{C} + P_{el,0} \quad ; \quad (22) \]

In the above formulation, we assume that $C$ and $E(= 1/C)$ remains constant throughout the ventilation cycle. However at the start of inspiration, $C = C_o$ at $t = 0$, and it decreases as the lung volume increases, based on the lung (static) volume vs pressure curve. So let us improve upon this equation(22) model, by making $P_{el}$ to be a non-linear function of volume, as follows:

\[ P_{el} = P_{el,o} + E_0 e^{kv} \quad (23) \]

Employing the above format of compliance, the governing $DE_q \quad (1)$ becomes
\[ R \dot{V} + E_0 e^{kV} = P_L(t) - P_{el,0} = P_0 + P_1 \cos \omega t + P_2 \sin \omega t - P_{el,0} \quad (24) \]

Again at end-expiration, \( P_{el,0} = \text{intra-pulmonary pressure} = (P_0 + P_1) \).

Hence equation (24) becomes:

\[ R \dot{V} + E_0 e^{kV} = -P_1 + P_1 \cos \omega t + P_2 \sin \omega t \quad (25) \]

whose RHS is similar to that of equation (2-a), and the values of \( P_1 \) & \( P_2 \) are given by equation (3) for the FIG 5b data.

In order to evaluate these parameters \( k \) & \( E_0 \), we again bring to bear the situation that at end-inspiration, for \( t = t_v = 1.6 \) s (for which \( \omega t = \omega t_v = 2.48 \text{ rad}, \sin \omega t_v = 0.62 \), \( \cos \omega t_v = -0.79 \)), we have

\[ \dot{V} = 0 \quad \text{and} \quad V = V_{max} = TV = 0.6 \text{ L}. \]

Hence, from fig (1) data, and equations (3 & 25), we obtain:

\[ E_0 e^{0.6k} = 8.75 \quad (26) \]

Let us now employ the volume data point at which \( \ddot{V} = 0 \). For this purpose, we differentiate equation (25), to obtain:

\[ R \dddot{V} + E_0 k e^{kV} = -P_1 \omega \sin (\omega t) + P_2 \omega \cos (\omega t) \quad (27) \]

From the Fig (1) data at about mid-inspiration, for which \( t = t_m = 0.87 \text{ s} \) & \( \omega t_m = 1.32 = 78^\circ \) with \( \cos (\omega t_m) = 0.2 \) & \( \sin (\omega t_m) = 0.98 \), we have \( \dddot{V} \approx 0, \quad \dddot{V} = 0.5 \text{ Ls}^{-1}, \quad V = 0.3 \text{ L}, \) from fig(1) data. Substituting these values into equation (27), we get:

\[ E_0 e^{0.3k} = 3.8 \quad (28) \]

Now from equation(s) (27) & (28), we get:

\[ e^{-0.3k} = 1.38 \quad (29) \]

for which, \( k = 1.07 \) and (from equation 26 or 28) \( E_0 = 2.75 \quad (30) \)

Hence, by employing the non-linear formulation,
we obtain the following expression for lung compliance (or elastance):

\[ P_{el} = P_{el,0} + E_o \cdot e^{k \cdot V} \]

Based on this expression, we obtain, for \( t = t_m \) and \( V = 0.3 \text{L} \):

\[ E = \frac{1}{C} = 4.06 \text{cm H}_2\text{O} / \text{L} \]
\[ C = 0.25 \text{L/cm H}_2\text{O} \]

Equation (32) can now provide us a more realistic characterization of lung compliance as follows:

At \( t = 0 \) and \( V = 0 \), we compute \( E = \frac{1}{C} = 2.94 \) and \( C = 0.34 \text{cm H}_2\text{O} / \text{L} \).

At \( t = t_m = 0.87 \text{s} \) and \( V = 0.3 \text{L} \), \( E = \frac{1}{C} = 4.06 \), and \( C = 0.25 \).

At \( t = t_v = 1.6 \text{s} \) and \( V = 0.6 \text{L} \), and \( E = \frac{1}{C} = 5.6 \) and \( C = 0.18 \),

which corresponds to the value of \( C_a \).

Our non-linear formulation of lung compliance, as depicted by equation (31 & 33), indicates that compliance decreases from \( 0.34 \text{cm H}_2\text{O} / \text{L} \) at start-inspiration to \( 0.25 \text{cm H}_2\text{O} / \text{L} \) at about mid-inspiration, and then to \( 0.18 \text{cm H}_2\text{O} / \text{L} \) at the end of inspiration. What this also tells us is that the ventilatory model equation (1) gives the correct reading of the compliance at \( V_{max} \), i.e. at end-inspiration. At other times of inspiration and expiration, the \( C_a \) parameter underestimates the instantaneous value of lung compliance. Now how about obtaining an analytical solution of equation (25) for \( V(t) \), and fitting the expression for \( V(t) \) to the lung volume data, to evaluate the parameters (i) \( R, E_0 \) & \( k \) for an intubated patient and (ii) \( R, E_0, k \) & \( P_1 \) & \( P_2 \) for a non-intubated patient in the outpatient clinic.

Finally, while it is important to determine the normal and pathological diagnostic ranges of \( C_a \) & \( R_a \), or better still of the parameters \( (E_0 \text{& } k) \) of the \( C \text{ vs } V \) and \( R \text{ vs } V \) relationships, it would be more useful to construct and employ a non-dimensional ventilatory index. We have already formulated \( VT I_1 \) & \( VT I_2 \) in equations (11) & (18), respectively. We will now formulate yet another index:
\[ VT I_3 = \frac{[60 \ (R_a/C_a) \ (BR) \ (TV)^2]}{\left| P_1 P_2 \right|} \]  

wherein (i) \( BR \) (the breathing rate in \#/sec) = 0.5 \( \omega \) / \( \pi \) (ii) and \( \left| P_1 P_2 \right| \) is the absolute value of the product \( P_1 P_2 \) (because of \( P_1 \) being negative). For the fig (1) clinical data, of \( BR = 0.25 \), with \( TV = 0.6L \) \& \( /P_1 P_2/^{(3)} = 18.1 \), and for the computed value of \( R_a/C_a = 18.33cm \ H_2O \ s \ L^{-1} \), we obtain \( VT I_3 = 5.47 \). Between \( VT I_1 \) and \( VT I_3 \), we can decide which index enables us to better differentially diagnose subjects with ventilatory disorders.

Now, let us go one step further and recognize that, for non-intubated patients, we cannot monitor \( P_1 \) and \( P_2 \), and hence cannot evaluate \( R_a \) \& \( C_a \) as demonstrated in § A. However for evaluating ventilatory index in out-patient clinics, we can in fact adopt \( (P_1 C) \) and \( (P_2 C) \) to be the model-system parameters, and evaluate them as delineated in § B. We can hence adopt the non-invasively-obtainable ventilatory-performance index \( VT I_2 \) (given by equation 18):

\[ VT I_2 = 30 \ \omega \pi \ (TV)^2 / \pi (P_1 C) \ (P_2 C); \ \omega = 2\pi (BR) \ (in \ #s^{-1}) \]

\[ = 60 \ (BR) \ (R/C) \ (TV)^2 / (P_1 P_2) = VT I_3 \]  

which is noted to be the same expression as for index \( VT I_3 \), except that it can be evaluated without intubating the patient. Hence, it would be even more useful to determine the distribution of \( VT I_2 \) for patients with a wide range of lung pathologies and ventilatory disorders. Then, we can delineate the normal and pathological ranges of this index, and employ this information to diagnose patients into different disease categories.

Now referring to FIG 6 and FIG 7, there is provided a more detailed description of the ways by which the PDDS searches the database. The index will fire up numerous search engine in finding the best match diseases. There is a possibility that there is more than one type of diseases being suspected. Statistical means are used to determine which is the best match diseases and thereby putting all these best fit diseases to the expert database system to further refine the possibilities.

This expert database will feedback data which is erroneous through a database interface to the intelligent DBMS for further confirmation by firing up other
possibilities of diseases type. This interface can be realise through a query module interface. The query module will consult the expert DB2 for expert information before in deciding the redundancy of the data.

The DISS (disease identification software system) is used to identify the best match disease after consulting the expert DB. The algorithm can be found in annex. The query module is responsible for all communication between the DISS, expert DB, GUI and also the intelligent DBMS. In particular, it can decide whether an DISS request can be displayed with the expert DB helps or whether it is necessary to require input from the user.

While the present invention has been described with reference to particular embodiments, it will be understood that the embodiments are illustrative and that the invention scope is not so limited. Alternative embodiments of the present invention will become apparent to those having ordinary skill in the art to which the present invention pertains. Such alternate embodiments are considered to be encompassed within the spirit and scope of the present invention. Accordingly, the scope of the present invention is described by the appended claims and is supported by the foregoing description.
CLAIMS

What is claimed is:

1. A pulmonary disease detection system for detecting breathing deficiencies of a test person, comprising:
   a breath analyser for analysing the inhale and exhale airs of the test person;
   a computer processor for receiving from the breath analyser the information and processing the received analysis data to give values to different parameters of the inhale and exhale airs of the test person; and
   a medical database for storing different parameters of breaths of the public and normal ranges for healthy persons;
   thereby the computer processor compares the values of different parameters of the inhale and exhale airs of the test person with the ones stored in the medical database so as to yield a test result of whether the test person is suffering breath deficiencies.

2. The pulmonary disease detection system of claim 1, wherein the breathing deficiencies may be caused by bacterial infection, viral infection, physical injuries and cancer.

3. The pulmonary disease detection system of claim 1, wherein the breath analyser comprises:
   a mask for covering the nose and mouth of the test person so as to maximizing the delivery of fresh air and minimizing the loss of the exhaled air;
   an air tank for supplying measurable and controllable air to the mask; and
   an acquisition unit electrically connected with the mask and the air tank so as to receive all the information from the air tank and the mask.

4. The pulmonary disease detection system of claim 3, wherein the mask comprises a group of electrodes including an oxygen electrode, a carbon dioxide gas electrode, a nitrogen electrode, a water vapor electrode, an inspired air flow rate electrode and an
expired air flow rate electrode; wherein each electrode detects each designated component of the inhale and exhale airs.

5. The pulmonary disease detection system of claim 4, wherein the computer processor is embedded with an algorithm for processing the information from the breath analyser; wherein the algorithm calculates the breathing rate, oxygen consumption rate and carbon dioxide generation rate from the composition information of the inhale and exhale airs of the test person; thereby comparing the rates of the test person with the ones stored in the medical database so as to conclude whether the test person is suffering any breath deficiencies.

6. The pulmonary disease detection system of claim 4, wherein the computer processor is embedded with an algorithm for processing the information from the breath analyser; wherein the algorithm calculates the composition values of the exhale air from the composition values of the inhale air and the assumed normal rates including breathing rate, oxygen consumption rate and carbon dioxide generation rate; thereby comparing the composition values of the exhale air with the ones stored in the medical database so as to conclude whether the test person is suffering any breath deficiencies.

7. The pulmonary disease detection system of claim 4, wherein the computer processor is embedded with an algorithm for processing the information from the breath analyser; wherein the algorithm calculates the volume compliance and air-flow resistance of the test person from the composition values and pressure values derived from the inhale air rate and exhale air rate; thereby comparing the volume compliance and air-flow resistance values with the ones stored in the medical database so as to conclude whether the test person is suffering any breath deficiencies.

8. The pulmonary disease detection system of claim 7, wherein the derived pressure values include pleural pressure and alveolar pressure.

9. The pulmonary disease detection system of claim 8, wherein the volume compliance and air-flow resistance are calculated by the equation:
\[ VTI_1 = \int (Ra \cdot Ca) \cdot (\text{Ventilatory rate in s}^{-1}) \cdot (60)^2 = \tau (BR)^2 \cdot 60^2 \]

wherein \( VTI_1 \) is denoted as ventilatory performance index; \( C \) as lung-volume compliance; and \( R \) as air-flow resistance; and wherein \( Ra \) and \( Ca \) are designated as the average values \((R \text{ and } C)\) for the ventilatory cycle, and \( BR \) is the breathing rate.

10. The pulmonary disease detection system of claim 8, wherein the volume compliance and air-flow resistance are calculated by the equation:
\[
VTI_2 = 60 \cdot (\omega \tau) \cdot (TV)^2 / 2\pi \cdot (P_1 \cdot C \cdot P_2 \cdot C) = 30 \cdot \omega \cdot (R/C) \cdot (TV)^2 / \pi \cdot P_1 \cdot P_2
\]

wherein \( VTI_2 \) is denoted as ventilatory performance index; \( C \) as lung-volume compliance; and \( R \) as air-flow resistance; and wherein \( TV \) is tidal volume; \( P_1 \) & \( P_2 \) as pleural pressures and \( \omega \tau \) as determined by equations (14-16).

11. The pulmonary disease detection system of claim 8, wherein the volume compliance and air-flow resistance are calculated by the equation:
\[
VTI_3 = [60 \cdot (Ra \cdot Ca) \cdot (BR) \cdot (TV)^2] / P_1 \cdot P_2
\]

wherein \( VTI_3 \) is denoted as ventilatory performance index; \( C \) as lung-volume compliance; and \( R \) as air-flow resistance; and wherein \( TV \) is tidal volume; \( P_1 \) & \( P_2 \) as pleural pressures.

12. A method of detecting a pulmonary disease of a test person by investigating the breath deficiencies of the test person:
   - acquiring the information of inhale and exhale airs of the test person;
   - processing the acquired information to give values of designated aspects of the inhale and exhale airs of the test person; and
   - comparing the calculated values with the ones stored in a medical database so as to conclude whether the test person is suffering any pulmonary diseases.

13. The method of claim 12, wherein the breathing deficiencies may be caused by bacterial infection, viral infection, physical injuries and cancer.

14. The method of claim 12, wherein the information of inhale and exhale airs of the test person is acquired by a breath analyser; and wherein the breath analyser comprises:
a mask for covering the nose and mouth of the test person so as to maximizing the
delivery of fresh air and minimizing the loss of the exhaled air;
an air tank for supplying measurable and controllable air to the mask; and
an acquisition unit electrically connected with the mask and the air tank so as to
receive all the information from the air tank and the mask.

15. The method of claim 14, wherein the mask comprises a group of electrodes
including an oxygen electrode, a carbon dioxide gas electrode, a nitrogen electrode, a water
vapor electrode, an inspired air flow rate electrode and an expired air flow rate electrode;
wherein each electrode detects each designated component of the inhale and exhale airs.

16. The method of claim 15, wherein the processing is executed within a computer
processor that is embedded with an algorithm for processing the information from the
breath analyser; wherein the algorithm calculates the breathing rate, oxygen consumption
rate and carbon dioxide generation rate from the composition information of the inhale and
exhale airs of the test person; thereby comparing the rates of the test person with the ones
stored in the medical database so as to conclude whether the test person is suffering any
breath deficiencies.

17. The method of claim 15, wherein the processing is executed within a computer
processor that is embedded with an algorithm for processing the information from the
breath analyser; wherein the algorithm calculates the composition values of the exhale air
from the composition values of the inhale air and the assumed normal rates including
breathing rate, oxygen consumption rate and carbon dioxide generation rate; thereby
comparing the composition values of the exhale air with the ones stored in the medical
database so as to conclude whether the test person is suffering any breath deficiencies.

18. The method of claim 15, wherein the processing is executed within a computer
processor that is embedded with an algorithm for processing the information from the
breath analyser; wherein the algorithm calculates the volume compliance and air-flow
resistance of the test person from the composition values and pressure values derived from
the inhale air rate and exhale air rate; thereby comparing the volume compliance and air-
flow resistance values with the ones stored in the medical database so as to conclude whether the test person is suffering any breath deficiencies.

19. The method of claim 18, wherein the derived pressure values include pleural pressure and alveolar pressure.

20. The method of claim 19, wherein the volume compliance and air-flow resistance are calculated by the equation:

\[ VTI_1 = f \left( \frac{R_a}{C_a} \right) \left( \text{Ventilatory rate in } s^{-1} \right) 60 \tau = \frac{\tau}{BR} \left( BR \right)^2 60^2 \]

wherein \( VTI_1 \) is denoted as ventilatory performance index; \( C \) as lung-volume compliance; and \( R \) as air-flow resistance; and wherein \( R_a \) and \( C_a \) are designated as the average values \( (R \text{ and } C) \) for the ventilatory cycle, and \( BR \) is the breathing rate.

21. The method of claim 19, wherein the volume compliance and air-flow resistance are calculated by the equation:

\[ VTI_2 = 60 \left( \omega \tau \right) (T V)^2 /2 \pi (P_1 C) (P_2 C) = 30 \omega (R/C) (T V)^2 / \pi P_1 P_2 \]

wherein \( VTI_2 \) is denoted as ventilatory performance index; \( C \) as lung-volume compliance; and \( R \) as air-flow resistance; and wherein \( TV \) is tidal volume; \( P_1 \) & \( P_2 \) as pleural pressures and \( \omega \tau \) as determined by equations (14-16).

22. The method of claim 19, wherein the volume compliance and air-flow resistance are calculated by the equation:

\[ VTI_3 = \left[ 60 \left( \frac{R_a}{C_a} \right) \left( BR \right) \left( TV \right)^2 / P_1 P_2 \right] \]

wherein \( VTI_3 \) is denoted as ventilatory performance index; \( C \) as lung-volume compliance; and \( R \) as air-flow resistance; and wherein \( TV \) is tidal volume; \( P_1 \) & \( P_2 \) as pleural pressures and \( \omega \tau \) as determined by equations (14-16).
SYSTEM AND METHOD FOR DETECTING OF PULMONARY DISEASES

ABSTRACT

The present invention provides a to be completed upon agreement of claims.

FIG 1
Data is fed into analysis computing system. Processed data is examined against databases. Database will also be updated with the next processed data.

**FIG 1**
Start 400
Data from the spirometer 401
Volume Growth Characteristics of the patient 402
Parameters identification of P0, P1, P2, Ra, Cs & w 403

Is the best fitted results with the parameters obtained? 404

Yes 405
Determination of VT1, VT2 & VT3 406
Access of reference database 407
Reference Medical Database

Initial Database Set up and Continual Improvement

No 408
Expert Advice
Diagnostics
Updating of database

Results 409

End 410

FIG 4
FIG 5a

FIG 5b
FIG 6
FIG 7
**TABLE – 1: Nomenclature**

<table>
<thead>
<tr>
<th>SYMBOL</th>
<th>MEANING</th>
<th>UNITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C$</td>
<td>Lung Complance</td>
<td>$(cmH_2O)^{-1}$</td>
</tr>
<tr>
<td>$C_a$</td>
<td>Average Lung Complance</td>
<td>$(cmH_2O)^{-1}$</td>
</tr>
<tr>
<td>$R$</td>
<td>Lung air-flow resistance</td>
<td>$cmH_2Osl^{-1}$</td>
</tr>
<tr>
<td>$R_a$</td>
<td>Average Lung air-flow resistance</td>
<td>$cmH_2Osl^{-1}$</td>
</tr>
</tbody>
</table>

**TABLE 2: ABBREVIATIONS**

- **VTI**: Lung-Ventilatory Index
- **WOB**: Work of Breathing
From: "Vladimir Vladimirovich Kulish (Assoc Prof)" <MVVKulish@ntu.edu.sg>
To: "Dhanjoo N Ghista (Prof)" <MDNGhista@ntu.edu.sg>, "Lua Aik Chong (Assoc Prof)"
<MACLUA@ntu.edu.sg>, <rjohn2@mednet.swmed.edu>, "#LOH KAH MENG#" <kmloh@technologist.com>, "Merryn Tawhai" <mtawahai@auckland.ac.nz>
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"Vladimir Vladimirovich Kulish (Assoc Prof)" <MVVKulish@ntu.edu.sg>
Subject: BOOK ON HUMAN RESPIRATION --- YOUR CONTRIBUTION IS ACCEPTED
Date: Fri, 13 Aug 2004 12:48:10 +0800

Dear Colleagues:

I would like to cordially thank all of you for your contributions.

According to the review received on our book: Human Respiration: Anatomy and Physiology, Mathematical Modeling, Numerical Simulation and Applications, all the chapters submitted by us are accepted for publication. Congratulations!!!

However, we need to make some minor additions and amendments.

The reviewer's comment is attached to this message (see below). In summary, we need to take the following steps:

1. All equations are to be numbered and typed by means of MS Word Equation Editor. Each equation should be a single object but not a mixture of text symbols and equations in one line.
2. All symbols that are used in equations and appear in text must be typed by means of MS Word Equation Editor within the text.
3. All repetitions among the chapters contributed by the same principal author should be removed.
4. Each principal author has to provide me with nomenclature (in a separate MS Word file), so that the same symbols were used by one principal author in all his/her chapters.
5. Each principal author has to provide me with key words to be included into Subject Index that will follow our book.
6. Each principal author has to send me the amended version of his/her contribution(s) in MS Word format together with the nomenclature and key words file by e-mail: mvvkulish@ntu.edu.sg. Please ensure that each chapter is formatted according to the template that was sent to you previously [otherwise, the production of the book can be delayed].

The deadline set by the publisher (WIT Press) is September 20, 2004. Hence, I have to receive all your amended

I am looking forward to hearing from you.

With kindest regards,

Vladimir V. Kulish, Ph. D.

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'Relevance

The bio-engineering discipline is now recognised as being of substantial importance. Human respiration is a significant, challenging and rewarding field: significant because of the increase in airborne pollutants and congenital respiratory diseases; challenging because of the wide range of scales in the pulmonary system, which span about three orders of magnitude (or five, if the thickness of the alveolar membrane is included); and rewarding because of the marvellous ingenuity that characterises the system. A text that covers highlights of the application of bio-engineering techniques to the study of human respiration is to be welcomed.
This text comprises twelve chapters dealing with various topics in human respiration, from fundamental aspects of anatomy and physiology through to numerical modelling of processes such as gas diffusion and practical applications in the field of respiratory physiotherapy. As such, there is material here that will be of interest to seasoned bio-engineers and clinical practitioners, as well as novices to the study of human respiration. There should be a good market for the text – WIT should use the success of their publication “Medical Application of Computer Modelling – the Respiratory System” as a guide.

Technical Correctness

The text encompasses such a wide range of material that I cannot comment on all of it. Nevertheless, I am satisfied that in the field that I do have some knowledge (fluid mechanics) the material presented is correct. Moreover, each chapter appears to be a distillation of a large body of work which has been presented and reviewed for publication in technical journals, and this gives me confidence that the whole work is accurate and reliable. There are several papers that deal with modelling of gas transfer across that alveolar lumen. The nomenclature employed in each paper (or group of papers, where a group is characterised by having the same principal author) is slightly different. It would be very helpful if a common nomenclature could be employed. A formal definition of nomenclature after the Table of Contents would be useful.

There are instances where relatively complex equations have been poorly constructed. For example, dots above symbols to represent differentiation with respect to time (e.g. _) have been replaced by small “o”s (e.g. _); in some instances the “o”s have been badly misplaced. This is not correct, and is unnecessary – the text appears to have been written using Microsoft Word, and Word includes an equation editor that has all the functionality required to produce neat equations employing standard notation. The final text should not contain any ambiguities in its formulae.

Quality of Text

The text is written in generally good English. While I am not sure whether it is the reviewer’s role to flag (what he thinks may be) grammatical errors, I have annotated the text where I think it might be improved. I offer these corrections not critically (they are few in number), but in the hope that through such minor corrections to the text, I might contribute to its acceptance in the academic community.

There are some instances of repetition of material between chapters by the same principal authors; there is also duplication of introductory material on respiratory anatomy between different authors. It would be beneficial to the ease with which the text can be used if (a) the repetitions were removed, (b) the duplication was minimised, and (c) the introductory material was brought forward to the first and second chapters (see below for more detail).

Order of Chapters
If the original 12 chapters are to be retained as they are, then I would suggest the following re-ordering of the text:

Anatomy and Physiology

1. Anatomy and Physiology of the Human Respiratory System
2. Fundamentals of Alveolar Gas Diffusion Mathematical Modelling and Numerical Simulation
3. Lung Gas Composition and Transfer Analysis: O2 and CO2 Diffusion Coefficients and Metabolic Rates
4. Lung Ventilation Modelling and Assessment
5. Visualisation of Alveolar Diffusion
6. Modelling of Two-Phase Flow in the Human Respiratory System
7. Impact of Microscopic Solid Particles on Alveolar Diffusion
8. Quantification of Human Physiological Response to Toxic Substances
9. Anatomically-based Modelling of Pulmonary Structure Applications
10. Applied Chest-Wall Vibration Therapy for Patients with Obstructive Lung Disease
11. Indicator for Lung Status in a Mechanically Ventilated COPD Patient using Lung Ventilation Modelling and Assessment
12. Mechanics of Proportional Assist Ventilation

I have suggested that “Anatomy and Physiology of the Human Respiratory System” should come before “Fundamentals of Alveolar Gas Diffusion”, and that “Lung Gas Composition and Transfer Analysis” and “Lung Ventilation Modelling and Assessment” should precede “Visualisation of Alveolar Diffusion”, “Modelling of Two-Phase Flow in the Human Respiratory System” and “Impact of Microscopic Solid Particles on Alveolar Diffusion”. This is because it may be easier for the reader to deal with the more general issue of lung respiration before approaching the topic of alveolar respiration. However, if some reordering of the material in chapters 2 and 5 can be allowed, then I would recommend the following titles for these chapters: 2. Fundamentals of Alveolar Gas Diffusion – Physiological Aspects 5. Alveolar Gas Diffusion – Numerical Modelling and Visualisation Here, chapter 2 would deal with the physiology of alveolar gas diffusion, and the modelling aspects would be placed in chapter 5. This would have the advantages that: (a) the first section is a relatively easy introduction of the topic of human respiration; and (b) the visualisation of the calculations by Kulish et al is presented in the best context.

It should also be possible to combine the chapters “Modelling of Two-Phase Flow in the Human Respiratory System” and “Impact of Microscopic Solid Particles on Alveolar Diffusion” into a single chapter, e.g. “Modelling the Impact of Microscopic Solid Particles on Alveolar Diffusion”. Certainly,
the material in “Impact of Microscopic Solid Particles on Alveolar Diffusion” which is a repetition of material in “Visualisation of Alveolar Diffusion” should be deleted.

I cannot decide whether the chapter entitled “Quantification of Human Physiological Response to Toxic Substances” should be left in the section on “Mathematical Modelling and Numerical Simulation” or placed in the section on “Applications”. Perhaps Kulish as the author is the deciding factor, and it should remain where it is in proximity to Kulish’s other papers. Thus, the chapter order becomes:

1. Anatomy and Physiology of the Human Respiratory System

2. Fundamentals of Alveolar Gas Diffusion – Physiological Aspects Mathematical Modelling and Numerical Simulation

3. Lung Gas Composition and Transfer Analysis: O2 and CO2 Diffusion Coefficients and Metabolic Rates

4. Lung Ventilation Modelling and Assessment

5. Alveolar Gas Diffusion – Numerical Modelling and Visualisation

6. Impact of Microscopic Solid Particles on Alveolar Diffusion

7. Quantification of Human Physiological Response to Toxic Substances

8. Anatomically-based Modelling of Pulmonary Structure Applications

9. Applied Chest-Wall Vibration Therapy for Patients with Obstructive Lung Disease

10. Indicator for Lung Status in a Mechanically Ventilated COPD Patient using Lung Ventilation Modelling and Assessment

11. Mechanics of Proportional Assist Ventilation
Lung gas composition and transfer analysis: O₂ and CO₂ diffusion coefficients and metabolic rates

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²School of Engineering (Electronics), Nanyang Polytechnic, Singapore
³Department of Nuclear Medicine and PET, Singapore General Hospital, Singapore

Abstract

The primary function of the lung is to (i) oxygenate the blood and thereby provide oxygen to the cells for metabolization purposes, and (ii) to remove the collected CO₂ from the pulmonary blood. Herein, we will analyze the compositions of the inspired and expired air per breath, and from there compute the O₂ consumption and CO₂ production rates. Next, we derive expressions for diffusion coefficients $D_{O₂}$ and $D_{CO₂}$ in terms of the evaluated cardiac output, O₂ and CO₂ concentrations in arterial and venous blood, alveolar and blood $O₂$ and CO₂ partial pressures. We then take up a typical case study, and demonstrate the computation of $D_{O₂}$ and $D_{CO₂}$, to represent the lung-performance capability to oxygenate the blood.
1 Introduction

The lung functional performance is characterized by (i) its ventilatory capacity, to bring air (and hence O₂) into the alveoli, and (ii) its capacity to transfer O₂ and CO₂ into and from the pulmonary capillary bed. Hence, the O₂ and CO₂ diffusion coefficients as well as the O₂ consumption rate and the CO₂ production rate represent the lung-performance indices.

2. Lung air composition analysis (and O₂ consumption and CO₂ production rates)

We carry out a mass balance analysis, involving:
(i) compositions of air breathed in and out
(ii) consumption or losses of O₂, CO₂ and H₂O.

The Table 1 below provides clinical data on partial pressures and volumes of N₂, O₂, CO₂ and H₂O of atmospheric air breathed in and expired in one breath cycle. The monitored breathing rate (BR) = 12 breaths/min, and we assume P₇₅ at 37°C = 47 mmHg.

<table>
<thead>
<tr>
<th>Resperatory gases</th>
<th>Atmospheric Air</th>
<th>Expired Air</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmHg</td>
<td>ml/%</td>
</tr>
<tr>
<td>N₂</td>
<td>597</td>
<td>393.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>78.55%</td>
</tr>
<tr>
<td>O₂</td>
<td>159</td>
<td>104.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20.84%</td>
</tr>
<tr>
<td>CO₂</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.04%</td>
</tr>
<tr>
<td>H₂O</td>
<td>3.7</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.49%</td>
</tr>
<tr>
<td>Total</td>
<td>760</td>
<td>500</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100%</td>
</tr>
</tbody>
</table>

It can be noted that the expired air volume exceeds the inspired air volume for this particular breath cycle. The H₂O loss of 30.1 ml (=32.6 ml – 2.5 ml) contributes the major portion of this difference.
2.1 Calculation of \( \text{O}_2 \) consumption-rate and \( \text{CO}_2 \) production-rate

We now determine the \( \text{O}_2 \) consumption rate and \( \text{CO}_2 \) production rates from the inspired and expired gases.

Assuming the patient breathes at 12 times per minute we have

\[
\begin{align*}
\text{\( \text{O}_2 \) Consumption Rate} &= (\text{Inspired } \text{\( \text{O}_2 \)} - \text{Expired } \text{\( \text{O}_2 \)}) \times 12 \\
&= (104.2 - 80.6) \times 12 \\
&= 283.2 \text{ ml/min}
\end{align*}
\]

\[
\begin{align*}
\text{\( \text{CO}_2 \) Production Rate} &= (\text{Expired } \text{\( \text{CO}_2 \)} - \text{Inspired } \text{\( \text{CO}_2 \)}) \times 12 \\
&= (19.1 - 0.2) \times 12 \\
&= 226.8 \text{ ml/min}
\end{align*}
\]

The amount of water vapor in the humidified expired air amounts to 6.2% of the expired air (compared to 0.49% of the dry inspired air) corresponding to the partial-pressure ratio of water vapor in the expired air (= 47/760). The volume of the dry expired air = (525.3 – 32.6) ml = 492.7 ml.

Now, assume that out of 500 ml of inspired air, the dead space air volume (not taking part in gas transfer process) is 150 ml and the alveolar air volume is 350 ml. We next compute the dead space air volume composition.
2.2 Dead space air composition

The clinical data of expired air composition is:

\[
\begin{align*}
N_2 &= 393.1 \text{ ml} \\
O_2 &= 83.36 \text{ ml} \\
CO_2 &= 16.87 \text{ ml} \\
H_2O &= 34.15 \text{ ml} \\
\text{Total} &= 527.49 \text{ ml}
\end{align*}
\]

Now, the dead-space air will be made up of (i) a dry air portion from the inspired air (assumed to be \(=141 \text{ ml}\)), plus (ii) the water vapor taken up by the dry air (estimated to be \(=9 \text{ ml}\)) since the expired air portion of 141 ml will not have undergone \(O_2\) and \(CO_2\) transfer, it’s composition is the same as that of inspired air:

\[
\begin{align*}
N_2 &= 111 \text{ ml (78.55%)}, \quad O_2 = 29.40 \text{ ml (20.84%)}, \quad CO_2 = 0.06 \text{ ml (0.04%)}, \\
H_2O &= 0.69 \text{ ml (0.49%)}. \\
\end{align*}
\]

When this inspired air (in the dead space) of 141 ml is fully humidified, it will take up a further \(X\) ml of \(H_2O\) vapor, in the ratio of the partial-pressures, as:

\[
\frac{X}{141} = \frac{47}{713} = 0.0659 \\
\therefore X = 0.0659 \times 141 = 9.29 \text{ ml of } H_2O \text{ vapor (which is close to our estimate)}. \\
\]

So, by adding 9.29 ml of \(H_2O\) vapor to 0.69 ml of water vapor in the inspired air volume of 141 ml, the total water vapor in the dead-space air is 9.98 ml. The humidified dead-space air composition will be:

\[
\begin{align*}
N_2 &= 111.00 \text{ ml (73.78%)} \\
O_2 &= 29.40 \text{ ml (19.55%)} \\
CO_2 &= 0.06 \text{ ml (0.04%)} \\
H_2O &= 9.98 \text{ ml (6.63%)} \\
\text{Total} &= 150.44 \text{ ml}
\end{align*}
\]
2.3 Alveolar air composition and partial pressures

We can now compute the alveolar air composition, by subtracting the dead-space air from the expired air. These values are tabulated in column 4 of the Table below.

<table>
<thead>
<tr>
<th></th>
<th>Expired Air (ml)</th>
<th>Dead Space Air (ml)</th>
<th>Alveolar Air (ml)</th>
<th>Alveolar Air Partial Pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N₂</td>
<td>393.1</td>
<td>111.00</td>
<td>282.1</td>
<td>569.41</td>
</tr>
<tr>
<td>O₂</td>
<td>80.53</td>
<td>29.40</td>
<td>51.13</td>
<td>103.21</td>
</tr>
<tr>
<td>CO₂</td>
<td>19.12</td>
<td>0.06</td>
<td>19.06</td>
<td>38.47</td>
</tr>
<tr>
<td>H₂O</td>
<td>34.21</td>
<td>9.98</td>
<td>24.23</td>
<td>48.91</td>
</tr>
<tr>
<td>Total</td>
<td>526.96</td>
<td>150.44</td>
<td>376.52</td>
<td>760</td>
</tr>
</tbody>
</table>

Finally, we compute the partial pressure of O₂ and CO₂ (as well as of N₂ and H₂O), so that we can determine next the diffusion coefficients of O₂ and CO₂ based on the monitoring of arterial and venous blood concentrations. These values are tabulated in column 5 of the above table.

Fig. 2: Schematic of blood-gas concentration in the Pulmonary Capillary.
3. Lung gas-exchange model & parametric analysis

3.1 Expressions for \( D_{O_2} \) and \( D_{CO_2} \)

The gas exchange between the alveolar air and pulmonary capillary blood is represented by the following \( O_2 \) and \( CO_2 \) conservation equations. (Fig. 2):

\[
Q^{VE}_{O_2} = Q^{AE}_{O_2} + V_{O_2} \quad \text{(from the alveolar air to capillary blood)}
\]

\[
= Q^{AE}_{O_2} + (\Delta P_{O_2}^{O_2}) D_{O_2} ; \quad P_{O_2}^{cap} = P_{O_2}^{AE} , \tag{1}
\]

in which \( P_{O_2}^{cap} = P_{O_2}^{PRB} \) (\( O_2 \) concentration of the pre oxygenated blood)

\[
Q^{VE}_{CO_2} = Q^{AE}_{CO_2} - V_{CO_2}
\]

\[
= Q^{AE}_{CO_2} - (\Delta P_{CO_2}^{O_2}) D_{CO_2} ; \quad P_{CO_2}^{cap} = P_{CO_2}^{VE} , \tag{2}
\]

in which \( P_{CO_2}^{cap} = P_{CO_2}^{PRB} \) (\( CO_2 \) concentration of the pre oxygenated blood), wherein

(i) \( Q^{AB} \) and \( Q^{VB} \) are arterial and venous blood flow-rates;

\( Q^{AB} = Q^{VE} \) (at venous end), \( Q^{VB} = Q^{AE} \) (at arterial end)

(ii) \( P_{O_2}^{al} \) and \( P_{O_2}^{cap} \) are the alveolar and capillary \( O_2 \) partial pressures

(iii) \( P_{CO_2}^{al} \) and \( P_{CO_2}^{cap} \) are the alveolar and capillary \( CO_2 \) partial pressure

(iv) \( D_{O_2} \) and \( D_{CO_2} \) are the \( O_2 \) and \( CO_2 \) diffusion coefficients

(v) \( \Delta P_{O_2}^{O_2} \) = average of \( (P_{O_2}^{al} - P_{O_2}^{cap}) \) over the capillary length;

\( \Delta P_{CO_2}^{CO_2} \) = average of \( (P_{CO_2}^{al} - P_{CO_2}^{cap}) \) over the capillary length

Now we can equate the arterial and venous blood flow rates, as

\( Q^{AB} = Q^{VB} = Q = \frac{SV}{EP} = CO / 60 \)

SV, EP and CO being the stroke volume, ejection period and cardiac output, respectively. Hence the above equations can be rewritten as:
(vi) $V_{O_2}^\circ$ is the $O_2$ transfer rate from alveolar air to capillary blood
\( (=O_2\) consumption rate), $V_{CO_2}^\circ$ is the $CO_2$ transfer rate from capillary blood to
alveolar air.

From eqn. (1):

\[
Q^{VE}_{O_2} C^{VE}_{O_2} = Q^{AE} C^{AB}_{O_2} + (\Delta P_{av}^{O_2}) D_{O_2}^\circ; \quad P^{cap}_{O_2} = P^{AE}_{O_2} = P_{O_2}
\]
\[
D_{O_2}^\circ = \frac{Q(C^{VE}_{O_2} - C^{AE}_{O_2})}{(\Delta P_{av}^{O_2})} = \frac{Q(C^{AE}_{O_2} - C^{VE}_{O_2})}{(\Delta P_{av}^{O_2})}.
\]  \( (3) \)

From eqn. (2):

\[
Q^{VE}_{CO_2} C^{VE}_{CO_2} = Q^{AE} C^{AB}_{CO_2} - (\Delta P_{av}^{CO_2}) D_{CO_2}; \quad P^{cap}_{CO_2} = P^{AE}_{CO_2} = P_{CO_2}
\]
\[
D_{CO_2}^\circ = \frac{Q(C^{VE}_{CO_2} - C^{AB}_{CO_2})}{(\Delta P_{av}^{CO_2})}, \quad (4)
\]

wherein

(i) $Q$, $C^{VE}_{O_2}$ and $C^{AE}_{O_2}$, $C^{VE}_{CO_2}$ and $C^{AE}_{CO_2}$ can be monitored because
$C^{VE}_{O_2}$ and $C^{VE}_{CO_2}$ = $C^{AB}_{O_2}$ and $C^{AB}_{CO_2}$ and $C^{AE}_{O_2}$ and $C^{AE}_{CO_2}$ = $C^{AE}_{O_2}$ and $C^{AE}_{CO_2}$

(ii) $D_{O_2}$ and $D_{CO_2}$ (eqns. (3) & (4)) represent the lung gas-exchange
parameters.

Now from eqns. (3) and (4), if we want to evaluate the diffusion coefficients
$D_{O_2}$ and $D_{CO_2}$, we need to also express $P^{al}_{O_2}$, $P^{cap}_{O_2}$ and $P^{al}_{CO_2}$, $P^{cap}_{CO_2}$ in terms of
monitorable quantities. In this regard,
(i) Alveolar $P_{O_2}^{al}$ can be expressed in terms of $V$ (the ventilation rate) and $V_O_2$ (the $O_2$ consumption rate) as Fig. 3:

$$P_{O_2}^{al} = k_1 \left[ 1 - e^{-k_2 \left( \frac{V}{V_m} \right) / V_O_2} \right], \quad (5)$$

where $V_m$ is the maximum ventilation rate and $V_O_2$ (the $O_2$ consumption rate or absorption rate from the alveoli) = $Q(C^{AB} - C^{VB})$. Eqn. (5) implies that as $\frac{V}{V_m}$ increases, (the exponential term decreases, and) $P_{O_2}^{al}$ increases (as in Fig. 3), and as $V_O_2$ increases $P_{O_2}^{al}$ decreases (as in Fig. 3).

(ii) Alveolar $P_{CO_2}^{al}$ can be expressed in terms of $V$ and $V_O_2$ as in Fig. 4.

$$P_{CO_2}^{al} = k_4 e^{-k_5 \left( \frac{V}{V_m} \right) / V_{CO_2}}, \quad (6)$$

where $V_{CO_2}$ (the $CO_2$ production rate or excretion rate from the blood) = $Q(C^{VB} - C^{AB})$. This equation implies that as $\frac{V}{V_m}$ increases, $P_{CO_2}^{al}$ decreases; also, as $V_{CO_2}$ increases (the exponential term decreases, and hence) $P_{CO_2}^{al}$ increases.

(iii) Blood $P_{O_2}$ can be obtained in terms of blood $CO_2$, from the $O_2$ disassociation curve (providing concentrations in arterial and venous blood), is represented in Fig. 5, as:

$$C_{O_2} = C_{O_2}^m (1 - e^{-k_5 P_{O_2}^{al}}), \quad \text{or} \quad C_{O_2}^* = 1 - e^{-k_5 P_{O_2}^{al}}, \quad (7)$$
where

- $C_{O_2}^m$ and $P_{O_2}^m$ are the maximum values of blood $O_2$ partial pressure
- $CO_2^* = CO_2/CO_2^m$
- $P_{O_2}^* = P_{O_2}/P_{O_2}^m$

(iv) Blood $P_{CO_2}$ can be obtained in terms of $C_{CO_2}$, from the $CO_2$ disassociation curve or $CO_2$ concentration in arterial and venous blood can be represented as per Fig. 6 as:

$$C_{CO_2} = C_{O_2}^m (1 - e^{-k_a(P_{CO_2}/P_{CO_2}^m)})$$

or,

$$C_{CO_2}^* = 1 - e^{-k_a(R_{CO_2}/P_{CO_2}^m)} = 1 - e^{-k_aP_{CO_2}^*} \quad (8)$$

3.2 Alveolar $O_2$ and $CO_2$ partial pressure expressions

Now, let us refer eqn. (4) for the $P_{O_2}^{al}$ partial pressure curve (Fig. 3), represented by the eqn.:

$$P_{O_2}^{al} = k_1 \left[ 1 - e^{-k_2 \left[ \frac{\nu}{\nu_m} \right]} \right]$$

$$= k_1 \left[ 1 - e^{-k_2 \left[ \frac{\nu^*}{\nu_{O_2}} \right]} \right], \text{ where } \nu^* = \frac{\nu}{\nu_m} \quad (9)$$

wherein $\nu$ is the alveolar ventilation rate (in liters/min), $\nu_m$ is the maximum ventilation rate (= 50 liters/min) and $\nu_{O_2}$ is the $O_2$ consumption rate (in liters/min). Herein, the coefficients $k_1$ and $k_2$ can be determined by having this
equation match the Fig. 3 data. Note, in this equation, when $V = 0$, $P_{O_2}^{al} = 0$ from the equation, which satisfies the data.

Now for $V_{O_2} = 0.25$ liters/min, when $V = \frac{V}{V_m} = 0.5$, $P_{O_2}^{al} = 140$ mmHg. Hence,

$$140 = k_f \left[ 1 - e^{-k_f \left[ \frac{0.5}{0.25} \right]} \right] = k_f (1 - e^{-2k_2}). \quad (10)$$

Also, when $V_{O_2} = 1 l/min$, $V = \frac{V}{V_m} = 0.3 l/min$, $P_{O_2}^{al} = 100$ mmHg. Hence

$$100 = k_f \left[ 1 - e^{-k_f \left[ \frac{0.3}{1} \right]} \right] = k_f (1 - e^{-0.3k_2}). \quad (11)$$

From eqns. (10) and (11), we get:

$$\begin{align*}
140 &= k_f (1 - e^{-2k_2}) \\
100 &= k_f (1 - e^{-0.3k_2})
\end{align*}
\therefore 140 - 100e^{-0.3k_2} = 100 - 100e^{-2k_2} \quad (12)
$$

or, $40 = 100e^{-2k_2} + 140e^{-0.3k_2}$, so that $k_2 = 4.18 min/l$

Upon substituting $k_2 = 4.18 \ min/l$ into eqn. (10) we obtain:

$$140 = k_f (1 - e^{-2\times4.18}), \text{ so that } k_f = 140 \ mmHg \quad (13)$$

Hence, the $P_{O_2}^{al}$ curve can be represented by:

$$P_{O_2}^{al} = 140 \left[ 1 - e^{-4.18 \left[ \frac{V^{*}}{V_{O_2}} \right]} \right], \quad (14)$$
wherein \( V_O^* = Q(C_{O_2}^{AB} - C_{O_2}^{VB}) \) and \( V = \frac{\dot{V}}{50} \text{l/min} \)

Now, let us look at the \( P_{CO_2}^{al} \) expression:

\[
P_{CO_2}^{al} = k_3 e^{-k_4} \left( \frac{\dot{V}}{V_m} \right) \left( \frac{\dot{V}}{V_{CO_2}} \right)
\]

We note from Fig. 4 that for \( V_{CO_2} = 0.2 \text{l/min} \) and \( V_m = 0.2 \), \( P_{CO_2}^{al} = 12 \). Hence, from the above eqn., we get:

\[
12 = k_3 e^{-k_4}
\]

Also, for \( V_O = 0.8 \text{l/min} \) and \( V_m = 0.2 \), \( P_{CO_2}^{al} = 62 \text{ mmHg} \). Hence

\[
62 = k_3 e^{-k_4}
\]

From eqn.s (15) and (16), we get:

\[
\frac{12}{62} = \frac{e^{-k_4}}{e^{-k_4}} = e^{-\frac{2}{3}k_4}
\]

\[
\ln \left( \frac{12}{62} \right) = -\frac{2}{3}k_4, \text{ so that } k_4 = 2.46
\]

Substituting \( k_4 = 2.46 \) into eqn. (16), we obtain:

\[
62 = k_3 e^{-\frac{4}{3}}, \therefore k_3 = 114.68
\]

Hence, the \( P_{CO_2}^{al} \) curve can be represented as

\[
P_{CO_2}^{al} = 114.68 e^{-2.46} \left( \frac{\dot{V}}{V_m} \right) \left( \frac{\dot{V}}{V_{CO_2}} \right)
\]

wherein \( V = \frac{\dot{V}}{50} \text{l/min} \) and \( V_{CO_2} = Q(C_{CO_2}^{VB} - C_{CO_2}^{AB}) \)
Fig. 3: Effect on alveolar $P_{O_2}$ of (i) alveolar ventilation, and (ii) rate of Oxygen absorption from alveolar $P_{O_2}$ or $O_2$ consumption rate [from Guyton (1971), p. 476].

Fig. 4: Effect on alveolar $P_{CO_2}$ of alveolar ventilation and rate of carbon dioxide excretion from the blood or $CO_2$ production rate [from Guyton (1971), p. 476].
3.3 Arterial and venous $O_2$ and $CO_2$ partial pressure expressions

We now need to express $P_{O_2}^{AB}$ and $P_{CO_2}^{VB}$ in terms of $C_{O_2}^{AB}$ and $C_{CO_2}^{VB}$.

So that let us look at the $O_2$ disassociation curve, as shown in Fig. 5.

$$C_{O_2} = C_{O_2}^{max} \left[ 1 - e^{-k_5 \frac{P_{O_2}}{P_{O_2}^{max}}} \right],$$

or,

$$C_{O_2}^* = 1 - e^{-k_5 \frac{P_{O_2}}{P_{O_2}^{max}}},$$

where $C_{O_2}^* = \frac{C_{O_2}}{C_{O_2}^{max}}$, $P_{O_2}^* = \frac{P_{O_2}}{P_{O_2}^{max}}$.

From Fig. 5, at $P_{O_2}^* = \frac{40 \text{ mmHg}}{140 \text{ mmHg}} = 0.29$ (for normal venous blood), and $C_{O_2}^* = \frac{15}{20} = 0.75$.

Hence from eqn. (20):

$$0.75 = 1 - e^{-0.29k_5},$$

$$\therefore k_5 = 4.78.$$  \hspace{1cm} (21)

Also, $P_{O_2}^* = \frac{95 \text{ mmHg}}{140 \text{ mmHg}} = 0.68$ (for normal arterial blood), and $C_{O_2}^* = \frac{19}{20} = 0.95$.

Hence from (20):

$$0.95 = 1 - e^{-0.68k_5}, \text{ or } k_5 = 4.4.$$  \hspace{1cm} (22)

So, we take the average value of $k_5$:

$$\therefore k_5 = \frac{(4.78+4.4)}{2} = 4.59.$$  \hspace{1cm} (23)

Then the $O_2$ disassociation curve is given by:
\[ C_{O_2} = C_{O_2}^B = 0.2 \left[ 1 - e^{-4.59 \left( \frac{P_{O_2}}{140} \right)} \right], \]  

and

\[ P_{O_2} = \frac{140}{4.59} \ln \left[ \frac{0.2}{0.2 - C_{O_2}^B} \right] = 30.5 \ln \left[ \frac{0.2}{0.2 - C_{O_2}^B} \right]. \]  

Finally, we look at the CO\textsubscript{2} disassociation curve

\[ C_{CO_2} = C_{CO_2/\max} (1 - e^{-k_6 P_{CO_2}/P_{CO_2/\max}}), \]

or, \[ C_{CO_2}^* = 1 - e^{-k_6 P_{CO_2}/P_{CO_2/\max}} = 1 - e^{-k_6 P_{CO_2}}. \]

Based on Fig. 6, when \[ P_{CO_2}^* = \frac{20 \text{ mmHg}}{140 \text{ mmHg}} = 0.14, \]
\[ C_{CO_2}^* = \frac{38}{80} = 0.475, \]
so that

\[ 0.475 = 1 - e^{-0.14k_6}, \quad k_6 = 4.60 \]  

when \[ P_{CO_2}^* = \frac{70 \text{ mmHg}}{140 \text{ mmHg}} = 0.5, \]
\[ C_{CO_2}^* = \frac{60}{80} = 0.75, \]
so that

\[ 0.75 = 1 - e^{-0.5k_6}, \quad k_6 = 2.77. \]  

So we take the average value of \( k_6 \):

\[ k_6 = \frac{(4.60 + 2.77)}{2} = 3.69 \]  

Then the CO\textsubscript{2} concentration is given (from eqns. 26-29) by:

\[ C_{CO_2} = C_{CO_2}^B = 0.8 \left[ 1 - e^{-3.69 \left( \frac{P_{CO_2}}{140} \right)} \right] \]
and

\[ P_{\text{CO}_2} = 37.94 \ln \left( \frac{0.8}{0.8 - C_{\text{CO}_2}} \right). \] (31)
Figure 5: O₂ dissociation curves, showing the total oxygen in each 100 ml of normal blood, the portion dissolved in the water of the blood [from Guyton (1971), p. 485].

Figure 6: The carbon dioxide dissociation curve [from Guyton (1971), p. 491].
3.4 Sequential procedure to compute $D_{O_2}$ and $D_{CO_2}$

(1) We first monitor: $V(t)$, $V'(t)$, SV(stroke volume), EP(cardiac ejection period), $C^{VB}_{O_2}$, $C^{AB}_{O_2}$, $C^{VB}_{CO_2}$, and $C^{AB}_{CO_2}$ ($O_2$ and $CO_2$ concentrations in pre oxygenated and post oxygenated blood).

(2) We substitute the values of $C^{AB}_{O_2}$ ($= C^{VE}_{O_2}$) and $C^{VB}_{O_2}$ ($= C^{AE}_{O_2}$) into eqn. (3), and the values of $C^{AB}_{CO_2}$ ($= C^{VE}_{CO_2}$) and $C^{VB}_{CO_2}$ ($= C^{AE}_{CO_2}$) into eqn. (4).

(3) We next determine:

$$Q = SV/ejection period,$$

$$V_{O_2}(t) = Q (C^{AB}_{O_2} - C^{VB}_{O_2}),$$

$$V_{CO_2}(t) = Q (C^{AB}_{CO_2} - C^{VB}_{CO_2}).$$

(4) We then substitute the expressions for $V_{O_2}(t)$ and $V_{CO_2}(t)$ into the eqns. for $P_2^{al}$ (eqn. (14)) and $P_2^{al}$ (eqn. (19)).

(5) We substitute the monitored values of $C^{VB}_{O_2}$ ($= C^{AE}_{O_2}$) and $C^{VB}_{CO_2}$ ($= C^{AE}_{CO_2}$) into eqns. (25) and (32), to obtain the values of $P_2^{AE}$ and $P_2^{AE}$.  

(6) Now, in order to determine the values of the lung gas-exchange parameters $D_{O_2}$ and $D_{CO_2}$, we substitute into eqns. (3) and (4) for $Q$ from eqn. (33), $P_2^{al}$ from (14), $P_2^{al}$ from eqn. (19), $P_2^{VB}$ from eqn. (26), and $P_2^{VB}$ from eqn. (32).

3.5 Determining $D_{O_2}$ and $D_{CO_2}$

Fig. 7 illustrates the variation of $\Delta P^{O_2} (= P_2^{al} - P_2^{cap} = P_2^{al} - P_2^{AB})$ along the length ($l$) of the capillary bed.
Let \( l^* = l/l_m \).

Then we can express:
\[
\Delta P_{O_2} = \Delta P_{O_2}^{\text{max}} f_{O_2}(l^*). \tag{36}
\]

Then,
\[
\Delta P_{O_2}^{\text{av}} = \Delta P_{O_2}^{\text{max}} \left\{ \frac{1}{0} \int f_{O_2}(l^*) dl^* \right\} = \Delta P_{O_2}^{\text{max}} \left( F_{O_2} \right), \tag{37}
\]

Based on data [3], since \( \Delta P_{O_2}^{\text{av}} = 12 \text{ mmHg} \) for \( \Delta P_{O_2}^{\text{max}} = 65 \text{ mmHg} \), we have \( F_{O_2} = 0.185 \).

We can similarly determine the average value of \( \Delta P_{CO_2}^{\text{av}} \) from Fig. 8 as:

Let \( l^* = l/l_m \).

Then, we can represent figure 8 as:
\[
\Delta P_{CO_2} = \Delta P_{CO_2}^{\text{max}} f_{CO_2}(l^*). \tag{38}
\]

Then,
\[
\Delta P_{CO_2}^{\text{av}} = \Delta P_{CO_2}^{\text{max}} \left\{ \frac{1}{0} \int f_{CO_2}(l^*) dl^* \right\} = \Delta P_{CO_2}^{\text{max}} \left( F_{CO_2} \right), \tag{39}
\]

Based on data [3], since \( \Delta P_{CO_2}^{\text{av}} = 0.5 \text{ mmHg} \) for \( \Delta P_{CO_2}^{\text{max}} = 5 \text{ mmHg} \), we have \( F_{CO_2} = 0.1 \).
From the $\Delta P_{av}^{O_2}$ and $\Delta P_{av}^{CO_2}$ expressions, we can determine the $O_2$ consumption and the $CO_2$ production rates, as follows:

$$D_{O_2} = \frac{\text{Total } O_2 \text{ consumed}}{\Delta P_{av}^{O_2}} = \frac{V_{O_2}^o}{\Delta P_{av}^{O_2}} = \frac{Q (C_{O_2}^{AB} - C_{O_2}^{VB})}{\Delta P_{av}^{O_2}}$$  \hspace{1cm} (40)

$$D_{CO_2} = \frac{\text{Total } CO_2 \text{ produced}}{\Delta P_{av}^{CO_2}} = \frac{V_{CO_2}^o}{\Delta P_{av}^{CO_2}} = \frac{Q (C_{CO_2}^{VB} - C_{CO_2}^{AB})}{\Delta P_{av}^{CO_2}}.$$  \hspace{1cm} (41)

4. Case Studies

(A) We monitor the partial pressures blood concentrations of $O_2$ and $CO_2$ as:

$$C_{O_2}^{AE} = C_{O_2}^{VE} = 0.13, \quad C_{O_2}^{E} = 0.18, \quad C_{CO_2}^{AE} = C_{CO_2}^{VE} = 0.525,$$

$$C_{CO_2}^{V} = 0.485$$

From eqn. (26), we obtain:

$$P_{O_2}^{VB} = 30.5 \ln \left[ \frac{0.2}{0.2 - C_{O_2}^{VE}} \right] = 30.5 \ln \left[ \frac{0.2}{0.2 - 0.13} \right]$$

$$= 32.02 \text{ mmHg} \hspace{1cm} (42)$$

From eqn. (32), we obtain:

$$P_{CO_2}^{VB} = 37.94 \ln \left[ \frac{0.8}{0.8 - C_{CO_2}^{VE}} \right] = 37.94 \ln \left[ \frac{0.8}{0.8 - 0.525} \right]$$

$$= 40.51 \text{ mmHg} \hspace{1cm} (43)$$

We now also monitor $Q=5 \text{ l/min}$, $V_1 = 0.1$ and $V_2 = 5 \text{ l/min}$:

Then from eqn. (34):

$$V_{O_2}^o (t) = Q \left( C_{O_2}^{AB} - C_{O_2}^{VB} \right),$$

so that from the above data,
\[ V_{O_2} (t) = 5000 \times 0.05 = 250 \text{ mlO}_2/\text{min consumption rate} \quad (44) \]

From eqn. (35):
\[ V_{CO_2} (t) = Q \left( C_{CO_2}^{VB} - C_{CO_2}^{AB} \right) = 5000(0.04) \]
\[ = 200 \text{ mlCO}_2/\text{min production rate.} \quad (45) \]

Now, from eqn. (14):

For \( V^* = 0.1 \) and \( V/O_2 = 0.25 \), we obtain \( P_{O_2}^{al} \):
\[
P_{O_2}^{al} = 140 \left( 1 - e^{-\frac{4.18 \left( 1/0.1 \right)}{140}} \right)
\]
\[ = 140 \left( 1 - e^{-4.18(0.1/0.25)} \right) = 113.7 \text{ mmHg} \quad (46) \]

From eqn. (19), for \( V^* = 0.1 \) and \( V/CO_2 = 0.20 \), we obtain \( P_{CO_2}^{al} \):
\[
P_{CO_2}^{al} = 107.18 e^{-2.19 \left( 1/0.2 \right)} = 107.18 e^{-2.19(0.1/0.2)}
\]
\[ = 35.86 \text{ mmHg} \quad (47) \]

Now, we can evaluate the diffusion coefficients:

From eqns. (3, 37, 42 and 46):
\[
D_{O_2} = \frac{Q(C_{O_2}^{AB} - C_{O_2}^{VB})}{\Delta P_{av}^{O_2}}
\]
\[ = \frac{5000(0.18 - 0.13)}{(113.7 - 31.2) \times 0.18} = 16.84 \text{ mlO}_2/\text{min/mmHg.} \quad (48) \]
From eqn. (4):

\[
D_{CO_2} = \frac{Q (C^{VB}_{CO_2} - C^{AB}_{CO_2})}{\Delta P_{av}}
\]

\[
= \frac{5000(0.04)}{(40.51 - 35.86) \times 0.1} = 430.11 \text{ m/CO}_2/\text{min/mmHg.} \tag{49}
\]

(B) Alternately, we derive data from:

(i) the inspired and expired air analysis (such as that carried out in section 2.3):

\[
\begin{align*}
\text{O}_2 \text{ consumption rate} &= 283.2 \text{ ml/min,} \\
\text{CO}_2 \text{ production rate} &= 226.8 \text{ ml/min,} \\
\text{P}^{\text{al}}_{\text{O}_2} &= 103.03 \text{ mmHg} \quad \text{and} \quad \text{P}^{\text{al}}_{\text{CO}_2} = 38.41 \text{ mmHg}
\end{align*}
\]

and (ii) venous blood gas analysis:

\[
C^{VB}_{\text{O}_2} = 0.13 \quad \text{and} \quad C^{VB}_{\text{CO}_2} = 0.548
\]

Then, as per eqn. (42), \(P^{VB}_{\text{O}_2} = 31.2 \text{ mmHg}\)

\[\text{corresponding to } C^{VB}_{\text{O}_2} = 0.13 \quad \text{and, as per eqn. (43):}\]

\[
\begin{align*}
P^{VB}_{\text{CO}_2} &= 37.94 \ln \left[ \frac{0.8}{0.8 - C^{VB}_{\text{CO}_2}} \right] = 37.94 \ln \left[ \frac{0.8}{0.8 - 0.548} \right] \\
&= 43.84 \text{ mmHg} \tag{51}
\end{align*}
\]

We obtain, from air composition analysis, that \(V^{\circ}_{\text{O}_2} (t) = 283.3 \text{ ml/min}\) \(\tag{52}\)

and \(V^{\circ}_{\text{CO}_2} (t) = 226.8 \text{ ml/min.}\) \(\tag{53}\)
Hence,

\[ D_{O_2} = \frac{V_{O_2}}{\Delta P_{av}^{O_2}} \]

\[ = \frac{283.2}{(103.03 - 31.2) \times 0.18} = 21.90 \text{ mLO}_{2}/\text{min/mmHg}, \quad (54) \]

and

\[ D_{CO_2} = \frac{V_{CO_2}}{\Delta P_{av}^{CO_2}} \]

\[ = \frac{226.8}{(43.84 - 38.41) \times 0.1} = 417.68 \text{ mLCO}_2/\text{min/mmHg}. \quad (55) \]

The advantage of this method (B) over (A) is that it does not require monitoring of the cardiac output, and is hence simpler to implement clinically.
Figure 7: Uptake of oxygen by the pulmonary capillary blood. (The curve in this figure was constructed from data in Mihorn and Pulley: Biophys. J., 8:337, 1968). [from Guyton (1971), p. 434.]

Figure 8: Diffusion of carbon dioxide from the pulmonary blood into the alveolus. (The curve in this figure was constructed from data in Mihorn and Pulley: Biophys. J., 8:337, 1968). [From Guyton (1971), p. 435.]
References


$O_2$ consumption
rate
$CO_2$ production
rate
Concentration
$C_{O_2}$
$C_{CO_2}$
Lung Air Composition
Dead Space Air
$D_{O_2}$
$D_{CO_2}$
Partial Pressure
$p_{O_2}^{al}$
$p_{CO_2}^{al}$

Pages
1, 2, 3, 7, 8, 9, 12, 20, 21
3
1, 2, 3, 7, 8, 9, 12, 20, 21
3
8, 13
9, 14
2, 3, 5, 21
4
1, 7, 17, 20, 22
22
1, 7, 17, 21, 22
5
8, 9, 10
8, 11
<table>
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<th>UNITS</th>
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<td>$p_{O_2}^{al}$</td>
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<tr>
<td>$p_{O_2}^{cap}$</td>
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<tr>
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<td>$mmHg$</td>
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<td>Arterial blood flow-rates at arterial end</td>
<td>$l/min$</td>
</tr>
<tr>
<td>$Q^{VB}$</td>
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<tr>
<td>$Q^{VE}$</td>
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</tr>
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</table>
Letter of Paper Acceptance

Date

Dear Kah Meng Loh, Dhanjoo Ghista*, Heiko Rudolph,

On behalf of the technical program committee, we are pleased to inform you paper entitled

"Determination of Pulmonary Gases (O2 & CO2) Metabolic-Rates and Lung Coefficients Based on the Inspired and Expired Air Compositions and Venous Gas Concentration"

with paper ID: 749

has been accepted after reviewing by experts for presentation at the 27th Annual International Conference of the IEEE Engineering in Medicine and Biology Society held on 1-4 September 2005 in Shanghai, China.

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Conference Website:  http://www.cuhk.edu.hk/embe05/shanghai
Letter of Paper Acceptance

Dear Kah Meng Loh, David Ng, Dhanjoo Ghista*,

On behalf of the technical program committee, we are pleased to inform you that your paper entitled

"Quantitation of Renal Function Based on Two-Compartmental Modeling of R with paper ID: 752"

has been accepted after reviewing by experts for presentation at the 27th Annual International Conference of the IEEE Engineering in Medicine and Biology Society held on 1-4 September 2005 in Shanghai, China.

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Abstract—The primary function of the lung is to (i) oxygenate the blood and thereby provide oxygen to the cells for metabolization purposes, and (ii) to remove the CO$_2$ produced by the tissues from the pulmonary blood. Herein, we provide a noninvasive methodology to assess the capacity of the lung to oxygenate the pulmonary capillary blood and to reduce its CO$_2$ concentration. For this purpose, we analyze the compositions of the inspired and expired air per breath, and therefrom compute the metabolic O$_2$ consumption rate ($\dot{V}$O$_2$) and CO$_2$ production rate ($\dot{V}$CO$_2$). Next we compute the cardiac out (CO) as $CO = \dot{V}_O_2 (C_{O_2}^{AB} - C_{O_2}^{VB})$.

We have derived the expressions for diffusion coefficients (i) $D_{O_2}$ in terms of $V_O_2$ and the alveolar and venous partial pressures, $P_{O_2}^{al}$ and $P_{O_2}^{VB}$ and (ii) $D_{CO_2}$ in terms of $V_{CO_2}$, $P_{CO_2}^{al}$ and $P_{CO_2}^{VB}$. The coefficients $D_{O_2}$ and $D_{CO_2}$ represent the gas transfer capacity of the lung.

The paper provides a case study for the determination of $Q$, $D_{O_2}$ and $D_{CO_2}$. The derived information of $D_{O_2}$ and $D_{CO_2}$ as well as of $O_2$ and $CO_2$ metabolic rates can be of considerable clinical use including for SARS assessment.

Keywords—gas exchange, $O_2$ metabolic-rates, $CO_2$ metabolic-rates, diffusion coefficients $D_{O_2}$, diffusion coefficients $D_{CO_2}$, blood flow rate

I. INTRODUCTION

The lung functional performance is characterized by (i) its ventilatory capacity, to bring air (and hence $O_2$) into the alveoli, and (ii) its capacity to transfer $O_2$ and $CO_2$ into and from the pulmonary capillary bed. Hence, the $O_2$ and $CO_2$ diffusion coefficients $D_{O_2}$ and $D_{CO_2}$ as well as the $O_2$ consumption-rate and the $CO_2$ production rate represent the lung performance indices. In this paper, we are demonstrating their evaluations.

II. LUNG GAS-EXCHANGED MODEL

Fig. 1 schematically illustrates the gas-exchange between the lung alveolus and the pulmonary capillary-vasculature. Based on our earlier work [1, 2] the gas exchange between the alveolar air and pulmonary capillary blood is represented by the following $O_2$ and $CO_2$ conservation equations and Fig. 2.

$$Q^{VE} C_{O_2}^{VE} = Q^{AE} C_{O_2}^{AE} + V_O_2$$ (from the alveolar air to capillary blood)

$$Q^{VE} C_{CO_2}^{VE} = Q^{AE} C_{CO_2}^{AE} - V_{CO_2}$$

wherein

(i) $Q^{AB}$ and $Q^{VB}$ are arterial and venous blood flow-rates;

(ii) $P_{O_2}^{al}$ and $P_{O_2}^{cap}$ are the alveolar and capillary $O_2$ partial pressures

(iii) $P_{CO_2}^{al}$ and $P_{CO_2}^{cap}$ are the alveolar and capillary $CO_2$ partial pressure.

(iv) $D_{O_2}$ and $D_{CO_2}$ are the $O_2$ and $CO_2$ diffusion coefficients

(v) $\Delta P_{av}^{O_2} = \text{average of (}P_{O_2}^{al} - P_{O_2}^{cap}\text{) over the capillary length; }$

$\Delta P_{av}^{CO_2} = \text{average of (}P_{CO_2}^{al} - P_{CO_2}^{cap}\text{) over the capillary length}$
(vi) \( P_{O_2}^{cap} = P_{O_2}^{PRB} \) (\( O_2 \) concentration of the pre-oxygenated blood) = \( P_{O_2}^{AE} \)

(vii) \( P_{CO_2}^{cap} = P_{CO_2}^{PRB} \) (\( CO_2 \) concentration of the pre-oxygenated blood) = \( P_{CO_2}^{VE} \)

(viii) \( V_{O_2}^\circ \) is the \( O_2 \) transfer rate from alveolar air to capillary blood (= \( O_2 \) consumption rate), \( V_{CO_2}^\circ \) is the \( CO_2 \) transfer-rate from capillary blood to alveolar air (= \( CO_2 \) production rate).

Now we can equate the arterial and venous blood flow rates, as \( Q^{AE} = Q^{AB} = Q^{VE} = Q = (SV)/(EP) \) = CO / 60

SV, EP and CO being the stroke-volume, ejection-period and cardiac-output respectively.

From equations (1) and (2):

\[
D_{O_2} = \frac{Q(C_{O_2}^{VE} - C_{O_2}^{AE})}{(\Delta P_{O_2}^{av})} = \frac{Q(C_{O_2}^{AB} - C_{O_2}^{VB})}{(\Delta P_{O_2}^{av})} = \frac{V_O}{\Delta P_{O_2}^{av}}
\]

\[
D_{CO_2} = \frac{Q(C_{CO_2}^{VE} - C_{CO_2}^{AB})}{(\Delta P_{CO_2}^{av})} = \frac{V_{CO}}{\Delta P_{CO_2}^{av}}
\]

III. CLINICAL DATA

The monitored data consists of inspired and expired air gas compositions (TABLE 1) and \( O_2 \) and \( CO_2 \) concentrations of arterial blood and venous blood (TABLE 2).

TABLE 1: Air Composition Analysis. Inspired and expired air composition and partial pressures are monitored. Assumed Breathing Rate (BR) = 12 breaths/min. Assumed \( P_{H_2O} \) at 37\(^\circ\)C = 47 mmHg.

<table>
<thead>
<tr>
<th>Respiratory gases</th>
<th>Atmospheric Air</th>
<th>Expired Air</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmHg</td>
<td>ml/%</td>
</tr>
<tr>
<td>N(_2)</td>
<td>597</td>
<td>78.55%</td>
</tr>
<tr>
<td>O(_2)</td>
<td>159</td>
<td>104.2%</td>
</tr>
<tr>
<td>CO(_2)</td>
<td>0.3</td>
<td>0.04%</td>
</tr>
<tr>
<td>H(_2)O</td>
<td>3.7</td>
<td>0.49%</td>
</tr>
<tr>
<td>Total</td>
<td>760</td>
<td>100%</td>
</tr>
</tbody>
</table>

TABLE 2: Blood Gas Analysis. The monitored blood \( O_2 \) and \( CO_2 \) concentration.

\( C_{O_2} \) of venous blood (\( C_{O_2}^{VB} \)) = 0.13
\( C_{O_2} \) of arterial blood (\( C_{O_2}^{AB} \)) = 0.18
\( C_{CO_2} \) of venous blood (\( C_{CO_2}^{VB} \)) = 0.56
\( C_{CO_2} \) of arterial blood (\( C_{CO_2}^{AB} \)) = 0.52
IV. EXPRESSIONS FOR $D_{O_2}$ AND $D_{CO_2}$

If we want to evaluate the diffusion coefficients $D_{O_2}$ and $D_{CO_2}$, we need to also express $P^{al}_{O_2}$, $P^{cap}_{O_2}$ and $P^{al}_{CO_2}$, $P^{cap}_{CO_2}$ in terms of monitorable quantities [1 & 2].

(i) Alveolar $P^{al}_{O_2}$ can be expressed in terms of $V$ (the ventilation rate) and $V_{O_2}$ (the $O_2$ consumption rate).

$$P^{al}_{O_2} = 140 \left[ -4.18 \left( \frac{V}{V_{O_2}} \right) \right]$$

wherein the normalized ventilation rate $V = V_{m}/V_{m} = V/60$ litres/min, is the consumption rate (in litres/min).

(ii) Alveolar $P^{al}_{CO_2}$ can be expressed in terms of $V$ and $V_{O_2}$.

$$P^{al}_{CO_2} = 107.18 e^{-2.19 \left( \frac{V}{V_{CO_2}} \right)}$$

wherein $V_{CO_2}$ is the $CO_2$ production rate (in liters/min).

(iii) Blood $P_{O_2}$ can be obtained in terms of blood $C_{O_2}$, from the $O_2$ dissociation curve.

$$P^{B}_{O_2} = 30.5 \ln \left[ \frac{0.2}{0.2 - C_{O_2}^{B}} \right]$$

(iv) Blood $P_{CO_2}$ can be obtained in terms of $C_{CO_2}^{B}$, from the $CO_2$ dissociation curve.

$$P^{B}_{CO_2} = 37.94 \ln \left[ \frac{0.8}{0.8 - C_{CO_2}^{B}} \right]$$

Now, $\Delta P_{O_2}$ ($= P^{al}_{O_2} - P^{cap}_{O_2} = P^{al}_{O_2} - P^{V}_{O_2}$) and $\Delta P_{CO_2}$ ($= P^{V}_{CO_2} - P^{al}_{CO_2}$) vary along the capillary bed. Based on [3], we have:

$$\Delta P_{O_2}^{AV} = 0.185 \Delta P_{max}^{O_2}$$

$$\Delta P_{CO_2}^{AV} = 0.1 \Delta P_{max}^{CO_2}$$

Hence, from equations (3 & 9) and (4 & 10),

$$D_{O_2} = \frac{V_{O_2}^{o}}{0.185(\rho^{al}_{O_2} - \rho^{B}_{O_2})}$$

$$D_{CO_2} = \frac{V_{CO_2}^{o}}{0.14(\rho^{al}_{CO_2} - \rho^{B}_{CO_2})}$$

V. EVALUATION OF $O_2$ AND $CO_2$ METABOLIC RATES AND CARDIAC OUTPUT

From monitored data of inspired-exhaled gas compositions, in TABLE 1:

$$O_2 \text{ consumption rate}, \dot{V}_{O_2} = BR(\text{Inspired } O_2 - \text{Expired } O_2) \text{ ml/min} = 12(104.2-80.6) = 283.2 \text{ ml/min}$$

$$CO_2 \text{ consumption rate}, \dot{V}_{CO_2} = BR(\text{Expired } CO_2 - \text{Inspired } CO_2) \text{ ml/min} = 12(19.1-0.2) = 226.8 \text{ ml/min}$$

From monitored $O_2$ and $CO_2$ concentrations of arterial and venous blood, in TABLE 2:

$$\dot{V}_{O_2} = Q \left( C_{O_2} - C_{O_2} \right) \text{ ml/min} = 283.2 \frac{\text{ml}}{0.05} = 5664 \text{ ml/min}$$

VI. EVALUATING OF THE LUNG DIFFUSION COEFFICIENTS $D_{O_2}$ AND $D_{CO_2}$

From equation (7) and TABLE 2 ($C_{O_2}^{V} = 0.13$), we get for (venous blood @ arterial end of the pulmonary capillary or $P_{O_2}^{V}$)

$$P_{O_2}^{V} = 30.5 \ln \left[ \frac{0.2}{0.2 - C_{O_2}^{V}} \right]$$

$\Delta P_{O_2}^{max} = 30.5 \ln \left[ \frac{0.2}{0.2 - 0.13} \right] = 32.02 \text{ mmHg}$

From equation (8) and TABLE 2 ($C_{CO_2}^{V} = 0.56$), we get for $P_{CO_2}^{V}$ (venous blood @ arterial end of the pulmonary capillary or $P_{CO_2}^{V}$)
\[ \begin{align*}
P_{CO_2}^o &= 37.94 \ln \left[ \frac{0.8}{0.8 - C_i^{TB}} \right] \\
&= 37.94 \ln \left[ \frac{0.8}{0.8 - 0.56} \right] \\
&= 45.68 \text{ mmHg} \quad (16)
\end{align*} \]

Also, from equation (5) and TABLE 1 \( (V^* = 0.1) \), we get:

\[ \begin{align*}
P_{O_2}^{al} &= 140 \left[ 1 - e^{-4.18 \left[ \frac{V^* / V}{V_{O_2}} \right]} \right] \\
&= 140 \left[ 1 - e^{-4.18 \left[ \frac{0.1/0.2832}{1} \right]} \right] = 108 \text{ mmHg} \quad (17)
\end{align*} \]

Hence, from equations (9, 15 & 17), we get:

\[ \Delta p_{av}^{O_2} = 0.185 \times (108 - 32.02) = 14.06 \text{ mmHg} \quad (18) \]

Finally, from equations (11) and (18), we get:

\[ \begin{align*}
D_{O_2}^o &= \frac{V_{O_2}}{\Delta p_{av}^{O_2}} = \frac{283.2 \text{ ml/min}}{14.06 \text{ mmHg}} \\
&= 20.14 \text{ ml/min } \text{ mmHg}^{-1} \quad (19)
\end{align*} \]

Then from equation (6), TABLE 1 \( (V = 0.1) \), and equation (12) we get:

\[ \begin{align*}
P_{CO_2}^{al} &= 107.18 e^{-2.19 \left[ \frac{V^* / V_{CO_2}}{V_{CO_2}} \right]} \\
&= 107.18 e^{-2.19 \left[ \frac{0.1/0.2268}{1} \right]} = 40.81 \text{ mmHg} \quad (20)
\end{align*} \]

Hence, from equations (10, 16 & 20), we get:

\[ \Delta p_{av}^{CO_2} = 0.1 \times (45.68 - 40.81) = 0.487 \text{ mmHg} \quad (21) \]

Finally, from equations (12 & 21), we get:

\[ \begin{align*}
D_{CO_2} = \frac{V_{CO_2}^o}{\Delta p_{av}^{CO_2}} &= \frac{226.8 \text{ ml/min}}{0.487 \text{ mmHg}} \\
&= 465.71 \text{ ml/min } \text{ mmHg}^{-1} \quad (22)
\end{align*} \]

VII. CONCLUSION

We have demonstrated a noninvasive clinical procedure
- for obtaining (i) \( O_2 \) consumption rate and \( CO_2 \) production rate, (ii) cardiac output, \( Q_o \), (iii) and lung diffusion capacities for \( O_2 \) and \( CO_2 \).
- from inhaled and exhaled air composition analysis and blood-gas analysis.

This work could have application to SARS testing and evaluation.

REFERENCES


Quantitation of Renal Function Based on Two-Compartmental Modeling of Renal Pelvis
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Abstract—The primary functions of the kidney are: (i) to get rid of the body waste materials that are either ingested or produced by metabolism, and (ii) to control the volume and composition of the body fluids. Herein, we provide a noninvasive methodology to assess physiological function of the kidneys. For this purpose, we analyze the renograms with 2-compartmental modelling of the kidney-renal outflow system, and therefrom compute the amount of flow of renal radionuclide into and out of the renal pelvis compartment.

The derived information of uptake \(k/A\) and washout \(e^{-\frac{Ve}{2V_c} sinhAt}\) rates can be of considerable use. The paper provides a number of case studies for the verification of the derived system governing equations against clinical renograms.

Keywords—Renal outflow obstruction, renal function, glomerular filtration rate, GFR

I. INTRODUCTION

The kidney functional performance is characterized by (i) its filtering capacity, getting rid the body waste materials that are either ingested or produced by metabolism, and (ii) control the volume and composition of the body fluids. Renogram studies have been used for the assessment of renal function for many years [1, 2]. Mathematical modelling has been performed for the kidneys, such as one-compartment model of clearance of tracer [3,4]. However, modeling of the tracer transport between renal parenchyma pool compartment and renal pelvis compartment; derivation of the governing equations for renogram curves has not been reported. Here, we note that the tracer uptake and washout rates can represent the performance indices. In this paper, we evaluate these rates and demonstrate their clinical relevance renogram data.

II. RENAL PELVIS TWO-COMPARTMENTAL MODEL

Fig. 1: illustrates the region of interest (ROI) and we have derived the compartmental model for renal pelvis and shown in Fig. 2.

\[ G_1 : \text{Tracer mass in the chamber 1 (renal parenchyma) in Counts.} \]
\[ G_2 : \text{Tracer mass in the chamber 2 (renal pelvis) in Counts.} \]
\[ C_1 : \text{Concentration of tracer in the chamber 1 in Counts/dL.} \]
\[ C_2 : \text{Concentration of tracer in the chamber 2 in Counts/dL.} \]
\[ V_1 : \text{Volume of chamber 1, renal parenchyma in dL.} \]
\[ V_2 : \text{Volume of chamber 2, renal pelvis in dL.} \]
\[ I(t) : \text{Tracer input function in Counts/sec.} \]
\[ F(t) : \text{Blood Flow from chamber 1 to chamber 2 in dL/sec.} \]
\[ U(t) : \text{Urine outflow in dL/sec.} \]
III. DERIVATION and PHYSIOLOGICAL SIGNIFICANCE of MODELING SOLUTIONS

From Fig. 2, we derive the following:

\[ \frac{dG_1}{dt} = -FC_1 + I(t), \text{ for chamber 1} \]  
\[ (1) \]

\[ \frac{dG_2}{dt} = FC_1 - C_2 U(t), \text{ for chamber 2} \]  
\[ (2) \]

where (i) \( G_1 (= C_1 V) \) represents the tracer amount in chamber 1, and (ii) \( G_2 (= C_2 V) \) represents the tracer amount in chamber 2.

In physiological studies of kidney function and urine outflow status (renography), the input function is a tracer bolus administered over a short period of time. Compared to the entire duration of the renal dynamics, this bolus injection of tracer can be approximated by an impulse function (Dirac’s delta function). In the following derivation, whenever \( I(t) \) appears it will be assumed to be equal to \( I(t) \).

We assume that the compartmental volumes \( V_1 \) and \( V_2 \) are constants (which they generally are), and the urinary flow rate \( U \) as unknown constant (urine flowing out of the kidney into the ureters is physiologically continuous and constant with time, unless there are changes in body fluid status). Here, we are only performing an intra-renal analysis for obstruction to the outflow, we have from (1) and (2):

\[ V_1 \frac{dC_1}{dt} = -FC_1 + I(t) \]  
\[ (3) \]

\[ V_2 \frac{dC_2}{dt} = FC_1 - C_2 U \]  
\[ (4) \]

By differentiating and combining (3) and (4), we arrive at:

\[ V_2 \frac{dC_2}{dt} + \beta C_2 + \gamma C_2 = \left( \frac{F}{V_1} \right) I(t) \]  
\[ or, \]

\[ V_2 \frac{dC_2}{dt} + \beta C_2 + \gamma C_2 = \left( \frac{F}{V_1} \right) I(t) \]  
\[ (5) \]

where:

\[ \left( \frac{FU_2}{V_2} + U \right) = \beta, \quad \left( \frac{FU}{V_1} \right) = \gamma \]  
\[ (6) \]

The equation (5) is a standard form of a linear second-order ordinary differential equation, with \( I(t) \) as the unit impulse function. This is the governing differential equation for the behavior of tracer within the renal pelvicycalceal compartment.

Solution by Laplace transform method yields the following equations, given the initial conditions of \( C(0) \) and \( C'(0) = 0 \).

\[ L \left\{ V_1 \frac{dC}{dt} + \beta C + \gamma C \right\} = L \left\{ \left( \frac{F}{V_1} \right) I(t) \right\} \]
\[ \therefore \left( V_2 s^2 + \beta s + \gamma \right) C_2(s) = \left( \frac{F}{V_1} \right) \]  
\[ C_2(t) = C(t) = \left( \frac{F}{V_1} \right) \left( \frac{1}{s^2 + \beta s + \gamma} \right) \]
\[ = \left( \frac{F}{V_1} \right) \left( \frac{1}{\sqrt{\frac{\gamma - \beta^2}{V_2} - \frac{\beta^2}{4V_2^2}}} \right) \]
\[ \left( \frac{\gamma - \beta^2}{V_2 - 4V_2} \right)^{1/2} \sin \left( \frac{\sqrt{\gamma - \beta^2}}{V_2 - 4V_2^2} \right) t \]  
\[ (7) \]

Solving the above Laplace transform and taking care of the characteristics of the roots (which is now in standard form, by looking up standard tables), we obtain the results for the dynamic behavior of the tracer concentration in the renal pelvis for this physiological system. The term underneath the square root is the determinant of the behavior of the system with regards to whether there is underdamped, critically damped or overdamped behaviour.

This term can be expressed as \( \beta^2 - 4V_2 \gamma \) and it yields a significant functional index for assessing the outflow status of the kidney. We will classify the observed physiological behaviours of renogram systems into underdamped, overdamped or critically damped systems based on the index, as follows:

Case 1:

If \( \beta^2 - 4V_2 \gamma < 0 \), the condition is underdamping, and (7) yields the solution:

\[ C(t) = \left( \frac{F}{V_1} \right) \left( \frac{1}{\sqrt{\frac{\gamma - \beta^2}{V_2} - \frac{\beta^2}{4V_2^2}}} \right) e^{-\beta t} \sin \left( \frac{\sqrt{\gamma - \beta^2}}{V_2 - 4V_2^2} \right) t \]
\[ \left( \frac{k}{A} \right)^{1/2} \left( \frac{1}{A} \right) \left( \frac{V_1}{V_2} \right) \]  
\[ (8) \]

As can be seen from equation (8), the terms which describe urine outflow and determine the shape of the tracer-concentration curve of the renogram during the tracer washout phase are the \( e^{-\beta t} \) and \( \sin \left( \frac{\sqrt{\gamma - \beta^2}}{V_2 - 4V_2^2} \right) t \). The important dynamic information captured in these two terms can be succinctly found in the physiological index that we have described. We will demonstrate the discriminatory nature of this index (which will be extracted as \( A \)) in section
IV when we analyze correlation with actual renogram studies.

Equation (8) is a linear second-order ordinary differential equation, very similar to that of the linear oscillator with damping. In a functioning renal system, the characteristic oscillating-underdamped conditions do not exist.

Case 2:
Whenever there is outflow obstruction, the key term
\[ \beta^2 - 4V_2 \gamma = \left( \frac{FV_2}{V_1} + U \right)^2 - 4V_2 \left( \frac{FU}{V_1} \right) = \left( \frac{FV_2}{V_1} - U \right)^2 > 0 \]
and the condition is overdamping. Then,
\[ C(t) = \left( \frac{F}{V_1 V_2} \right) \frac{1}{\sqrt{\frac{\gamma}{V_2} - \beta^2}} \sinh \left( \sqrt{\frac{\gamma - \beta^2}{4V_2}} t \right) \]
(9)

We can express output segment of the tracer curve of compartment 2 looks different from that of the tracer input so the key term actually reflects the rate of tracer input \((FC_l)\) minus the rate of tracer output \((UC_2)\).

Case 3:
In the normal case, most physiological systems are well-compensated, and hence the output are fairly similar, hence,
\[ \beta^2 - 4V_2 \gamma = \left( \frac{FV_2}{V_1} + U \right)^2 - 4V_2 \left( \frac{FU}{V_1} \right) = \left( \frac{FV_2}{V_1} - U \right)^2 = 0 \]
In other words, the renal system is critically damped.
The governing equations for this will be
\[ C(t) = \left( \frac{F}{V_1 V_2} \right) t e^{\frac{\beta}{2V_2}} \]
(10)

For model analysis, because of complications involved in monitoring \(U\) (urine flow rate), \(F\) (plasma flow rate into the renal pelvis) and \(V_1\) control volume, we propose that our model parameters will be lumped parameters \(k\) and \(A\). Next our parameters identification will be carried out for \(k\), \(A\), \(V_2\) and \(\beta\).

IV. CLINICAL DATA & EVALUATION

We will demonstrate and verify the application of our models using the renograms obtained from the Nuclear Medicine and PET Department. The radionuclide used are \(^{99m}\)Tc-DTPA and \(^{99m}\)Tc-MAG3. The degree of match with the governing equations is based on the area under the left and right kidney curves against the clinical curves between 60 and 120 seconds.

Model Application:
We will first digitize and normalized the renograms. Next, we will perform parameters identification and obtain the system parameters: \(k\), \(A\), \(\beta\) and \(V_2\). We will only accept the results of the best fit.

![Fig. 3: Clinical renograms of volunteer coded Patient 7. Note that the (QR-RR) segment of the tracer curve for the right kidney is similar to the (PR-QR) segment and demonstrates good outflow-rate compared to the (QL-RL) segment of the obstructive curve for the left kidney.](image_url)

<table>
<thead>
<tr>
<th>Identity</th>
<th>% Clinical Area Under the curves between 60 to 120 sec.</th>
<th>% Calculated Area Under the curves between 60 to 120 sec</th>
<th>% Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 7</td>
<td>44 56</td>
<td>43.87 56.13</td>
<td>0.29 -0.23</td>
</tr>
<tr>
<td>Patient 8</td>
<td>50 50</td>
<td>49.69 50.31</td>
<td>0.61 -0.61</td>
</tr>
</tbody>
</table>
V. RESULTS

We have performed parametric identification for equations (9) and (10) using MatLab 7. The following are the best fitted results for patients 7 & 8.

**Fig. 5:** Simulated renograms of volunteer coded Patient 7. The clinical data for both kidneys is best fitted by equation (9). The identified parameters are:

\[ \begin{align*}
  k_L &= 0.0124; \quad A_L = 5.48E-03; \quad \beta_L = 0.0107 \quad \text{and} \quad V_{2L} = 0.8664 \\
  k_R &= 0.0221; \quad A_R = 8.68E-03; \quad \beta_R = 0.0103 \quad \text{and} \quad V_{2R} = 0.4928
\end{align*} \]

**Fig. 6:** Simulated renograms of volunteer coded Patient 8. The clinical data for both kidneys is best fitted by equation (9). The identified parameters are:

\[ \begin{align*}
  k_L &= 0.0221; \quad A_L = 7.61E-03; \quad \beta_L = 0.0098 \quad \text{and} \quad V_{2L} = 0.4959 \\
  k_R &= 0.0221; \quad A_R = 8.59E-03; \quad \beta_R = 0.0125 \quad \text{and} \quad V_{2R} = 0.6248
\end{align*} \]

**TABLE 1** shows that the area under the curves from the simulation matches that of the clinical with an error less than 1%.

VI. CONCLUSION

We have demonstrated modeling of kidney-renal outflow tract compartments with derivation of the governing equations from second-order differential equations and assessed the clinical relevance with comparison with clinical renogram studies.

REFERENCES


# Technical Programme

## Scientific Programme – DAY 1

**Wednesday, September 08 2004**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>0800 – 0920</td>
<td>Registration</td>
</tr>
<tr>
<td>0920 – 0940</td>
<td>Opening Ceremony</td>
</tr>
<tr>
<td>0940 – 1010</td>
<td>Nanostructure Processing of Advanced Biomaterials</td>
</tr>
<tr>
<td></td>
<td>Invited Speaker: Dr. Jackie Ying</td>
</tr>
<tr>
<td>1010 – 1040</td>
<td>Bioengineering, Technology Commercialization and Entrepreneurship</td>
</tr>
<tr>
<td></td>
<td>Invited Speaker: Dr. Yongmin Kim</td>
</tr>
<tr>
<td>1040 - 1100</td>
<td>Tea break</td>
</tr>
<tr>
<td>1100 – 1130</td>
<td>Esophageal Tissue Engineering</td>
</tr>
<tr>
<td></td>
<td>Invited Speaker: Dr. Buddy Ratner</td>
</tr>
<tr>
<td>1130 – 1200</td>
<td>A Case Study of Integrated Biomedical Engineering: A Novel Method for Creating an Automated Sutureless Anastomosis</td>
</tr>
<tr>
<td></td>
<td>Invited Speaker: Dr. Adam Sharkawy</td>
</tr>
<tr>
<td>1200 –1230</td>
<td>Advances in Cancer Imaging</td>
</tr>
<tr>
<td></td>
<td>Invited Speaker: Dr. James Khoo</td>
</tr>
<tr>
<td>1230 – 1330</td>
<td>Lunch</td>
</tr>
<tr>
<td>1330 – 1400</td>
<td>Tissue Engineering Heart Constructs using Bone Marrow Stem Cells</td>
</tr>
<tr>
<td></td>
<td>Invited Speaker: Dr. Philip Wong</td>
</tr>
<tr>
<td>1400 – 1430</td>
<td>Computational Technologies to Accelerate Biotech Innovation</td>
</tr>
<tr>
<td></td>
<td>Invited Speaker: Dr. Ulrich Meier</td>
</tr>
<tr>
<td>1430 – 1500</td>
<td>A new Approach to Protein Structure Prediction</td>
</tr>
<tr>
<td></td>
<td>Invited Speaker: Dr. Heiko Schroder</td>
</tr>
<tr>
<td>1500 – 1515</td>
<td>Tea break</td>
</tr>
</tbody>
</table>
### Session 01 Tissue Engineering (Room 1) 1515 – 1730
Chairs: S. Chian, P. Wong

- Enhancement of Meniscus Repair using Mesenchymal Stem Cells in a Porcine Model
  Dutton A., Hui J.P.P., Lee E.H.

- Cardiac Differentiation of Adult Bone Marrow Mesenchymal Stem Cells

- Polyurethane Membranes for Chondrocyte Transplantation and Cartilage Engineering
  Chia S.L., Gorna K., Gogolewski K., Alini M.

- Theoretical and Experimental Determination of State of Two Dimensional Strain in a Bioreactor
  Ong W.F., Wijaya S., Ritchie A.C.

- Culture of Rodent Hepatocytes on Microgrooved Surfaces: Application for a Flat-Plate Bioartificial Liver Device
  Ting K.S., Wang N.D., Grant M.H., Henderson C.

- Simultaneous Probing of Morphology, Cytoskeleton, and Adhesion Dynamics of HepG2 Cells
  Feng Z. Q., Liao K., Chan V.

- ECM-Dependent Proliferation of Adult Bone Marrow Mesenchymal Stem Cells

- Parameters for Scaffold Design of Esophageal Tissue from a Structural Constitutive Model
  Yang W., Fung T.C., Chian K. S., Chong C. K.

- Surface modification of biodegradable poly(L-lactide-co-caprolactone) (PLLC) membrane with proteins to enhance the growth of esophageal smooth muscle cells
  Yabin Z., Chan-Park M.B., Chian K.S

### Session 02 Cancer Detection & Therapy (Room 2) 1515 – 1715
Chair: J. Khoo

- Automated Segmentation of Breast Masses in Mammograms
  Zhang H., Foo S.W., Thng C.H.

- Diagnosis of Lung Cancer Using NIR Raman Spectroscopy
  Huang Z., McWilliams A., Lam S., McLean D.I., Lui H., Zeng H.

- Extraction of head and neck tumors using deformation models from MR images
  Zhou J., Chong V.

- Breast Cancer Diagnosis using Thermography and complementary learning fuzzy neural network
  Tan T.Z., Quek C., Ng G.S., Ng E.Y.K.

- Magnetic Particles for Hyperthermia Treatment of Cancer
  Ramanujan R.V., Lao L.L.

- Gene Selection for Cancer Classification from Microarray Data using PLS-RLSC
  Shen L., Tan E. C.

- Micelle-like Nanoparticles of Linear and Branched PLA/PEG Block Copolymer as Anti-Cancer Drug Carrier
  Shen L., Tan E. C.

- Identification of human colorectal cancerous via Laser Induced Autofluorescence spectra confocal image
  Sheng F., Chia T.C., Kwek L.C., Dione C.H., Tang, C.L.

### Session 03A Medical Image Processing (Room 3) 1515 – 1745
Chairs: Z. Kuanyi

- ALA-Induced-PPIX Fluorescence Imaging of Normal and Neoplastic Tongue Tissue using Confocal Endomicroscopy
  Zheng W., Harris M., Kho K.W., Thong P.S.P., Hibbs A., Soo K.C., Olivo M.

- A Simulation System for Remote Interventional Radiology Procedures
  Zhao L., Ma X., Aziz A., Zheng W., Nowinski W.L.

- An Improved Active Contour Method for Heart Wall Boundary Detection in Echocardiographic Image Sequence
  Fang W., Chan K.L., Anantharaman V.

- Augmented Reality Assisted Sinus Surgery
  Shi D. M., Ng W. S., Ling K. V., Shao W., Chen H. J., Kwoh C. K.

- Brain Atlas-assisted Segmentation of the Hippocampus from MR Neuroimages
  Minh P.D., Prakash K.N.B., Nowinski W.L.

- Removing Blocking Artifacts in Compressed Medical Images
  Singh S., Vinod K., Verma H.K.

- Simulated Annealing based Simplified Snakes for Weak Edged Medical Image Segmentation
  You J., Zhou Z., Heng P.A., Xia D.

- Extraction of the Two Modified Talairach Cortical LandMarks (I and S) from MR T1-Weighted Images
  Hu Q., Qian G., Nowinski W.L.

- Knowledge-based Interpolation of the Talairach-Tournoux Brain Atlas
  Liu J., Nowinski W.L.

- Mapping Human Skin and Aural Temperature with ANNs and IR Imager
  Ng E.Y.K., Chong C.

### Session 04 Microfluidics/MEMS (Room 2) 1715-1800
Chair: D. Trau

- AFM Characterization and Selectivity of Immobilization of Antibodies in Bio-MEMS
  Joshi M., Rao R., Mukherji S.

- Cross-Talk, a Potential Source of Noise in a Fluorescence Multi-channel Microfluidic System
  Irawan R., Tjin S.C., Yager P., Zhang D.W.

- Microfluidic Protein Patterning using Embedded Cavities in Microchannels
  Garcia E., Yager P.
## Scientific Programme – DAY 2

**Thursday, September 09 2004**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>0830 – 0900</td>
<td>Development of Microfluidic-Based Point-of-Care Diagnostic Systems</td>
</tr>
<tr>
<td></td>
<td>Invited Speaker: Dr. Paul Yager</td>
</tr>
<tr>
<td>0900 – 0930</td>
<td>Innovation in The Medical Device Industry: Development of Cypher - the first Drug-Eluting Stent</td>
</tr>
<tr>
<td></td>
<td>Invited Speaker: Mr. Alok Mishra</td>
</tr>
<tr>
<td>0930 – 1000</td>
<td>Heart Tissue Engineering</td>
</tr>
<tr>
<td></td>
<td>Invited Speaker: Dr. Buddy Ratner</td>
</tr>
<tr>
<td>1000 – 1015</td>
<td>Tea break</td>
</tr>
<tr>
<td>Session 05 Biomaterials &amp; Drug Delivery (Room 1)</td>
<td>Session 06 Biomechanics (Room 2)</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>• Smart Polymer Nanocarriers for Targeted Delivery Yang Y.Y</td>
<td>• Biomechanics Highlights in Sports, Physiology and Medicine Ghista D.N.</td>
</tr>
<tr>
<td>• Release of Lipoplexes from a Biodegradable Polymer Film: Preliminary Study Chan W.A., Ramgopal Y.</td>
<td>• Evolution and Biomechanics of the Cruciate Ligaments Fuss F.K.</td>
</tr>
<tr>
<td>• Cross linking of Bovine Serum Albumin with Genipin: Investigation of Mechanical Properties Sathappan K., Chian K.S., Chua L.P.</td>
<td>• The Double-Bundle ACL Graft Reconstruction: A superior technique to restore knee kinematics Lie D.T.T., Amis A.</td>
</tr>
<tr>
<td>• In vitro Study on the Release Kinetics of Bovine Serum Albumin (BSA) from Injectable PLGA/BB Depot Wang L.W., Venkatraman S.</td>
<td>• A Comparative Study of Different Gripping Methods for Tendons Ng B.H., Chou S.M., Krishna V.</td>
</tr>
<tr>
<td></td>
<td>• BioSequence Comparison for Large Database on Reconfigurable Platforms Wong M.T., Schmidt B.</td>
</tr>
<tr>
<td>Session 08A Cardiovascular Engineering 1 (Room 1)</td>
<td>Session 09A Sport Engineering 1 (Room 2)</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td><strong>Chair:</strong> A.C. Ritchie</td>
<td><strong>Chair:</strong> W. Kim, F.K. Fuss</td>
</tr>
<tr>
<td><strong>1330 – 1530</strong></td>
<td><strong>1330 – 1530</strong></td>
</tr>
<tr>
<td>A Decoupled Control Method for the Magnetic Bearings of a Blood Pump</td>
<td>Quantitative analysis of Singapore Golfers</td>
</tr>
<tr>
<td>Lim T.M., Zhang D., Kim M.T.</td>
<td>Lim S. L., Xie X., Ong V., Teh K. C.</td>
</tr>
<tr>
<td>Computation of Gap Flow Field in a Bio-Centrifugal Blood Pump</td>
<td>Investigation of Weight Transfer during Golf Swing</td>
</tr>
<tr>
<td>Computational Studies of Steady Flows In Designed Sleeve Models At Distal Anastomoses</td>
<td>Biomechanics of Push-up Exercise and Triceps Contractility</td>
</tr>
<tr>
<td>Contractility of the Left Ventricle in Terms of its Sacromere Power Generation</td>
<td>Comparison of Pinch- and Open Hand Grip during Sport Climbing</td>
</tr>
<tr>
<td>Detection of Cardiac Arrhythmia using Phase Space Analysis</td>
<td>Friction at the Climbing Handhold under Different Conditions and its Implications for Sport Climbing</td>
</tr>
<tr>
<td>Wong M. T., Srinivasan N., Chan Y.W.</td>
<td>Tan M. A., Fuss F. K., Niegl G.</td>
</tr>
<tr>
<td>LV Twisting Analyzed for Pressure-Increase During Iso-Volumic Contraction</td>
<td>Analysis of Badminton Smash Using Dual Euler Angles Algorithm</td>
</tr>
<tr>
<td><strong>Tea Break</strong></td>
<td><strong>Tea Break</strong></td>
</tr>
<tr>
<td><strong>1530 -1545</strong></td>
<td><strong>1530 -1545</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Tea Break</strong></td>
</tr>
<tr>
<td></td>
<td><strong>1530 -1545</strong></td>
</tr>
</tbody>
</table>
Day 2 (continued)

<table>
<thead>
<tr>
<th>Session 08B Cardiovascular Engineering 2 (Room 1) 1545 – 1645 Session Chair: A.C. Ritchie</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Multiple-Model Adaptive Control by Means of a Fuzzy Controller-based Control System Zheng H., Zhu K. Y., Tan Y. S.</td>
</tr>
<tr>
<td>• Numerical Investigation of Stress Field in Distal End-to-side Anastomoses Liu L., Chua L.P., Ghista D.N., Tan Y.S.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session 09B Sport Engineering 2 (Room 2) 1545 – 1630 Chairs: B. Tan, K.C. Teh</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Comparative Study on the techniques of Singapore and Thailand Table Tennis players during SEA Games 2001 Lee K.T., Xie W., Teh K.C.</td>
</tr>
<tr>
<td>• Experimental Study on Different Types of Service Spins for Singapore National Table Tennis players Lee K.T., Xie W.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session 10B Ultrasonic Imaging 2 (Room 3) 1545 – 1645 Chair: M. Kezhi</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Field of View-based Imaging for Efficient Beamforming in Low-end Portable Ultrasound Systems Agarwal A., Schneider F.K., Yoo Y.M., Kim Y.</td>
</tr>
<tr>
<td>• Low Sampling Frequency Digital Beamformer for Ultrasonic Imaging without Interpolation Gao C.Q., Zhang L.C., Wong E.M.C.</td>
</tr>
<tr>
<td>• Comparative Evaluation of Wavelet Filters for Speckle Reduction in Ultrasound Medical Images Thakur A., Anand R.S.</td>
</tr>
<tr>
<td>• Window Function Optimization by Genetic Algorithm for Ultrasound Imaging System Cao J., Koh L.M.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session 11 Respiratory Biomechanics (Room 1) 1645 – 1730 Chair: V. V. Kulish</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Determination of O2 and CO2 Metabolic Rates and Lung O2 and CO2 Diffusion Coefficients Loh K.M., Ghista D.N.</td>
</tr>
<tr>
<td>• Oxygen Saturation Profiles in a Hollow Fibre Oxygenator Ritchie A.C., Thimm G.</td>
</tr>
<tr>
<td>• Graphical Technique for Assessing Pulmonary Disease Loo C. M., Ang K. C., Ong J. H., Ghista D. N., Lim G. H.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session 12A Orthopaedic Engineering 1 (Room 2) 1630 – 1745 Chairs: S.M. Chou, D.T.T. Lie</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Design Optimisation in BioMedical Engineering Koh E.C.Y., Fuss F. K.</td>
</tr>
<tr>
<td>• Design Classification and Mechanics of Artificial Discs Fuss F.K.</td>
</tr>
<tr>
<td>• Extraforaminal Lumbar Interbody Fusion: Simulation of the Fusion Process Based on Different Implant Materials Fuss F. K., Sabitzer R. J.</td>
</tr>
<tr>
<td>• FE Investigation on Spinal Interbody Fusion Lee K. K., Teo E. C., Fuss F. K., Sabitzer R. J.</td>
</tr>
<tr>
<td>• Optimization of Cervical Ring Cage by Taguchi Philosophy Yang K., Teo E. C., Fuss F. K.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session 13A Biosignal Processing 1 (Room 3) 1645 – 1745 Chair: O. Chutatape</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A Novel Approach to Automatic Left Ventricular Contour Tracking Cheng J.R., Foo S.W.</td>
</tr>
<tr>
<td>• A Novel Wavelet Based ECG Compression with X-tree Coding Swain S., Chutatape O., Dandapat S.</td>
</tr>
<tr>
<td>• Left Ventricular Surface Kinematics During Isovolumic Contraction Yeo S.Y., Tan R. S., Liu L., Chai G.B., Ghista D.N.</td>
</tr>
<tr>
<td>• Evaluation of Slice Sensitivity Profiles for TPRF Algorithm Yan M., Zhang C.S.</td>
</tr>
</tbody>
</table>

END OF DAY 2
<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0830-0900</td>
<td>Biological Resurfacing of Articular Cartilage – from Bench to Bedside</td>
<td>Dr. Lee Eng Hin</td>
</tr>
<tr>
<td>0900-0930</td>
<td>Virtual Reality, Augmented Reality and its Medical Application</td>
<td>Dr. Uli Bockholt</td>
</tr>
<tr>
<td>0930-1000</td>
<td>Vital Signs in the Real World</td>
<td>Mr. Stephen Wilson</td>
</tr>
<tr>
<td>1000-1030</td>
<td>Clinical Endoscopy System: Present and Future</td>
<td>Dr. Tsuneo Hidaka</td>
</tr>
<tr>
<td>1030-1045</td>
<td>Tea break</td>
<td></td>
</tr>
<tr>
<td>Session 14 Biosensors/Diagnostic Tools (Room 1)</td>
<td>Session 13B Biosignal Processing 2 (Room2)</td>
<td>Session 15 Distributed Diagnosis &amp; Home Healthcare (Room 3)</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-------------------------------------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Chair: K. L. Chan</td>
<td>Chair: C. Zhang</td>
<td>Chair: S. C. Tjin</td>
</tr>
</tbody>
</table>
| • Multi-Parameter Clinical Diagnosis using Neural Networks  
  Tan E.K.                                       | • Uni-channel PCA for noise reduction from ECG signals  
  Palaniappan R., Tan E.K.                        | • Distributed Diagnosis and Home Healthcare (D2H2) and  
  Patient-Centered Electronic Medical Record  
| • An Otoacoustic Emissions Detecting System using USB AD/DA Board  
  Qian X., Ye D.                                   | • Wavelet-Based Denoising and Analysis of Phonocardiogram  
  Wang P., Anantharaman V.                         | • Advanced System Architecture for Telecardiology  
  Goh K. W., Kugean C., Tan E. K., Prabaharan K.  |
| • Oral Glucose Tolerance Test Modeling For Diabetes Characterization  
  Loh K.M., Ghista D.N.                            | • Dynamical Analysis of Heart Rate Variability Signals  
  Rajendra A.U., Kannathal N., Lim C.M.           | • Disposable Microfluidic Card and Fluorescence Detection System for Point-of-Care Diagnostic Applications  
  Irawan R., Tjin S. C., Fu C. Y., Ng B.K., Yuan X.C., Zhang D.W. |
| • Feasibility of biosensing based on two-dimensional square photonic lattice  
  Zhang D. W., Irawan R., Tjin S. C., Yuan X. C. |                                           |                                                         |
| • Application of Artificial Neural Network Technique in Healthcare Expenditure Analysis  
  Chia E., Khong P.W., Ghista D.N.                |                                           |                                                         |
| Session 12B Orthopaedic Engineering 2 (Room 2) | Session 03B Medical Image Processing (Room 3) | Session 03B Medical Image Processing (Room 3) |
| 1130-1215                                       | 1130-1215                                 | 1130-1215                                               |
| Chairs: D. Ghista, S. Idapalapati               | Chair: S. C. Tjin                         |                                                         |
| • Integration of CAD to FEA for Prosthetic Socket Design  
  Goh J. C. H., Lee P. V. S., Toh S. L., Ooi C. K.  | • Automatic 3-D optic Disk Image Reconstruction from Low-Resolution Fundus Image for Glaucoma Analysis  
  Xu J., Chutatape O.                             |                                                         |
| • Analyses of Fractured Bone (Femur) with Plate and Intra-Medullary Rod Fixations  
  Chen Q., Fan S.C., Ghista D.N.                  | • Low-Complexity Unified-Adaptive Compression of Biomedical Images Using Integer Hartley Transform  
  Meher P.K., Srikanthan T., Agarwal H.K., Gupta J.  |                                                         |
| • Biomechanics of Long Bone Geometry and Fracture Fixation  
  Krishna K.R., Sridhar I., Sivashanker S., Khong K.S., Ghista D. N. | • Modified Deformable region model for Lumen Extraction from Colonoscopic Image and Comparison with FCM  

End of Conference
## Authors’ Index

<table>
<thead>
<tr>
<th>Author</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal A.</td>
<td>345, 361</td>
</tr>
<tr>
<td>Agarwal H.K.</td>
<td>125</td>
</tr>
<tr>
<td>Alini M.</td>
<td>33</td>
</tr>
<tr>
<td>Amis A.</td>
<td>185</td>
</tr>
<tr>
<td>Anand R. S.</td>
<td>369</td>
</tr>
<tr>
<td>Anantharaman V.</td>
<td>89, 440</td>
</tr>
<tr>
<td>Ang K.C.</td>
<td>385</td>
</tr>
<tr>
<td>Aziz A.</td>
<td>85</td>
</tr>
<tr>
<td>Aziz A.R.</td>
<td>328</td>
</tr>
<tr>
<td>Bockholt U.</td>
<td>25</td>
</tr>
<tr>
<td>Boey F.Y.C.</td>
<td>77</td>
</tr>
<tr>
<td>Cai Y.Y.</td>
<td>232</td>
</tr>
<tr>
<td>Cao J</td>
<td>373</td>
</tr>
<tr>
<td>Chai G.B.</td>
<td>278, 428</td>
</tr>
<tr>
<td>Chan K.L.</td>
<td>89, 217</td>
</tr>
<tr>
<td>Chan V</td>
<td>42</td>
</tr>
<tr>
<td>Chan W.A.</td>
<td>77, 150</td>
</tr>
<tr>
<td>Chan Y.W.</td>
<td>217, 271</td>
</tr>
<tr>
<td>Chaudhari N.S.</td>
<td>228</td>
</tr>
<tr>
<td>Chen C.</td>
<td>209</td>
</tr>
<tr>
<td>Chen H.J.</td>
<td>93</td>
</tr>
<tr>
<td>Chen Q.</td>
<td>412</td>
</tr>
<tr>
<td>Cheng J.</td>
<td>420</td>
</tr>
<tr>
<td>Chew W.</td>
<td>213</td>
</tr>
<tr>
<td>Chia E.</td>
<td>469</td>
</tr>
<tr>
<td>Chia S.L.</td>
<td>33</td>
</tr>
<tr>
<td>Chian K.S.</td>
<td>51, 154</td>
</tr>
<tr>
<td>Chong A.</td>
<td>196</td>
</tr>
<tr>
<td>Chong C.</td>
<td>117</td>
</tr>
<tr>
<td>Chong C.K.</td>
<td>51</td>
</tr>
<tr>
<td>Chong V.</td>
<td>61</td>
</tr>
<tr>
<td>Chou S.M.</td>
<td>192, 196</td>
</tr>
<tr>
<td>Chu F.</td>
<td>244</td>
</tr>
<tr>
<td>Chua A.W.C.</td>
<td>213</td>
</tr>
<tr>
<td>Chua L.P.</td>
<td>154, 259, 263, 274, 278, 286, 289, 293</td>
</tr>
<tr>
<td>Chua T.</td>
<td>30, 49</td>
</tr>
<tr>
<td>Chui Y.L.</td>
<td>30</td>
</tr>
<tr>
<td>Chutatape O.</td>
<td>424, 121</td>
</tr>
<tr>
<td>Dandapat S.</td>
<td>424</td>
</tr>
<tr>
<td>Dhar P.K.</td>
<td>221</td>
</tr>
<tr>
<td>Diao X.N.</td>
<td>240</td>
</tr>
<tr>
<td>Doraiswami R.</td>
<td>129</td>
</tr>
<tr>
<td>Drerup B.</td>
<td>202</td>
</tr>
<tr>
<td>Dutton A.Q.</td>
<td>27</td>
</tr>
<tr>
<td>Fan S.C.</td>
<td>412</td>
</tr>
<tr>
<td>Fang W.</td>
<td>89</td>
</tr>
<tr>
<td>Feng M.</td>
<td>77</td>
</tr>
<tr>
<td>Feng Z. Q.</td>
<td>42</td>
</tr>
<tr>
<td>Foo S.W.</td>
<td>54, 420</td>
</tr>
<tr>
<td>Fu C.Y.</td>
<td>141</td>
</tr>
<tr>
<td>Fung T.C.</td>
<td>51</td>
</tr>
<tr>
<td>Fuss F.K.</td>
<td>181, 312, 392, 397</td>
</tr>
<tr>
<td>Gao C.</td>
<td>224</td>
</tr>
<tr>
<td>Gao C.Q.</td>
<td>365</td>
</tr>
<tr>
<td>Garcia E.</td>
<td>145</td>
</tr>
<tr>
<td>Gogolewski K.</td>
<td>33</td>
</tr>
<tr>
<td>Goh J.</td>
<td>27</td>
</tr>
<tr>
<td>Goh J.C.H.</td>
<td>408</td>
</tr>
<tr>
<td>Goh K.W.</td>
<td>473</td>
</tr>
<tr>
<td>Gorna K.</td>
<td>33</td>
</tr>
<tr>
<td>Grant M.H.</td>
<td>38</td>
</tr>
<tr>
<td>Gu H.</td>
<td>213</td>
</tr>
<tr>
<td>Guo N. Q.</td>
<td>357</td>
</tr>
<tr>
<td>Gupta J.</td>
<td>125</td>
</tr>
<tr>
<td>Harris M.</td>
<td>81</td>
</tr>
<tr>
<td>Henderson C.</td>
<td>38</td>
</tr>
<tr>
<td>Heng P.A.</td>
<td>105</td>
</tr>
<tr>
<td>Hibbs A.</td>
<td>81</td>
</tr>
<tr>
<td>Ho K.L.I.</td>
<td>199</td>
</tr>
<tr>
<td>Hu Q</td>
<td>109</td>
</tr>
<tr>
<td>Hu Y.</td>
<td>170</td>
</tr>
<tr>
<td>Huang Z.</td>
<td>58</td>
</tr>
<tr>
<td>Hui J.P.P.</td>
<td>27</td>
</tr>
<tr>
<td>Indhumath C.</td>
<td>232</td>
</tr>
<tr>
<td>Irawan R.</td>
<td>137, 141, 457</td>
</tr>
<tr>
<td>Ji W.F.</td>
<td>293</td>
</tr>
<tr>
<td>Joshi M.</td>
<td>133</td>
</tr>
<tr>
<td>Kannathal N.</td>
<td>444</td>
</tr>
<tr>
<td>Kho K.W.</td>
<td>81</td>
</tr>
<tr>
<td>Khong K.S.</td>
<td>416</td>
</tr>
<tr>
<td>Khong P.W.</td>
<td>469</td>
</tr>
<tr>
<td>Khoo J.</td>
<td>21</td>
</tr>
<tr>
<td>Kim E.H.</td>
<td>461</td>
</tr>
<tr>
<td>Kim J.J.</td>
<td>461</td>
</tr>
<tr>
<td>Kim M.T.</td>
<td>251</td>
</tr>
<tr>
<td>Kim W.</td>
<td>202, 301, 305, 324</td>
</tr>
<tr>
<td>Kim Y.</td>
<td>19, 339, 345, 361, 461</td>
</tr>
<tr>
<td>Koh E.C.Y.</td>
<td>389</td>
</tr>
<tr>
<td>Koh L.M.</td>
<td>353, 373</td>
</tr>
<tr>
<td>Krishna K.R.</td>
<td>416</td>
</tr>
<tr>
<td>Krishna V.</td>
<td>192</td>
</tr>
<tr>
<td>Kugean C.</td>
<td>473</td>
</tr>
<tr>
<td>Kurniawati T.</td>
<td>158</td>
</tr>
</tbody>
</table>

Proceedings of IBEC 2004 477
Kwoh C. K. 93
Lam S. 58
Lao L.L. 69
Lee E.H. 24, 27
Lee K.K. 401
Lee K.T. 333, 336
Lee P.V.S. 408
Li J.Z. 213
Li P. 217
Liao K. 42
Lie D.T.T. 185
Liew C.S. 228
Lim B.H. 196
Lim C.H. 30
Lim C.M. 444
Lim G.H. 385
Lim S.L. 297
Lim T.M. 251
Ling K.V. 93
Liu J. 113, 170
Liu L. 278, 289, 428
Liu T.C. 30, 49
Liu W. 205
Liu X. 202, 324
Loh K.H. 170
Loh K.M. 377, 453
Loo C.M. 385
Lu B.F. 232
Lui H. 58
Ma X. 85
Mackie H. 328
Mao K.Z. 240
Matsen F.A. 461
McLean D.I. 58
McWilliams A. 58
Meena S. 274
Meher P.K. 125
Miao X. 158, 170
Minh P.D. 97
Mukherji S. 133
Ng B.H. 192
Ng B.K. 141
Ng E.Y.K. 65, 117, 267
Ng G.S. 65
Ng M.Y. 170
Ng S.Y. 196
Ng W. S. 93
Niegl G. 188, 312, 320
Nowinski W.L. 85, 97, 109, 113, 224, 247
Olivo M. 81
Ong J.H. 385
Ong V. 297
Ong W.F. 34
Ooi C.K. 408
Palaninippan R. 436
Pan J. 77
Prabaharan K. 473
Prakash K.N.B. 97
Qian G. 109
Qian X. 450
Quek C. 65
Rajendra A.U. 444
Ramanujan R.V. 69, 174
Ramgopal Y. 150
Rao R. 133
Ritchie A.C. 34, 381
Roy A. 247
Sabitizter R.J. 397, 401
Sathappan K. 154
Schmidt B. 205, 209, 237
Schneider F.K. 345, 361
Schroder H. 22
See W.N.W. 320
Shao W. 93
Sharkawy A. 20
Shen L. 73
Shi D. M. 93
Shim W.S.N. 30, 49
Sim E.K.W. 49
Sin E.K. 30
Singh S. 101
Sivasankar S. 416
Song C. 213
Song G.L. 259
Soo K.C. 81
Sourway N.C. 328
Sridhar I. 416
Srikanth T. 125
Srinivasan N. 271
Sung P.F. 166
Swain S. 424
Tai C.H. 255
Tan B. 328
Tan B.K. 213
Tan E.C. 73
Tan E.K. 436, 447, 473
Tan G.M.Y. 30, 49
Tan J. 30, 301, 305, 324
Tan L.P. 166
Tan M.A. 188, 312, 316, 308
The papers presented in this Proceedings of the 1st International BioEngineering Conference 2004 in conjunction with 6th Annual NTU-SGH Biomedical Engineering Symposium 2004 “BioEngineering: Challenges and Innovations”, comprises of contributions made by the authors participating in the Conference. Therefore, the opinions expressed and contents provided herein reflect those of the authors and does not necessarily constitute endorsement by editors, organizers and sponsors of the Conference. All the papers have been peer-reviewed for the contents and their suitability for presentation at the Conference. The final papers sent by authors as Camera Ready Paper might have been modified and altered a bit to suit presentation and print style. The editors, organizers and sponsors are not liable to any claim whatsoever, arising out of the publication of these proceedings.

Editors: F. K. Fuss, S. L. Chia, S. S. Venkatraman, S. M. Krishnan, and B. Schmidt
## Conference Papers

### Invited Speakers

<table>
<thead>
<tr>
<th></th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nanostructure Processing of Advanced Biomaterials (Ying J.)</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>Bioengineering, Technology Commercialization and Entrepreneurship (Kim Y.)</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>Esophageal Tissue Engineering (Ratner B.)</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>A Case Study of Integrated Biomedical Engineering: A Novel Method for Creating an Automated Sutureless Anastomosis (Sharkawy A.)</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>Advances in Cancer Imaging (Khoo J.)</td>
<td>21</td>
</tr>
<tr>
<td>6</td>
<td>Tissue Engineering Heart Constructs using Bone Marrow Stem Cell (Wong P.)</td>
<td>--</td>
</tr>
<tr>
<td>7</td>
<td>Computational Technologies to Accelerate Biotech Innovation (Meier U.)</td>
<td>--</td>
</tr>
<tr>
<td>8</td>
<td>A new Approach to Protein Structure Prediction (Schroder H.)</td>
<td>22</td>
</tr>
<tr>
<td>9</td>
<td>Development of Microfluidic-Based Point-of-Care Diagnostic Systems (Yager P.)</td>
<td>23</td>
</tr>
<tr>
<td>10</td>
<td>Innovation in The Medical Device Industry: Development of Cypher - the first Drug-Eluting Stent (Mishra A.)</td>
<td>--</td>
</tr>
<tr>
<td>11</td>
<td>Heart Tissue Engineering (Ratner B.)</td>
<td>--</td>
</tr>
<tr>
<td>12</td>
<td>Biological Resurfacing of Articular Cartilage - from Bench to Bedside (Lee E.H.)</td>
<td>24</td>
</tr>
<tr>
<td>13</td>
<td>Virtual Reality, Augmented Reality and its Medical Application (Bockholt U.)</td>
<td>25</td>
</tr>
<tr>
<td>14</td>
<td>Vital Signs in the Real World (Wilson S.)</td>
<td>26</td>
</tr>
<tr>
<td>15</td>
<td>Clinical Endoscopy System: Present and Future (Hidaka T.)</td>
<td>--</td>
</tr>
</tbody>
</table>

### Session: 01 Tissue Engineering  Day 1 1515- 1715 hrs

<table>
<thead>
<tr>
<th></th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Polyurethane Membranes for Chondroctye Transplantation and Cartilage Engineering (Chia S.L., Gorna K., Gogolewski K., Alini M.)</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>Theoretical and Experimental Determination of State of Two Dimensional Strain in a Bioreactor (Ong W.F., Wijaya S., Ritchie A.C.)</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>Culture of Rodent Hepatocytes on Microgrooved Surfaces: Application for a Flat-Plate Bioartificial Liver Device (Ting K.S., Wang N.D., Grant M.H., Henderson C.)</td>
<td>38</td>
</tr>
<tr>
<td>6</td>
<td>Simultaneous Probing of Morphology, Cytoskeleton, and Adhesion Dynamics of HepG2 Cells (Feng Z. Q., Liao K., Chan V.)</td>
<td>42</td>
</tr>
<tr>
<td>7</td>
<td>ECM-Dependent Proliferation of Adult Bone Marrow Mesenchymal Stem Cells (Tan G.M.Y., Shim W.S.N., Chua T., Liu T.C., Teh M., Sim E.K.W., Wong P.)</td>
<td>49</td>
</tr>
<tr>
<td>8</td>
<td>Parameters for Scaffold Design of Esophageal Tissue from a Structural Constitutive Model (Yang W., Fung T.C., Chian K.S., Chong C.K.)</td>
<td>51</td>
</tr>
</tbody>
</table>

### Session 02: Cancer Detection & Therapy  Day 1 1515-1700 hrs

<table>
<thead>
<tr>
<th></th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Automated Segmentation of Breast Masses in Mammograms (Zhang H., Foo S.W., Thng C.H.)</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>Diagnosis of Lung Cancer Using NIR Raman Spectroscopy (Huang Z., McWilliams A., Lam S., McLean D.I., Lui H., Zeng H.)</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>Extraction of head and neck tumors using deformation models from MR images (Zhou J., Chong V.)</td>
<td>61</td>
</tr>
</tbody>
</table>
Proceedings of IBEC 2004 13

4 Breast Cancer Diagnosis using Thermography and complementary learning fuzzy neural network (Tan T.Z., Quek C., Ng G.S., Ng E.Y.K.)
5 Magnetic Particles for Hyperthermia Treatment of Cancer (Ramanujan R.V., Lao L.L.)
6 Gene Selection for Cancer Classification from Microarray Data using PLS-RLSC (Shen L., Tan E. C.)
7 Micelle-like Nanoparticles of Linear and Branched PLA/PEG Block Copolymer as Anti-Cancer Drug Carrier (Pan J., Feng M., Chan W.A., Venkatraman S., Boey F.Y.C.)

**Session 03A: Medical Image Processing**  
**Day 1 1515-1745 hrs**

2 A Simulation System for Remote Interventional Radiology Procedures (Zhao L., Ma X., Aziz A., Zheng W., Nowinski W.L.)
3 An Improved Active Contour Method for Heart Wall Boundary Detection in Echocardiographic Image Sequence (Fang W., Chan K.L., Anantharaman V.)
4 Augmented Reality Assisted Sinus Surgery (Shi D. M., Ng W. S., Ling K. V., Shao W., Chen H.J., Kwoh C. K.)
5 Brain Atlas-assisted Segmentation of the Hippocampus from MR Neuroimages (Minh P.D., Prakash K.N.B., Nowinski W.L.)
6 Removing Blocking Artifacts in Compressed Medical Images (Singh S., Vinod K., Verma H.K.)
7 Simulated Annealing based Simplified Snakes for Weak Edged Medical Image Segmentation (You J., Zhou Z., Heng P.A., Xia D.)
8 Extraction of the Two Modified Talairach Cortical LandMarks (I and S) from MR T1-Weighted Images (Hu Q., Qian G., Nowinski W.L.)
9 Knowledge-based Interpolation of the Talairach-Tournoux Brain Atlas (Liu J., Nowinski W.L.)
10 Mapping Human Skin and Aural Temperature with ANNs and IR Imager (Ng E.Y.K., Chong C.)

**Session 03B: Medical Image Processing**  
**Day 3 1130-1215 hrs**

1 Automatic 3-D optic Disk Image Reconstruction from Low-Resolution Fundus Image for Glaucoma Analysis (Xu J., Chutatape O.)
2 Low-Complexity Unified-Adaptive Compression of Biomedical Images Using Integer Hartley Transform (Meher P.K., Srikanthan T., Agarwal H.K., Gupta J.)

**Session 04: Microfluidics/MEMS**  
**Day 1 1700-1800 hrs**

1 AFM Characterization and Selectivity of Immobilization of Antibodies in Bio-MEMS (Joshi M., Rao R., Mukherji S.)
3 Disposable Microfluidic Card and Fluorescence Detection System for Point-of-Care Diagnostic Applications (Irawan R., Tjin S.C., Fu C.Y., Ng B.K., Yuan X.-C., Zhang D.W.)
4 Microfluidic Protein Patterning using Embedded Cavities in Microchannels (Garcia E., Yager P.)
<table>
<thead>
<tr>
<th>Session 05: Biomaterials &amp; Drug Delivery</th>
<th>Day 2 1015-1230 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Smart Polymer Nanocarriers for Targeted Delivery (Yang Y.Y.)</td>
<td>149</td>
</tr>
<tr>
<td>2 Release of Lipoplexes from a Biodegradable Polymer Film: Preliminary Study (Chan W.A., Ramgopal Y.)</td>
<td>150</td>
</tr>
<tr>
<td>3 Cross linking of Bovine Serum Albumin with Genipin: Investigation of Mechanical Properties (Sathappan K., Chian K.S., Chua L.P.)</td>
<td>154</td>
</tr>
<tr>
<td>4 Porous Beta-TCP and Its Modification with PLGA Coating for Bone Regeneration (Miao X., Kurniawati T.)</td>
<td>158</td>
</tr>
<tr>
<td>5 In vitro Study on the Release Kinetics of Bovine Serum Albumin (BSA) from Injectable PLGA/BB Depot (Wang L.W., Venkatraman S.)</td>
<td>162</td>
</tr>
<tr>
<td>7 Porous Bioinert Alumina Prepared by Vacuum Infiltration (Liu J., Ng M.Y., Loh K.H., Hu Y., Miao X.)</td>
<td>170</td>
</tr>
<tr>
<td>8 Clinical Applications of Magnetic Nanomaterials (Ramanujan R.V.)</td>
<td>174</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session 06: Biomechanics</th>
<th>Day 2 1015-1230 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Biomechanics Highlights in Sports, Physiology and Medicine (Ghista D.N.)</td>
<td>178</td>
</tr>
<tr>
<td>2 Evolution and Biomechanics of the Cruciate Ligaments (Fuss F.K.)</td>
<td>181</td>
</tr>
<tr>
<td>3 The Double-Bundle ACL Graft Reconstruction: A superior technique to restore knee kinematics (Lie D.T.T., Amis A.)</td>
<td>185</td>
</tr>
<tr>
<td>4 Finger Pulley Injuries are Self-Propagating: A Mathematical Analysis of the A2-Pulley (Tan M.A., Fuss F.K., Niegl G.)</td>
<td>188</td>
</tr>
<tr>
<td>5 A Comparative Study of Different Gripping Methods for Tendons (Ng B.H., Chou S.M., Krishna V.)</td>
<td>192</td>
</tr>
<tr>
<td>6 Statistical Analysis of Human Metacarpal Morphology using CT Scan Data (Zhai L.Y., Chou S.M., Lim B.H., Chong A., Tsou I., Ng S.Y.)</td>
<td>196</td>
</tr>
<tr>
<td>7 Mechanics and Finite Element Analysis of the Auditory Ossicles (Ho K.L.I., Fuss F.K.)</td>
<td>199</td>
</tr>
<tr>
<td>8 Foot Characterization and Anatomical Landmarks Localization (Liu X., Kim W., Drerup B.)</td>
<td>202</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session 07A: Computational Bioengineering 1</th>
<th>Day 2 1015-1230 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 A Case Study on Pattern-based Systems for Computational Biology (Liu W., Schmidt B.)</td>
<td>205</td>
</tr>
<tr>
<td>2 A Grid Implementation of Database Searching (Chen C., Schmidt B.)</td>
<td>209</td>
</tr>
<tr>
<td>3 The Use of Computer Modelling to elucidate the Efficacy of Slit Arteriotomy for End-to-side Arterial Anastomosis in Microsurgery (Chua A.W.C., Gu H., Tan B.K., Chew W., Li J.Z., Song C.)</td>
<td>213</td>
</tr>
<tr>
<td>4 A Mixed SVM-Based Hierarchical Learning Approach for Abnormal ECG Beat Recognition (Li P., Chan K.L., Chan Y.W.)</td>
<td>217</td>
</tr>
<tr>
<td>5 Capturing Cellular Life In-Silico (Dhar P.K.)</td>
<td>221</td>
</tr>
<tr>
<td>6 Finite Element Modeling of the Human Brain with Detailed Anatomy for Surgery Simulation Based on a Brain Atlas (Gao C., Tay F. E. H., Nowinski W.L.)</td>
<td>224</td>
</tr>
<tr>
<td>7 Fuzzy c-Means and Neural Network Framework for Arrhythmia Classification (Chaudhari N.S., Siang L.C.)</td>
<td>228</td>
</tr>
<tr>
<td>8 VRML Modeling for Bio-Molecular Structures (Indhumathi C., Lu B.F., Cai Y.Y.)</td>
<td>232</td>
</tr>
<tr>
<td>9 BioSequence Comparison for Large Database on Reconfigurable Platforms (Wong M.T., Schmidt B.)</td>
<td>237</td>
</tr>
</tbody>
</table>
### Session 07B: Computational Bioengineering 2  
**Day 2 1330-1415 hrs**

1. Clustering Based Watershed Segmentation for Two-Dimensional Gel Electrophoresis Image (Diao X.N., Mao K.Z.)

### Session 08A: Cardiovascular Engineering 1  
**Day 2 1330-1530 hrs**

5. Contractility of the Left Ventricle in Terms of its Sacromere Power Generation (Zhong L., Ghista D.N., Ng E.Y.K.)
6. Detection of Cardiac Arrhythmia using Phase Space Analysis (Wong M.T., Srinivasan N., Chan Y.W.)
8. LV Twisting Analyzed for Pressure-Increase During Iso-Volumic Contraction (Liu L., Yeo S.Y., Ghista D.N., Chua L.P., Chai G.B., Tan Y.S., Tan R.S.)

### Session 08B: Cardiovascular Engineering 2  
**Day 2 1545-1645 hrs**


### Session 09A: Sports Engineering 1  
**Day 2 1330-1530 hrs**

1. Quantitative analysis of Singapore Golfers (Lim S.L., Xie X., Ong V., Teh K.C.)
2. Three-Dimensional Kinematics Study of Left Hand During Golf Swing (Teu K.K., Kim W., Fuss F.K., Tan J.)
3. Investigation of Weight Transfer during Golf Swing (Teu K.K., Kim W., Fuss F.K., Tan J.)
5. Comparison of Pinch- and Open Hand Grip during Sport Climbing (Yap Y.H., Fuss F.K., Niegl G., Tan M.A.)
6. Friction at the Climbing Handhold under Different Conditions and its Implications for Sport Climbing (Tan M.A., Fuss F.K., Niegl G.)
<table>
<thead>
<tr>
<th>Session 09B: Sports Engineering 2</th>
<th>Day 2 1545-1630 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Comparative Study on the techniques of Singapore and Thailand Table Tennis players during SEA Games 2001 (Lee K.T., Xie W., Teh K.C.)</td>
<td>333</td>
</tr>
<tr>
<td>3 Experimental Study on Different Types of Service Spins for Singapore National Table Tennis players (Lee K.T., Xie W.)</td>
<td>336</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session 10A: Ultrasonic Imaging 1</th>
<th>Day 2 1415-1530 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Medical Ultrasound Imaging: Current Status and Future Trends (Yoo Y.M., Kim Y.)</td>
<td>339</td>
</tr>
<tr>
<td>2 Reconfigurable and Programmable Architecture for Digital Receive Beamformer (Schneider F.K., Yoo Y.M., Agarwal A., Kim Y.)</td>
<td>345</td>
</tr>
<tr>
<td>3 Adaptive Speckle Reduction Based on Nakagami Distribution in Medical Ultrasound Imaging (Zhang L.C., Wong E.M.C.)</td>
<td>349</td>
</tr>
<tr>
<td>4 Specific Homomorphic Nonlinear Diffusion for Speckle Reduction in Ultrasound B-mode Images (Zhang F., Koh L.M.)</td>
<td>353</td>
</tr>
<tr>
<td>5 Design and Optimization of Broadband Ultrasonic Sparse Array Transducers for Medical Imaging Applications (Wang Q. B., Guo N. Q.)</td>
<td>357</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session 10B: Ultrasonic Imaging 2</th>
<th>Day 2 1545-1645 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Field of View-based Imaging for Efficient Beamforming in Low-end Portable Ultrasound Systems (Agarwal A., Schneider F.K., Yoo Y.M., Kim Y.)</td>
<td>361</td>
</tr>
<tr>
<td>2 Low Sampling Frequency Digital Beamformer for Ultrasonic Imaging without Interpolation (Gao C.Q., Zhang L.C., Wong E.M.C.)</td>
<td>365</td>
</tr>
<tr>
<td>3 Comparative Evaluation of Wavelet Filters for Speckle Reduction in Ultrasound Medical Images (Thakur A., Anand R.S.)</td>
<td>369</td>
</tr>
<tr>
<td>4 Window Function Optimization by Genetic Algorithm for Ultrasound Imaging System (Cao J., Koh L.M.)</td>
<td>373</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session 11: Respiratory Biomechanics</th>
<th>Day 2 1645-1730 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Determination of O₂ and CO₂ Metabolic Rates and Lung O₂ and CO₂ Diffusion Coefficients (Loh K.M., Ghista D.N.)</td>
<td>377</td>
</tr>
<tr>
<td>2 Oxygen Saturation Profiles in a Hollow Fibre Oxygenator (Ritchie A.C., Thimm G.)</td>
<td>381</td>
</tr>
<tr>
<td>3 Graphical Technique for Assessing Pulmonary Disease (Loo C.M., Ang K.C., Ong J.H., Ghista D.N., Lim G.H.)</td>
<td>385</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session 12A: Orthopaedic Engineering 1</th>
<th>Day 2 1630-1745 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Design Optimisation in BioMedical Engineering (Koh E.C.Y., Fuss F.K.)</td>
<td>389</td>
</tr>
<tr>
<td>2 Design Classification and Mechanics of Artificial Discs (Fuss F.K.)</td>
<td>392</td>
</tr>
<tr>
<td>3 Extraforaminal Lumbar Interbody Fusion: Simulation of the Fusion Process Based on Different Implant Materials (Fuss F.K., Sabitzer R.J.)</td>
<td>397</td>
</tr>
<tr>
<td>4 FE Investigation on Spinal Interbody Fusion (Lee K.K., Teo E.C., Fuss F.K., Sabitzer R.J.)</td>
<td>401</td>
</tr>
<tr>
<td>5 Optimization of Cervical Ring Cage by Taguchi Philosophy (Yang K., Teo E.C., Fuss F.K.)</td>
<td>405</td>
</tr>
</tbody>
</table>
**Session 12B: Orthopaedic Engineering 2**  
Day 3 1130-1215 hrs

1. Integration of CAD to FEA for Prosthetic Socket Design (Goh J.C.H., Lee P.V.S., Toh 408  
   S.L., Ooi C.K.)
2. Analyses of Fractured Bone (Femur) with Plate and Intra-Medullary Rod Fixations (Chen 412  
   Q., Fan S.C., Ghista D. N.)
   Sivashanker S., Khong K.S., Ghista D.N.)

**Session 13A: Biosignal Processing 1**  
Day 2 1645-1745 hrs

1. A Novel Approach to Automatic Left Ventricular Contour Tracking (Cheng J., Foo S.W.) 420
2. A Novel Wavelet Based ECG Compression with X-tree Coding (Swain S., Chutatape O., 424  
   Dandapat S.)
3. Left Ventricular Surface Kinematics During Isovolumic Contraction (Yeo S.Y., Tan R.S., 428  
   Liu L., Chai G.B., Ghista D.N.)
4. Evaluation of Slice Sensitivity Profiles for TPRF Algorithm (Yan M., Zhang C.) 432

**Session 13B: Biosignal Processing 2**  
Day 3 1045-1130 hrs

1. Uni-channel PCA for noise reduction from ECG signals (Palaninippan R., Tan E.K.) 436
2. Wavelet-Based Denoising and Analysis of Phonocardiogram (Wang P., Anantharaman 440  
   V.)
3. Dynamical Analysis of Heart Rate Variability Signals (Rajendra A.U., Kannathal N., Lim 444  
   C.M.)

**Session 14: Biosensors/ Diagnostic Tools**  
Day 3 1045-1145 hrs

1. Multi-Parameter Clinical Diagnosis Using Neural Networks (Tan E.K.) 447
2. An Otoacoutic Emissions Detecting System using USB AD/DA Board (Qian X., Ye D.) 450
3. Oral Glucose Tolerance Test Modeling For Diabetes Characterization (Loh K.M., Ghista 453  
   D.N.)
4. Feasibility of biosensing based on two-dimensional square photonic lattice (Zhang D.W., 457  
   Irawan R., Tjin S.C., Yuan X.C.)

**Session 15: Distributed Diagnosis & Home Healthcare**  
Day 3 1045-1130 hrs

1. Distributed Diagnosis and Home Healthcare (D2H2) and Patient-Centered Electronic 461  
   Medical Record (Kim E.H., Kim J.J., Matsen F.A., Kim Y.)
2. Application of Artificial Neural Network Technique in Healthcare Expenditure Analysis 469  
   (Chia E., Khong P.W., Ghista D.N.)
3. Advanced System Architecture for Telecardiology (Goh K.W., Kugean C., Tan E.K., 473  
   Prabaharan K.)
Abstract—The primary function of the lung is to (i) oxygenate the blood and thereby provide oxygen to the cells for metabolism purposes, and (ii) to remove the collected $CO_2$ from the pulmonary blood. Herein, we provide a noninvasive methodology to assess physiological metabolic rates as well as blood-oxygenation capacity of the lung. For this purpose, we analyze the compositions of the inspired and expired air per breath, and therefrom compute the metabolic $O_2$ consumption and $CO_2$ production rates.

Next, we derive expressions for diffusion coefficients $D_{O_2}$ and $D_{CO_2}$, in terms of the evaluated cardiac-output $CO$, $O_2$ and $CO_2$ concentrations in arterial and venous blood as well as alveolar and blood $O_2$ and $CO_2$ partial-pressure. The coefficients $D_{O_2}$ and $D_{CO_2}$ represent the lung capability to oxygenate the blood. We can then also determine the cardiac output, from knowing the concentrations of oxygen and carbon dioxide in the arterial and venous bloods.

The derived information of $D_{O_2}$ and $D_{CO_2}$ as well as of $O_2$ and $CO_2$ metabolic rates can be of considerable use (including for SARS assessment). The paper provides a case study for the determination of $Q$, $D_{O_2}$ and $D_{CO_2}$.

Keywords—gas exchange, $O_2$ metabolic-rates, $CO_2$ metabolic-rates, diffusion coefficients $D_{O_2}$, diffusion coefficients $D_{CO_2}$, blood flow rate

I. SCOPE

The lung functional performance is characterized by (i) its ventilatory capacity, to bring air (and hence $O_2$) into the alveoli, and (ii) its capacity to transfer $O_2$ and $CO_2$ into and from the pulmonary capillary bed. Hence, the $O_2$ and $CO_2$ diffusion coefficients $D_{O_2}$ and $D_{CO_2}$ as well as the $O_2$ consumption-rate and the $CO_2$ production rate represent the lung performance indices. In this paper, we are demonstrating their evaluations.

II LUNG GAS-EXCHANGED MODEL

Figure 1 schematically illustrates the gas-exchange between the lung alveolus and the pulmonary capillary-vasculature. Based on our earlier work [2] the gas exchange between the alveolar air and pulmonary capillary blood is represented by the following $O_2$ and $CO_2$ conservation equations and Figure 2.

\[ Q^{VE} C_{O_2}^{VE} = Q^{AE} C_{O_2}^{AE} + V O_2 \] (from the alveolar air to capillary blood)
\[ = Q^{AE} C_{O_2}^{AE} + (\Delta P_{O_2}^{al}) D_{O_2} \] (1)
\[ Q^{VE} C_{CO_2}^{VE} = Q^{AE} C_{CO_2}^{AE} - V CO_2 \]
\[ = Q^{AE} C_{CO_2}^{AE} - (\Delta P_{CO_2}^{al}) D_{CO_2} \] (2)

wherein

(i) $Q^{AB}$ and $Q^{VB}$ are arterial and venous blood flow-rates;
(ii) $P_{O_2}^{al}$ and $P_{O_2}^{cap}$ are the alveolar and capillary $O_2$ partial pressures
(iii) $P_{CO_2}^{al}$ and $P_{CO_2}^{cap}$ are the alveolar and capillary $CO_2$ partial pressures
(iv) $D_{O_2}$ and $D_{CO_2}$ are the $O_2$ and $CO_2$ diffusion coefficients
(v) $\Delta P_{O_2}^{al} = \text{average of } (P_{O_2}^{al} - P_{O_2}^{cap}) \text{ over the capillary length}$
(vi) $P_{O_2}^{cap} = P_{O_2}^{PRB}$ ($O_2$ concentration of the pre-oxygenated blood) = $P_{O_2}^{AE}$
(vii) $P_{CO_2}^{cap} = P_{CO_2}^{PRB}$ ($CO_2$ concentration of the pre-oxygenated blood) = $P_{CO_2}^{VE}$
(viii) \( V_{O_2}^o \) is the \( O_2 \) transfer rate from alveolar air to capillary blood (= \( O_2 \) consumption rate), \( V_{CO_2}^o \) is the \( CO_2 \) transfer-rate from capillary blood to alveolar air.

Now we can equate the arterial and venous blood flow rates, as
\[
Q^{aE} = Q^{aB} + Q^{vB} = Q^{vE} = Q = (SV)/(EP) = CO / 60
\]

SV, EP and CO being the stroke-volume, ejection-period and cardiac-output respectively.

### III. CLINICAL DATA

The monitored data consists of inspired and expired air gas compositions (Table 1) and \( O_2 \) and \( CO_2 \) concentrations of arterial blood and venous blood (Table 2).

#### Table 1: Air Composition Analysis. Inspired and expired air composition and partial pressures are monitored. Assumed Breathing Rate (BR) = 12 breaths/min. Assumed \( P_{H_2O}^o \) at 37°C = 47 mmHg.

<table>
<thead>
<tr>
<th>Respiratory gases</th>
<th>Atmospheric Air</th>
<th>Expired Air</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmHg</td>
<td>ml/%</td>
</tr>
<tr>
<td>N(_2)</td>
<td>597</td>
<td>78.55%</td>
</tr>
<tr>
<td>O(_2)</td>
<td>159</td>
<td>20.84%</td>
</tr>
<tr>
<td>CO(_2)</td>
<td>0.3</td>
<td>0.04%</td>
</tr>
<tr>
<td>H(_2)O</td>
<td>3.7</td>
<td>0.49%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>760</td>
<td>100%</td>
</tr>
</tbody>
</table>

#### Table 2: Blood Gas Analysis. The monitored blood \( O_2 \) and \( CO_2 \) concentration .

\[
\begin{align*}
C_{O_2} \text{ of venous blood (} C_{O_2}^{vB} \text{)} &= 0.13 \\
C_{O_2} \text{ of arterial blood (} C_{O_2}^{aB} \text{)} &= 0.18 \\
C_{CO_2} \text{ of venous blood (} C_{CO_2}^{vB} \text{)} &= 0.5 \\
C_{CO_2} \text{ of arterial blood (} C_{CO_2}^{aB} \text{)} &= 0.46
\end{align*}
\]

### IV. EXPRESSIONS FOR \( D_{O_2} \) AND \( D_{CO_2} \)

If we want to evaluate the diffusion coefficients \( D_{O_2} \) and \( D_{CO_2} \), we need to also express \( P_{O_2}^{al} \), \( P_{O_2}^{cap} \) and \( P_{CO_2}^{al} \), \( P_{CO_2}^{cap} \) in terms of monitorable quantities [1 & 2].

(i) Alveolar \( P_{O_2}^{al} \) can be expressed in terms of \( V \) (the ventilation rate) and \( V_{O_2} \) (the \( O_2 \) consumption rate).
wherein the normalised ventilation rate, \( \nu^* = \frac{\nu}{\nu_{m}} = \frac{\nu}{60} \) litres/min, is the consumption rate (in liters/min).

(ii) Alveolar \( P_{al}^{\text{CO}_2} \) can be expressed in terms of \( \nu, \nu_{al} \) and \( \nu_{o}. \)

\[
P_{al}^{\text{CO}_2} = 114.68e^{-2.46\left[\frac{\nu}{\nu_{al}}\right]} \tag{4}
\]

wherein \( \nu_{al} \) is the \( \text{CO}_2 \) production rate (in liters/min).

(iii) Blood \( P_{o}^{\text{al}} \) can be obtained in terms of blood \( \text{CO}_2 \), from the \( \text{O}_2 \) disassociation curve.

\[
P_{o}^{\text{al}} = 29.72\ln\left[\frac{0.2}{0.2 - C^B_{o}}\right] \tag{5}
\]

(iv) Blood \( P_{CO_2}^{B} \) can be obtained in terms of \( C^B_{CO_2} \), from the \( \text{CO}_2 \) disassociation curve.

\[
P_{CO_2}^{B} = 29.72\ln\left[\frac{0.8}{0.8 - C^B_{CO_2}}\right] \tag{6}
\]

Now, \( P_{al}^{\text{CO}_2} - P_{o}^{\text{al}} = P_{al}^{\text{CO}_2} - P_{o}^{\text{al}} \) both \( \Delta P_{O_2} \) and \( \Delta P_{CO_2} \) vary along the capillary bed. Based on [3], we have:

\[
\Delta P_{O_2}^{av} = 0.185\Delta P_{O_2}^{max} \tag{7}
\]

\[
\Delta P_{CO_2}^{av} = 0.1 \Delta P_{CO_2}^{max} \tag{8}
\]

From the above expressions, we obtain:

\[
D_{O_2}^{a} = \frac{\nu_{O_2}}{\Delta P_{O_2}^{av}} = \frac{\nu_{O_2}}{0.185(p_{al}^{O_2} - p_{o}^{O_2})} \tag{9}
\]

\[
D_{CO_2} = \frac{\nu_{CO_2}}{\Delta P_{CO_2}^{av}} = \frac{\nu_{CO_2}}{0.1(p_{al}^{CO_2} - p_{o}^{CO_2})} \tag{10}
\]

V. DETERMINATION OF \( \text{O}_2 \) AND \( \text{CO}_2 \) METABOLIC RATES AND CARDIAC OUTPUT

From monitored data of inspired-exhaled gas compositions, in Table 1:

\[
\nu_{o} \text{ consumption rate, } \nu_{o} = BR(\text{Inspired } \text{O}_2 - \text{Expired } \text{O}_2) \text{ml/min} = 12(104.2 - 83.37) = 250 \text{ ml/min} \tag{11}
\]

\[
\nu_{CO_2} \text{ consumption rate, } \nu_{CO_2} = BR(\text{Expired } \text{CO}_2 - \text{Inspired } \text{CO}_2) \text{ ml/min} = 12(16.87 - 02) = 200 \text{ ml/min} \tag{12}
\]

From monitored \( \text{O}_2 \) and \( \text{CO}_2 \) concentrations of arterial and venous blood, in Table 2:

\[
\nu_{o} = Q(\text{O}_2 \text{ of arterial blood} - \text{CO}_2 \text{ of venous blood})
\]

where \( Q \) = blood flow rate = cardiac output

\[
\nu_{o} = \frac{Q}{(0.18 - 0.13)} = \frac{250}{0.05} = 5000 \text{ ml/ min}
\]

VI. EVALUATING OF THE LUNG DIFFUSION COEFFICIENTS \( D_{O_2} \) AND \( D_{CO_2} \)

From equation (3) and Table 2 \( C_{O_2}^{AB} = 0.18 \), we get for (arterial blood @ venous end of the pulmonary capillary or \( p_{o}^{AB} \))

\[
p_{o}^{AB} = 29.72\ln\left[\frac{0.2}{0.2 - C_{O_2}^{AB}}\right] = 29.72\ln\left[\frac{0.2}{0.2 - 0.18}\right] = 68.43 \text{ mmHg} \tag{13}
\]

From equation (5) and Table 2 \( C_{CO_2}^{VB} = 0.13 \), we get for

\[
p_{o}^{VB} \text{ (venous blood @ arterial end of the pulmonary capillary or } p_{o}^{VB})
\]

\[
D_{O_2}^{a} = \frac{\nu_{O_2}}{\Delta P_{O_2}^{av}} = \frac{\nu_{O_2}}{0.185(p_{al}^{O_2} - p_{o}^{O_2})}
\]
\[ p_{O_2} = 29.72 \ln \left( \frac{0.2}{0.2 - C_{O_2}^{V_B}} \right) \]
\[ = 29.72 \ln \left( \frac{0.2}{0.2 - 0.13} \right) \]
\[ = 31.20 \text{ mmHg} \] (14)

Also, from equation (3) and Table 1 \( V^* =0.1 \), we get:

\[ p_{O_2}^{al} = 140 \left[ 1 - e^{-4.18 \left( \frac{V^*/V_{O_2}}{0.1/0.25} \right)} \right] \]
\[ = 140 \left[ 1 - e^{-4.18 \left( \frac{0.1}{0.25} \right)} \right] = 113 \text{ mmHg} \] (15)

Hence, from equations (14 & 15), we get:

\[ \Delta p_{O_2} = 0.185 \times (113 - 31.2) = 14.95 \text{ mmHg} \] (16)

Finally, from equations (11) and (16), we get:

\[ D_2 = \frac{V_{O_2}^{\circ}}{\Delta p_{O_2}^{av}} = \frac{250 \text{ ml/min}}{14.95 \text{ mmHg}} \]
\[ = 16.72 \text{ ml/min}^{-1} \text{ mmHg}^{-1} \] (17)

From equation (6) and Table 2 \( C_{CO_2}^{V_B} =0.5 \), we get:

\[ p_{CO_2} = p_{CO_2}^{AE} = 29.72 \ln \left( \frac{0.8}{0.8 - C_{CO_2}^{V_B}} \right) \]
\[ = 29.72 \ln \left( \frac{0.8}{0.8 - 0.5} \right) = 29.15 \text{ mmHg} \] (18)

Then from equation (4), Table 1 \( V = 0.1 \), and equation (12) we get:

\[ p_{CO_2}^{al} = 114.68e^{-2.46 \left( V^*/V_{CO_2} \right)} \]
\[ = 114.68e^{-2.46 \left( 0.1/0.2 \right)} = 33.52 \text{ mmHg} \] (19)

Hence, from equations (8, 18 & 19), we get:

\[ \Delta p_{CO_2} = 0.1 \times (33.52 - 29.15) = 0.44 \text{ mmHg} \] (20)

Finally, from equations (10 & 20), we get:

\[ D_{CO_2} = \frac{V_{CO_2}^{\circ}}{\Delta p_{CO_2}^{av}} = \frac{200 \text{ ml/min}}{0.44 \text{ mmHg}} \]
\[ = 454.55 \text{ ml/min}^{-1} \text{ mmHg}^{-1} \] (21)

VII. CONCLUSION

We have demonstrated a noninvasive clinical procedure:

- for obtaining (i) \( O_2 \) consumption rate and \( CO_2 \) production rate, (ii) cardiac outflow-rate or output, \( Q \), (iii) and lung diffusion capacities for \( O_2 \) and \( CO_2 \),
- from inhaled and exhaled air composition analysis, and blood-gas analysis.

This work could have application to SARS testing and evaluation.

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[1] Loh Kah Meng, Dhanjoo N. Ghista and Heiko Rudolph, Determination of \( O_2 \) and \( CO_2 \) Metabolic Rates and Lung Diffusion Coefficients, based on the Data of Inspired and Expired Air Compositions, Annals, Academy of Medicine.


Abstract—This paper provides a systems-engineering analysis of the glucose-insulin responses to an ingested bolus of glucose for OGTT (Oral Glucose Tolerance Test). The clinical data of patients is fitted by either under-damped or over-damped or critically-damped solutions of the model’s governing equations for glucose and insulin responses to glucose bolus ingestion. Based on the best fit of the three types of solutions, we designate the patients (and their response) to be normal (and under-damped), diabetic (and over-damped) and either border-line or at-risk of becoming diabetic (and critically-damped). In this way, the model simulation of the clinical data enables more reliable diagnosis relative to the clinical assessment.

Keywords—diabetic, systems-engineering model, under-damp, over-damp, critically-damped, R-square, fitting, clinical diagnosis

I. INTRODUCTION

Oral Glucose Tolerance Testing Protocol

The test subjects need to fast for 12 hours before the test and during the 2-hour test. A blood sample of the subject is taken before the beginning of the test. Then after the subject drinks a 75 g of glucose solution dissolved in 250–300 mL of water, the subject’s blood glucose and insulin concentrations are measured at specified intervals 30 minutes, 60 minutes, 90 minutes and 120 minutes [1, 2, 4].

Qualitative interpretation of the results, for preliminary categorization of the patients [1, 2, 4]:

(a) Blood glucose normal values:
   - fasting: 70 to 115 mg/dl
   - 30 min.: less than 200 mg/dl
   - 1 hour : less than 200 mg/dl
   - 2 hour : less than 140 mg/dl

(b) Normal insulin level (reference range): 1-30 mU/L

When a person has a fasting glucose equal to or greater than 110 mg/dl and less than 126 mg/dl, it is considered as impaired fasting glucose. This is considered a risk factor for future diabetes and will likely trigger another test in the future, but, by itself, does not make the diagnosis of diabetes.

A person is said to have impaired glucose tolerance when the 2-hour glucose results from the oral glucose tolerance test are greater than or equal to 140 but less than 200 mg/dl. This is also considered a risk factor for future diabetes. A person has diabetes when oral glucose tolerance tests show that the blood glucose level at 2 hours is equal to or more than 200 mg/dl. This must be confirmed by a second test (any of the three) on another day.

II. SYSTEM SOLUTIONS FOR DIABETIC, NON-DIABETIC AND AT-RISK PATIENTS

The governing differential equation for glucose response to glucose bolus intake is:

\[ y' = q(t) - \gamma x - \delta y \]  (1)

The governing differential equation for insulin response to glucose bolus intake is:

\[ x' = p(t) - \alpha x + \beta y \]  (2)

\[ y(t) : \text{Glucose response of the patient to the oral bolus of glucose.} \]

\[ x(t) : \text{Insulin response of the patient due to } y(t). \]

Solution For Underdamped Case (non-diabetic):

\[ y(t) = \frac{G}{\omega} e^{-\omega t} \sin \omega t \]  (3)

\[ x(t) = \frac{-\sin(\omega t) e^{-\omega t} - \sin(\omega t) e^{-\omega t} + e^{(-\omega t)} w + \cos(\omega t) e^{(-\omega t)} w}{\left( \alpha^2 + 2A \alpha + A^2 + w^2 \right)} \]  (4)
Solution For Overdamped Case (diabetic):

\[ y(t) = \frac{G}{\omega} e^{-\alpha t} \sinh(\omega t) \]  \hspace{1cm} (5)

\[
x(t) = \frac{1}{2} \left( \cosh(wt + At - \alpha t)A + \sinh(wt + At - \alpha t)A \right.
\]
\[
- \cosh(wt + At - \alpha t)A - \sinh(wt + At - \alpha t)A
\]
\[
+ \sinh(wt + At - \alpha t)w - \cosh(wt + At - \alpha t)w
\]
\[
- \sinh(wt - At - \alpha t)\alpha + \sinh(wt + At - \alpha t)\alpha
\]
\[
- \cosh(wt + At - \alpha t)\alpha - \cosh(wt - At - \alpha t)w
\]
\[
+ \cosh(wt + At - \alpha t)\alpha + 2w
\]
\[
+ \sinh(wt + At - \alpha t)w e^{-(\alpha t)} \beta \frac{G}{w}
\]
\[
\left( -w^2 + A^2 - 2A\alpha + \alpha^2 \right) \]  \hspace{1cm} (6)

Solution For Critically Damped Case (at the dangerous boundary):

\[ y(t) = Ge^{-\alpha t} \]  \hspace{1cm} (7)

\[
x(t) = -\beta G (t A e^{(-\alpha t)} - t A e^{(-\alpha t)} + e^{(-\alpha t)} - e^{(-\alpha t)}) \]  \hspace{1cm} (8)

III. CLINICAL APPLICATION AND DISCUSSION

Under-damped Category and Normal Designated Patient

These \( y(t) \) and \( x(t) \) response solutions are fitted to the monitored glucose and insulin data, and the fitness coefficients are determined. Based on the high degree of fit, patient S14 fits best the under-damped category, and hence is designated to be normal. His Glucose and Insulin responses, shown in Figure 1, illustrates the fast recovery of blood glucose and insulin concentrations.

The below table displays the values of the model parameters and the R-Square coefficients of fitness and the model solution to the clinical data.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
<th>Fitting</th>
</tr>
</thead>
<tbody>
<tr>
<td>( A )</td>
<td>2.007</td>
<td>SES</td>
</tr>
<tr>
<td>( G )</td>
<td>2.795</td>
<td>SES</td>
</tr>
<tr>
<td>( \omega )</td>
<td>1.882</td>
<td>R-Square</td>
</tr>
<tr>
<td>( \alpha  )</td>
<td>2.8245</td>
<td>SES</td>
</tr>
<tr>
<td>( \beta   )</td>
<td>0.1059</td>
<td>SES</td>
</tr>
<tr>
<td>( \gamma  )</td>
<td>1.1895</td>
<td>R-Square</td>
</tr>
<tr>
<td>( \delta  )</td>
<td>2.6355</td>
<td>R-Square</td>
</tr>
</tbody>
</table>

Figure 1: Patient S14 is designated to be under-damped and normal. However, this patient is quite hyper-insulinemic; in other words, this patient has elicited considerable insulin response in order to maintain an under-damped glucose response.

Over-damped Category of Patients Designated as Diabetic

For patients D05, our over-damped model solution fits the clinical data best of the 3 solution categories. Hence, this patient is designated to be diabetic. His Glucose and Insulin responses are shown in Figure 2, and the model parameters are given in the Table.
Figure 2: This patient D05 has the higher R-Square value when fitted by the over-damped solution, and is hence classified as diabetic.

Critically-damped Category of Patients

There are some patients clinically diagnosed to be normal for which the critically-damped solution gives a better fit of the data (and a higher value of R-Square) than the under-damped solution. One such patient is S04, whose under-damped and critically-damped model response-curves are shown in Figures 3 and 4. Similarly, patients S06 and S19 are not normal as clinically diagnosed, but at the risk of becoming diabetic. Their response curves are illustrated in Figures 5 and 6.

Figure 4: This S04 patient’s data is better fitted (i.e. at higher R-Square value) by the critically-damped solution than by the under-damped solution. Because of the critically-damped model solution giving us a better fit (iterations of a higher value of R-Square), we differ from the clinical diagnosis and alert this patient that he is at risk at becoming diabetic.
Figure 5: This S06 patient’s data is better fitted (i.e. at higher R-Square value) by the critically-damped solution than by the under-damped solution. Hence, we will differ from the clinical diagnosis and designate this patient to be at risk of becoming diabetic.

Figure 6: This S19 patient’s response curves are best fitted (with a higher value of R-Square) by the critically-damped solution than by the under-damped solution.

V. CONCLUSION

We have shown that we can obtain more accurate assessment of diabetic patients by means of our under-damped, over-damped and critically-damped simulation model solutions. Some patients (diagnosed to be normal) were designated by us to be in the borderline category. However, some patients who were clinically declared to be diabetic turned out to be only border-line. As we continue this work, we will develop a clinically-implementable software for model parameter identification and designation of the subjects as normal or at-risk of becoming diabetic or border-line diabetic or distinctly diabetic.

REFERENCES


Biofeedback as validated by EEG/QEEG

ERAS 2002
22 Nov 2002

By Loh Kah Meng and Prof Ghista
Introduction

- Biofeedback entails providing a person with information about his own on-going physiological processes through parameters such as EEG or QEEG, ECG, EMG, etc.
Types of Biofeedback

- There are two types of biofeedback systems: Volitional Feedback Systems (VBFS) and Non-Volitional Feedback Systems (NVFS).
Types of Biofeedback

- The VBFS require conscious effort to attain a desired physiological state. They hence cannot be used in the case of subjects who have mental dysfunction or mentally depressed.
- The NVFS do not require subjects to be conscious.
Objectives

- The NVFS presented in this paper is designed for rehabilitation purpose. We will also present to you some results that we have gathered in our experiments with subjects with eyes opened with aids and eyes closed with and without aids.
International 10-20-2. EEGs are taken at 19 different channels to give us spatial & temporal information.
The Lexicor system that our experiments were conducted with.
Screen snap shot of the EEG display
Screen shot of the QEEG

The image shows a screen shot of a QEEG (Quantitative Electroencephalography) analysis. The software interface displays various parameters and data points, with regions highlighted in different colors indicating different frequency bands. The frequency bands are labeled as (4.0 - 8.0), (8.0 - 12.0), and (12.0 - 16.0). The screen also shows the file path 'C:\\V151\data\example' and other technical details such as epoch, gain, sample rate, and statistics.
Experimental Results

Objective: Similar to experiment 1. This time for open-eyes, we have the psychological board. Each setup up 10 minutes.

Date of experiment: 7 Sep 2002
Location of experiment: NIE RM 07-02-10
Name of subjects:
- V [under stress, attempted suicide victim]
- W [normal subject]

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<th>(2) W</th>
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(1) Eyes Open. Subjects concentrate on the psychological board
(2) Eyes Closed. Unaided
(3) Eyes Closed. Worn Goggles with LEDs flashing at a constant frequency.
Alpha waves in units of μV² (mean power).
Experimental results of subjects. Note that alpha energies are greatest when eyes closed with the goggles active. The goggles are designed to flash at 10 Hz. It has been found that the Red super-bright LEDs are most efficient.

![Graph showing results of V and W](image-url)
Application of the Concept
Conclusions

- The above results have significant influence to the system we are designing for rehab purpose.
- The details will be elaborated later in our next coming presentation.
Thank You
Introduction

- The use of Virtual Reality (VR) to enhance rehabilitation is a relatively new concept.
- The novel aspect of using VR as an evoked-psychological therapy for rehabilitation will cause a revolution in rehab technology.
Objectives

- In this paper we will discuss some of these concepts. There may be some ideas that could be obscure to some of the audience, so we elicit an open mind.
Firstly we would like to share with you the concept about stressed and relaxed mind. Next we would like to share with you how this concept can be incorporated into a rehabilitation system for spinal-cord injured patients.
Deformed Mind’s Transcendence into a high-conscious environment.
Evoked-Psychological Response to Initiate Rehabilitation Process

- When a person is under stress her/his mind is compressed and deformed as compared to a relaxed mind under a high consciousness level.
- This is especially so when the patients are undergoing long monotonous physical therapies without experiencing some definitive progress.
Then this self-induced frustration acts as a positive feedback, further bringing down the consciousness level.
Application of VR

- Our objective is to use VR to help conjure a curative and healthy environment, which can also bring her/him into a relaxed and higher consciousness level, which can be verified by examining the EEG alpha-wave energy-content. The amount of improvement is proportional to the increase in alpha wave density.
For Spinal Cord Injury (SCI) patients, the VR system will be designed to psychologically made the patient feel that the resected spinal cord reconnected, and thereby the associated physiologically disordered (such as bladder control, temperature regulation, etc) are also remedied.

For sitting and lying-down, we can design a mattress, of skin-breathing synthetic material.
Spinal-Cord Injury Rehabilitation
Spinal-Cord Injury Rehabilitation

- The mattress will be designed as a controllable pneumatic bed with turbulence generators.
- The waves will act as physiotherapists’ fingers, giving massage. The warm fluid with the massage can facilitate blood flow to the patient and reduce sustained-pressure bed-ridden related skin diseases.
Spinal-Cord Injury Rehabilitation System Block Diagram
SSREFS

- Additionally, a Sympathetic Signal-Reinforcing EEG Feedback System (SSREFS) will be designed to extract alpha signals and filter beta signals from the EEG. The extracted alpha signals can be fed into patient’s spinal cord, to stimulate cerebral-neuronal growth.
Conclusions

For paraplegic patients, the VR would be employed to make the patient feel that she/he is ambulatory, and that autonomic system is reconnected and working, so that the patient can void independently and feel the outside temperature so the VR will help the patient develop a strong will power to be cured and adopt independent living mood.
Thank You
Appendix I

Published Papers and Book Chapters
7th Annual NTU-SGH Symposium 2005
Moving Technology Towards Better Patient Care

11–12 August 2005
Singapore National Eye Centre Auditorium

Programme & Abstracts

Organised by

Singapore General Hospital
Nanyang Technological University
## Daily Programme

**11 August 2005**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>0800–0900</td>
<td>Registration</td>
</tr>
<tr>
<td>0900–0930</td>
<td><strong>OPENING CEREMONY</strong></td>
</tr>
<tr>
<td></td>
<td>Welcome Address</td>
</tr>
<tr>
<td></td>
<td>Organising Chairman, Dr Denny Lie</td>
</tr>
<tr>
<td></td>
<td><strong>Opening Address</strong></td>
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<tr>
<td></td>
<td>Guest-of-honour</td>
</tr>
<tr>
<td></td>
<td>Prof Su Guaning, President, NTU</td>
</tr>
<tr>
<td>0930–1030</td>
<td><strong>PLENARY LECTURE 1</strong></td>
</tr>
<tr>
<td></td>
<td>Systems Integration in Genomics and Biomedicine</td>
</tr>
<tr>
<td></td>
<td><em>Dr Edison Liu</em></td>
</tr>
<tr>
<td></td>
<td>Chair: Prof Soo Khee Chee</td>
</tr>
<tr>
<td>1030–1100</td>
<td>Tea Break and Exhibition</td>
</tr>
<tr>
<td>1100–1200</td>
<td><strong>PLENARY LECTURE 2</strong></td>
</tr>
<tr>
<td></td>
<td>Research in Bioengineering and Nanotechnology</td>
</tr>
<tr>
<td></td>
<td><em>Prof Jackie Ying</em></td>
</tr>
<tr>
<td></td>
<td>Chair: Prof Michael Khor</td>
</tr>
<tr>
<td>1200–1315</td>
<td><strong>SHOWCASE OF NTU-SGH JOINT PROJECTS</strong></td>
</tr>
<tr>
<td></td>
<td>Piezoelectric Pumps for Biomedical Applications</td>
</tr>
<tr>
<td></td>
<td><em>Asst/Prof Ma Jan</em></td>
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<tr>
<td></td>
<td>Adult Bone Marrow Mesenchymal Stem Cells for Cardiac Tissue Engineering</td>
</tr>
<tr>
<td></td>
<td><em>Dr Philip Wong</em></td>
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<tr>
<td></td>
<td>Rapid Portable System for Screening Tuberculosis</td>
</tr>
<tr>
<td></td>
<td><em>A/Prof Lim Chu Sing</em></td>
</tr>
<tr>
<td></td>
<td>A Bilayered Scaffold for the Development of Composite Skin Construct</td>
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<tr>
<td></td>
<td><em>Mr Alvin Chua &amp; Mr Leong Meng Fatt</em></td>
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<tr>
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<td>Single Living Cell Detection and Sorting Using Biophotonic Integrated Chip</td>
</tr>
<tr>
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<td><em>A/Prof Liu Ai Qun</em></td>
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<tr>
<td></td>
<td>Chair: A/Prof Tay Boon Keng</td>
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<tr>
<td>1315–1400</td>
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<td><strong>MODERATED POSTER SESSION</strong></td>
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<td>Asst/Prof Ang Wei Tech/ Dr Png Hong Hock</td>
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1400–1500  
**PLENARY LECTURE 3**
Distributed Diagnosis and Home Healthcare – Bringing Affordable Healthcare to the Home  
*A/Prof Tjin Swee Chuan*  
Chair: *A/Prof Chan Yew Weng*

1500–1610  
**FREE PAPERS 1 (BIOMECHANICS)**
- Intrameniscal Forces Determined by Fibre Bragg Grafting Sensors  
  *Ms Goh Peck Keng (NTU)*
- Determination of in vivo Constitutive Properties of Aortic Valve Leaflets from Phono-echo-cardiograms  
  *Dr Liu Li (NTU)*
- Prostate Slicer Box and its Validation  
  *Ms Ma Hong Yun (SGH)*
- Tibiofemoral Pressure Mapping with Fibre Grafting Sensor  
  *Ms Lipi Mohanty (NTU)*
- Dynamics of A2 Finger Pulley Rupture  
  *Mr Tan Ming (NTU)*
- Instantaneous Axes of Rotation of Thoracolumbar T12-L1 Intervertebral Joints  
  *A/Prof Teo Ee Chon (NTU)*
- EOG Based Control of Assistive Platform for the Severely Disabled  
  *A/Prof Sardha Wijerupage Wijesoma (NTU)*
- Chair: *A/Prof Lim Chu Sing & Dr Mathew Sebastian*

1610–1630  
Tea Break and Exhibition

1630–1740  
**FREE PAPERS 2 (DIAGNOSTICS)**
- Activity-based Dynamic Insulin Infusion System  
  *Mr Chan Ting Kwan (TechSource Systems Pte Ltd)*
- Volume Visualisation for Surgical Planning System  
  *Mr Chan Chee Fatt (National Neuroscience Institute)*
- Saliva Analysis in the Early Detection of Oral Cancer Using Surface Enhanced Raman Spectroscopy (SERS)  
  *Mr Kho Kiang Wei (National Cancer Centre)*
- Bioenergy Based Medical Diagnostic Application Based on Gas Discharge Visualization  
  *Mr Lee Hwa Chiang Ricky (NTU)*
- Determination of Urine Outflow and Renal Function Quantitatively  
  *Mr Loh Kah Meng (Nanyang Polytechnic)*
- Antibody-conjugated Gold Nanoparticles and its Interaction with Epithelial Carcinoma Cells for Optical Molecular Imaging  
  *Dr Olivo Malini (National Cancer Centre)*
- Development of a Laser Confocal Endomicroscope as a Novel Technique for in vivo Fluorescence Imaging of the Oral Cavity  
  *Dr Thong Soo-Ping Patricia (National Cancer Centre)*

1740  
End of Scientific Sessions
<table>
<thead>
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<th>Time</th>
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<tr>
<td>0800–0900</td>
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<td><strong>SYMPOSIUM – MEDICAL INFORMATICS 1</strong></td>
</tr>
<tr>
<td></td>
<td>Medical Informatics in the New Millennium</td>
</tr>
<tr>
<td></td>
<td><em>Prof KC Lun</em></td>
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<td></td>
<td><em>Dr Wong Merng Koon</em></td>
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<td>Chair: Dr Wong Merng Koon</td>
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<tr>
<td>1015–1045</td>
<td>Tea Break and Exhibition</td>
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<tr>
<td>1045–1145</td>
<td><strong>SYMPOSIUM – MEDICAL INFORMATICS 2</strong></td>
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<tr>
<td></td>
<td>Nursing IT</td>
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<td><em>Ms Tan Siok Bee</em></td>
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<td>Using Reconfigurable Hardware to Accelerate Biomedical Computation</td>
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<td>Chair: Dr Wong Merng Koon</td>
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<tr>
<td>1145–1215</td>
<td><strong>LUNCH SYMPOSIUM</strong></td>
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<tr>
<td></td>
<td>Biotechnological Inventions &amp; Intellectual Property: A Challenge for Patent Law(s)</td>
</tr>
<tr>
<td></td>
<td><em>Mr Gianfranco Matteucci</em></td>
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<tr>
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<td>Chair: Dr Philip Wong</td>
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<tr>
<td>1215–1315</td>
<td>Lunch</td>
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<tr>
<td>1315–1415</td>
<td><strong>FREE PAPERS 3 (MEDICAL INFORMATICS/MEDICAL SIGNAL PROCESSING)</strong></td>
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<tr>
<td></td>
<td>IT Security in Biomedical Imaging Informatics: The Hidden Vulnerability</td>
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<td><em>A/Prof Vladimir Kulish (NTU)</em></td>
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<td>Comparison of Linear Transforms in Power Spectrum Analysis of DNA</td>
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<td><em>Mr Lo Chong Chiah (NTU)</em></td>
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<td>FREE PAPERS 4 (ADVANCED BIOMATERIALS/MODELLING/TISSUE ENGINEERING)</td>
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<tr>
<td></td>
<td>Fabrication and Near-Physiological Testing of a Biodegradable Metallic Coronary Stent</td>
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<td>A/Prof Lim Chu Sing (NTU)</td>
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<td>A New Concept of Active and Passive Elastance to Explain Left Ventricular Pressure Dynamics</td>
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<tr>
<td></td>
<td>Dr Zhong Liang (NTU)</td>
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<tr>
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<td>Dr Tan Teing Ee (National Heart Centre)</td>
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<tr>
<td>1455–1525</td>
<td>Tea Break and Exhibition</td>
</tr>
<tr>
<td>1525–1625</td>
<td>FREE PAPERS 5 (NURSING)</td>
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<tr>
<td></td>
<td>An Analysis of the Skin Prick Test Results of Rhinitis Patients at ENT Centre, SGH</td>
</tr>
<tr>
<td></td>
<td>Ms Aishah bte Abdul Latiff</td>
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<td></td>
<td>Ms Norhayati Ahmad</td>
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<td>To Reduce Time in Levelling Transducer to Axis Point</td>
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<td></td>
<td>Ms Kamsiah Jaafar</td>
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<tr>
<td></td>
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<td>Ms Josephine Teo</td>
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<td>Ms Tamilchelvi Sinnapan</td>
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<td>Perineal Cold Pads Vs Oral Analgesics in the Relief of Post Partum Perineal Wound Pain</td>
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<tr>
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<td>Ms Punasundri Thangaraju</td>
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<tr>
<td>1625–1630</td>
<td>Closing Remarks</td>
</tr>
<tr>
<td></td>
<td>A/Prof Kwoh Chee Keong, Co-chairman</td>
</tr>
<tr>
<td>1630</td>
<td>End of Scientific Sessions</td>
</tr>
<tr>
<td>Time</td>
<td>Session</td>
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IT in Clinical Healthcare Administration  
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Chair: Dr Wong Merng Koon |
|              | 1015–1045 Tea Break and Exhibition |                                                                         |
| 1045–1145    | SYMPOSIUM – MEDICAL INFORMATICS 2 | Nursing IT  
**Ms Tan Siok Bee**  
Using Reconfigurable Hardware to Accelerate Biomedical Computation  
**Asst/Prof Bertil Schmidt**  
Chair: Dr Wong Merng Koon |
| 1145–1215    | LUNCH SYMPOSIUM                  | Biotechnological Inventions & Intellectual Property: A Challenge for Patent Law(s)  
**Mr Gianfranco Matteucci**  
Chair: Dr Philip Wong |
| 1215–1315    | Lunch                            |                                                                         |
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<table>
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<td>1625–1630</td>
<td>Closing Remarks A/Prof Kwoh Chee Keong, Co-chairman</td>
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<td>1630</td>
<td>End of Scientific Sessions</td>
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</table>
DETERMINATION OF URINE OUTFLOW AND RENAL FUNCTION QUANTITATIVELY

Loh Kah Meng, David Ng, Dhanjoo N Ghista, Heiko Rudolph

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Summary – In this paper, we provide a noninvasive methodology to assess physiological function of the kidneys. We analyze the renograms with 2-compartmental modelling of the kidney-renal outflow system, and then compute the amount of flow of renal radionuclide into and out of the renal pelvis compartment.

Index Terms – glomerular filtration rate, GFR, renal outflow obstruction, renal function

I. MOTIVATION
Currently there is no mathematical model for renal function and urine outflow rate based on non-invasive renography.

II. METHODOLOGY
We will first digitalize and normalized the renograms. The 2-compartmental modelling of the kidney outflow system was performed with derivation of system parameters: $A_A$ and $\frac{dV}{dt} (m^3)$ [1]. We will only accept the results of the best fit (R-Square > 95%). From these parameters, we will determine the urine outflow ($U(t)$) dl/sec.

III. RESULTS

Figure 1. Clinical renogram of volunteer coded Patient 7.

Note that the $(Q_t, R_t)$ segment of the tracer curve for the right kidney is similar to the $(P_t, Q_t)$ segment and demonstrates good outflow-rate compared to the $(Q_t, R_t)$ segment of the obstructive curve for the left kidney.

We have performed parametric identification for equations (9) and (10) using MatLab 7 in the paper [1]. The following are the best fitted results for patients 7.

Table 1. Comparison of clinical and calculated results. We can observe that the errors for each kidney is less than 1%.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Clinical %</th>
<th>Calculated %</th>
<th>% Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>44</td>
<td>56</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>43.87</td>
<td>56.13</td>
<td>0.23</td>
</tr>
</tbody>
</table>

IV. CONCLUSION
We have demonstrated the techniques of using the two-compartmental model of kidney-renal outflow tract [1] to assess the clinical relevance with comparison with clinical renogram studies.

REFERENCES

ACTIVITY-BASED DYNAMIC INSULIN INFUSION SYSTEM
Loh Kah Meng, Chan Ting Kwan, Dhanjoo N. Ghista, Heiko Rudolph
1 School of Engineering (Electronics), Nanyang Polytechnic, Singapore, 2 TechSource Systems Pte Ltd, Singapore, 3 Department of Biomedical Engineering, Nanyang Technological University, Singapore, 4 School of Electrical and Computer Engineering, Biomedical, RMIT, Australia

Summary – This paper has demonstrated the operation of an activity-based dynamic insulin infusion system. The amount of insulin infused to bring the blood glucose concentration down is regulated by a closed-loop PD (Proportional-Derivative) control algorithm.

Index Terms – dynamic, clinical diagnosis, insulin release, systems-engineering model

I. MOTIVATION
The current insulin infusion systems are based on the previously known individual’s activities history to estimate the required insulin amount. The techniques adopted do not allow the patients to deviate too much from their normal daily activities [3]. Our work focuses on regular sampling of diabetic patients’ blood glucose concentration through a sensor to compute the required amount of insulin to be released into the blood stream.

II. METHODOLOGY
The closed loop system will continuously monitor the blood glucose concentration at 0.5h interval. Once the system detects that the blood glucose concentration exceeds a predetermined threshold e.g. 120mg/dl [1], the system will be armed and calculate the amount of insulin required [2] to bring the blood glucose concentration below the threshold.

Figure 1. System Block diagram of the insulin release system. The error is generated from glucose sensor and computed glucose concentration after the release of insulin into the blood stream at 0.5h interval.

III. RESULTS
The figure 2 shows the results of the insulin infusion system. The diabetic subject D18’s unaided glucose clinical data is fed into the system. After the release of insulin at 0.5h, 1h and 1.5h intervals, the final blood glucose concentration drops below the threshold and the controller will stop releasing insulin into the blood stream.

Figure 2. The subject’s unaided blood glucose concentration at time 0 is above 120mg/dl. The system is armed and re-sampled the blood glucose concentration at 0.5h (170 mg/dl). The system will send a bolus of insulin; 10mU/dl into the blood stream. The system will keep monitoring the resulting blood glucose concentration at 1.0h and 1.5 hour intervals. If the blood glucose concentration is above the threshold, the system will infuse a computed insulin bolus into blood stream.

IV. CONCLUSION
We have demonstrated the capabilities of an activities-adaptive dynamic real-time insulin release system. The system is able to protect the users from hypoglycemia and hyperglycemia. As we continue this work, we will develop a clinically-implementable hardware system for diabetic patients.

REFERENCES
CHAPTER 3

Lung-gas composition and transfer analysis: O₂ and CO₂ diffusion coefficients and metabolic rates

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Abstract

The primary function of the lung is to (i) oxygenate the blood and thereby provide oxygen to the cells for metabolism purposes, and (ii) to remove the collected CO₂ from the pulmonary blood. Herein, we will analyze the compositions of the inspired and expired air per breath, and from there compute the O₂ consumption and CO₂ production rates. Next, we derive expressions for diffusion coefficients $D_{O₂}$ and $D_{CO₂}$ in terms of the evaluated cardiac output, O₂ and CO₂ concentrations in arterial and venous blood, alveolar and blood O₂ and CO₂ partial pressures. We then take up a typical case study, and demonstrate the computation of $D_{O₂}$ and $D_{CO₂}$, to represent the lung-performance capability to oxygenate the blood.

1 Introduction

The lung-functional performance is characterized by (i) its ventilatory capacity, to bring air (and hence O₂) into the alveoli, and (ii) its capacity to transfer O₂ and CO₂ into and from the pulmonary capillary bed. Hence, the O₂ and CO₂ diffusion coefficients as well as the O₂ consumption rate and the CO₂ production rate represent the lung-performance indices.
2 Lung-air composition analysis (and O₂ consumption and CO₂ production rates)

We carry out a mass-balance analysis, involving:

(i) compositions of air breathed in and out
(ii) consumption or losses of O₂, CO₂ and H₂O.

Table 1 provides clinical data on partial pressures and volumes of N₂, O₂, CO₂ and H₂O of atmospheric air breathed in and expired out, one breath cycle. The monitored breathing rate (BR) = 12 breaths/min, and we assume $P_{\text{H₂O}}$ at 37°C = 47 mmHg.

It can be noted that the expired air volume exceeds the inspired air volume for this particular breath cycle. The H₂O loss of 30.1 ml (=32.6–2.5 ml) contributes the major portion of this difference.

2.1 Calculation of O₂ consumption rate and CO₂ production rate

We now determine the O₂ consumption rate and CO₂ production rates from the inspired and expired gases.

Assuming the patient breathes at 12 times per minute we have

$$O₂ \text{ Consumption Rate} = (\text{Inspired } O₂ - \text{Expired } O₂) \times 12$$

$$= (104.2 - 80.6) \times 12$$

$$= 283.2 \text{ ml/min}$$

<table>
<thead>
<tr>
<th>Respiratory gases</th>
<th>Atmospheric air</th>
<th>Expired air</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmHg</td>
<td>ml/%</td>
</tr>
<tr>
<td>N₂</td>
<td>597</td>
<td>393.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>78.55%</td>
</tr>
<tr>
<td>O₂</td>
<td>159</td>
<td>104.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20.84%</td>
</tr>
<tr>
<td>CO₂</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.04%</td>
</tr>
<tr>
<td>H₂O</td>
<td>3.7</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.49%</td>
</tr>
<tr>
<td>Total</td>
<td>760</td>
<td>500</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100%</td>
</tr>
</tbody>
</table>
CO₂ Production Rate = (Expired CO₂ - Inspired CO₂) × 12
= (19.1 - 0.2) × 12
= 226.8 ml/min

The amount of water vapor in the humidified expired air amounts to 6.2% of the expired air (compared to 0.49% of the dry inspired air) corresponding to the partial-pressure ratio of water vapor in the expired air (= 47/760). The volume of the dry expired air = (525.3 - 32.6) ml = 492.7 ml.

Now, assume that out of 500 ml of inspired air, the dead-space air volume (not taking part in the gas-transfer process) is 150 ml and the alveolar air volume is 350 ml. We next compute the dead-space air volume composition.

### 2.2 Dead-space air composition

The clinical data of expired air composition is:

\[ \begin{align*}
N₂ &= 393.1 \text{ ml} \\
O₂ &= 83.36 \text{ ml} \\
CO₂ &= 16.87 \text{ ml} \\
H₂O &= 34.15 \text{ ml} \\
\text{Total} &= 527.49 \text{ ml}
\end{align*} \]

Now, the dead-space air will be made up of (i) a dry air portion from the inspired air (assumed to be = 141 ml), plus (ii) the water vapor taken up by the dry air
(estimated to be $= 9 ml$) since the expired air portion of 141 ml will not have undergone O$_2$ and CO$_2$ transfer, its composition is the same as that of the inspired air:

$$N_2 = 111 ml \ (78.55\%), \ O_2 = 29.40 ml \ (20.84\%), \ CO_2 = 0.06 ml \ (0.04\%), \ H_2O = 0.69 ml \ (0.49\%).$$

When this inspired air (in the dead space) of 141 ml is fully humidified, it will take up a further $X$ ml of H$_2$O vapor, in the ratio of the partial-pressures, as:

$$\frac{X}{141} = \frac{47}{713} = 0.0659$$

$$\therefore X = 0.0659 \times 141 = 9.29 ml \text{ of H}_2\text{O vapor (which is close to our estimate).}$$

So, by adding 9.29 ml of H$_2$O vapor to 0.69 ml of water vapor in the inspired air volume of 141 ml, the total water vapor in the dead-space air is 9.98 ml. The humidified dead-space air composition will be:

$$N_2 = 111.00 ml \ (= 73.78\%)$$
$$O_2 = 29.40 ml \ (= 19.55\%)$$
$$CO_2 = 0.06 ml \ (= 0.04\%)$$
$$H_2O = 9.98 ml \ (= 6.63\%)$$
$$\text{Total} = 150.44 ml$$

### 2.3 Alveolar-air composition and partial pressures

We can now compute the alveolar air composition, by subtracting the dead-space air from the expired air. These values are tabulated in column 4 of the table below.

Finally, we compute the partial pressure of O$_2$ and CO$_2$ (as well as of N$_2$ and H$_2$O), so that we can determine next the diffusion coefficients of O$_2$ and CO$_2$ based on the monitoring of arterial and venous blood concentrations. These values are tabulated in column 5 of the below table.

<table>
<thead>
<tr>
<th></th>
<th>Expired air (ml)</th>
<th>Dead-space air (ml)</th>
<th>Alveolar air (ml)</th>
<th>Alveolar-air partial pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N$_2$</td>
<td>393.1</td>
<td>111.00</td>
<td>282.1</td>
<td>569.41</td>
</tr>
<tr>
<td>O$_2$</td>
<td>80.53</td>
<td>29.40</td>
<td>51.13</td>
<td>103.21</td>
</tr>
<tr>
<td>CO$_2$</td>
<td>19.12</td>
<td>0.06</td>
<td>19.06</td>
<td>38.47</td>
</tr>
<tr>
<td>H$_2$O</td>
<td>34.21</td>
<td>9.98</td>
<td>24.23</td>
<td>48.91</td>
</tr>
<tr>
<td>Total</td>
<td>526.96</td>
<td>150.44</td>
<td>376.52</td>
<td>760</td>
</tr>
</tbody>
</table>
3 Lung gas-exchange model and parametric analysis

3.1 Expressions for \( D_{O_2} \) and \( D_{CO_2} \)

The gas exchange between the alveolar air and pulmonary capillary blood is represented by the following \( O_2 \) and \( CO_2 \) conservation equations (Fig. 2):

\[
Q^{VE} C_{O_2}^{VE} = Q^{AE} C_{O_2}^{AE} + \dot{V}\bar{O}_2 \quad \text{(from the alveolar air to capillary blood)}
\]

\[
= Q^{AE} C_{O_2}^{AE} + (\Delta P_{av}^{O_2}) D_{O_2}; \quad P_{O_2}^{cap} = P_{O_2}^{AE},
\]

in which \( P_{O_2}^{cap} = P_{O_2}^{PRB} \) (\( O_2 \) concentration of the preoxygenated blood)

\[
Q^{VE} C_{CO_2}^{VE} = Q^{AE} C_{CO_2}^{AE} - \dot{V}\bar{CO}_2
\]

\[
= Q^{AE} C_{CO_2}^{AE} - (\Delta P_{av}^{CO_2}) D_{CO_2}; \quad P_{CO_2}^{cap} = P_{CO_2}^{VE},
\]

in which \( P_{CO_2}^{cap} = P_{CO_2}^{PRB} \) (\( CO_2 \) concentration of the preoxygenated blood), wherein

(i) \( Q^{AB} \) and \( Q^{VB} \) are arterial and venous blood flow-rates;

\[
Q^{AB} = Q^{VE} \quad \text{(at venous end)}, \quad Q^{VB} = Q^{AE} \quad \text{(at arterial end)}
\]

(ii) \( P_{O_2}^{al} \) and \( P_{O_2}^{cap} \) are the alveolar and capillary \( O_2 \) partial pressures

(iii) \( P_{CO_2}^{al} \) and \( P_{CO_2}^{cap} \) are the alveolar and capillary \( CO_2 \) partial pressure

(iv) \( D_{O_2} \) and \( D_{CO_2} \) are the \( O_2 \) and \( CO_2 \) diffusion coefficients

(v) \( \Delta P_{av}^{O_2} \) = average of \( (P_{O_2}^{al} - P_{O_2}^{cap}) \) over the capillary length;

\( \Delta P_{av}^{CO_2} \) = average of \( (P_{CO_2}^{al} - P_{CO_2}^{cap}) \) over the capillary length.

Now we can equate the arterial and venous blood flow rates, as

\[
Q^{AB} = Q^{VB} = Q = (SV)/(EP) \simeq CO/60,
\]

SV, EP and CO being the stroke volume, ejection period and cardiac output, respectively. Hence the above equations can be rewritten as:

(vi) \( \dot{V}\bar{O}_2 \) is the \( O_2 \) transfer rate from alveolar air to capillary blood (= \( O_2 \) consumption rate), \( \dot{V}\bar{CO}_2 \) is the \( CO_2 \) transfer rate from capillary blood to alveolar air.

![Figure 2: Schematic of blood-gas concentration in the pulmonary capillary.](image-url)
From eqn. (1):

\[
Q^{VE}C_{O_2}^{VE} = Q^{AB}C_{O_2}^{AB} + (\Delta P_{av}^{O_2})D_{O_2}; \quad P_{O_2}^{cap} = P_{O_2}^{AE} = P_{O_2}
\]

\[
Q^{VE}C_{O_2}^{VB} = Q^{AB}C_{O_2}^{AB} + (\Delta P_{av}^{O_2})D_{O_2}
\]

\[
D_{O_2} = \frac{Q(C_{O_2}^{VE} - C_{O_2}^{AE})}{(\Delta P_{av}^{O_2})} = \frac{Q(C_{O_2}^{AB} - C_{O_2}^{VB})}{(\Delta P_{av}^{O_2})}.
\]  (3)

From eqn. (2):

\[
Q^{VE}C_{CO_2}^{VE} = Q^{AE}C_{CO_2}^{AE} - (\Delta P_{av}^{CO_2})D_{CO_2}; \quad P_{CO_2}^{cap} = P_{CO_2}^{AE} = P_{CO_2}^{VB}
\]

\[
Q^{VE}C_{CO_2}^{VB} = Q^{AE}C_{CO_2}^{AE} - (\Delta P_{av}^{CO_2})D_{CO_2}
\]

\[
D_{CO_2} = \frac{Q(C_{CO_2}^{VE} - C_{CO_2}^{AB})}{(\Delta P_{av}^{CO_2})}.
\]  (4)

wherein

(i) \( Q, C_{O_2}^{VE}, C_{O_2}^{AB}, C_{CO_2}^{VE} \) and \( C_{CO_2}^{AB} \) can be monitored because \( C_{O_2}^{VE} \) and \( C_{CO_2}^{VE} = C_{O_2}^{AB} \) and \( C_{CO_2}^{AB} \) and \( C_{CO_2}^{AE} = C_{O_2}^{VB} \) and \( C_{CO_2}^{VB} \)

(ii) \( D_{O_2} \) and \( D_{CO_2} \) (eqns. (3) and (4)) represent the lung gas-exchange parameters.

Now from eqns. (3) and (4), if we want to evaluate the diffusion coefficients \( D_{O_2} \) and \( D_{CO_2} \), we need to also express \( P_{O_2}^{al}, P_{CO_2}^{cap} \) and \( P_{O_2}^{al}, P_{CO_2}^{cap} \) in terms of monitorable quantities. In this regard,

(i) Alveolar \( P_{O_2}^{al} \) can be expressed in terms of \( \dot{V} \) (the ventilation rate) and \( \dot{V}_{O_2} \) (the \( O_2 \) consumption rate) as Fig. 3:

\[
P_{O_2}^{al} = k_{1} \left[ 1 - e^{-k_{2} \left[ (\dot{V}/\dot{V}_m)/\dot{V}_{O_2} \right]} \right],
\]  (5)

where \( \dot{V}_m \) is the maximum ventilation rate and \( \dot{V}_{O_2} \) (the \( O_2 \) consumption rate or absorption rate from the alveoli) = \( Q(C_{O_2}^{AB} - C_{O_2}^{VB}) \). Equation (5) implies that as \( (\dot{V}/\dot{V}_m) \) increases, (the exponential term decreases, and) \( P_{O_2}^{al} \) increases (as in Fig. 3), and as \( \dot{V}_{O_2} \) increases \( P_{O_2}^{al} \) decreases (as in Fig. 3).

(ii) Alveolar \( P_{CO_2}^{al} \) can be expressed in terms of \( \dot{V} \) and \( \dot{V}_{O_2} \) as in Fig. 4.

\[
P_{CO_2}^{al} = k_{3}e^{-k_{4} \left[ (\dot{V}/\dot{V}_m)/(\dot{V}_{CO_2}) \right]},
\]  (6)

where \( \dot{V}_{CO_2} \) (the \( CO_2 \) production rate or excretion rate from the blood) = \( Q(C_{CO_2}^{VB} - C_{CO_2}^{AB}) \). This equation implies that as \( \dot{V}/\dot{V}_m \) increases, \( P_{CO_2}^{al} \) decreases; also, as \( \dot{V}_{CO_2} \) increases (the exponential term decreases, and hence) \( P_{CO_2}^{al} \) increases.
Figure 3: Effect on alveolar $P_{O_2}$ of (i) alveolar ventilation, and (ii) rate of oxygen absorption from alveolar $P_{O_2}$ or $O_2$ consumption rate [from Guyton (1971), p. 476].

Figure 4: Effect on alveolar $P_{CO_2}$ of alveolar ventilation and rate of carbon dioxide excretion from the blood or $CO_2$ production rate [from Guyton (1971), p. 476].

(iii) Blood $P_{O_2}$ can be obtained in terms of blood $CO_2$, from the $O_2$ disassociation curve (providing concentrations in arterial and venous blood), is represented in Fig. 5 as:

$$C_{O_2} = C_{O_2}^m \left(1 - e^{-k_{PO_2}^{O_2}}\right), \quad \text{or} \quad C_{O_2} = 1 - e^{-k_{5}^{P_{O_2}}}, \quad (7)$$
Figure 5: O$_2$ dissociation curves, showing the total oxygen in each 100 ml of normal blood, the portion dissolved in the water of the blood [from Guyton [2], p. 485].

Figure 6: The carbon dioxide dissociation curve [from Guyton [2], p. 491].

where

- $C_{O_2}^m$ and $P_{O_2}^m$ are the maximum values of blood O$_2$ partial pressure
- $CO_2^2 = CO_2/CO_2^m$
- $P_{O_2}^c = P_{O_2}/P_{O_2}^m$.

(iv) Blood $P_{CO_2}$ can be obtained in terms of $C_{CO_2}$, from the CO$_2$ disassociation curve or CO$_2$ concentration in arterial and venous blood can be represented
as per Fig. 6 as:

\[ C_{CO_2} = C_{O_2}^m \left( 1 - e^{-k_6 \left(P_{CO_2}/P_{CO_2}^m\right)} \right) \]

or, \[ C_{CO_2}^{*} = 1 - e^{-k_6 \left(P_{CO_2}/P_{CO_2}^m\right)} = 1 - e^{-k_6 P_{CO_2}^*}. \] (8)

### 3.2 Alveolar \(O_2\) and \(CO_2\) Partial-pressure Expressions

Now, let us refer eqn. (4) for the \(P_{O_2}^{al}\) partial pressure curve (Fig. 3), represented by the equation:

\[ P_{O_2}^{al} = k_1 \left[ 1 - e^{-k_2 \left(V^* / V_m\right)} \right] \]

\[ = k_1 \left[ 1 - e^{-k_2 \left(V^* / V_{O_2}\right)} \right], \text{ where } V^* = \frac{\dot{V}}{V_m} \] (9)

where \(\dot{V}\) is the alveolar ventilation rate (in liters/min), \(\dot{V}_m\) is the maximum ventilation rate (= 50 l/min) and \(\dot{V}_{O_2}\) is the \(O_2\) consumption rate (in liters/min). Herein, the coefficients \(k_1\) and \(k_2\) can be determined by having this equation match the Fig. 3 data. Note, in this equation, when \(\dot{V} = 0, P_{O_2}^{al} = 0\) from the equation, which satisfies the data.

Now for \(\dot{V}_{O_2} = 0.25\) l/min, when \(V^* = \frac{\dot{V}}{V_m} = 0.5, P_{O_2}^{al} = 140\) mmHg. Hence,

\[ 140 = k_1 \left[ 1 - e^{-k_2 \left[0.5 / 0.25\right]} \right] = k_1(1 - e^{-2k_2}). \] (10)

Also, when \(\dot{V}_{O_2} = 11/\text{min}, V^* = 0.31/\text{min}, P_{O_2}^{al} = 100\) mmHg. Hence

\[ 100 = k_1 \left[ 1 - e^{-k_2 \left[0.31 / V_m\right]} \right] = k_1(1 - e^{-0.3k_2}). \] (11)

From eqns. (10) and (11), we get:

\[ \frac{140}{100} = \frac{k_1(1 - e^{-2k_2})}{k_1(1 - e^{-0.3k_2})} = \frac{1 - e^{-2k_2}}{1 - e^{-0.3k_2}} \]

\[ \therefore 140 - 140e^{-0.3k_2} = 100 - 100e^{-2k_2} \]

or, \(40 = 100e^{-0.3k_2} + 100e^{-2k_2}\), so that \(k_2 = 4.18\) min/l. \] (12)

Upon substituting \(k_2 = 4.18\) min/l into eqn. (10) we obtain:

\[ 140 = k_1(1 - e^{-(2 \times 4.18)}), \text{ so that } k_1 \approx 140\text{ mmHg}. \] (13)
Hence, the $P_{O_2}^{al}$ curve can be represented by:

$$P_{O_2}^{al} = 140 \left[ 1 - e^{-4.18 \left( \frac{\dot{V}_*}{\dot{V}_{O_2}} \right)} \right], \quad (14)$$

where, $\dot{V}_{O_2} = Q(C_{O_2}^{AB} - C_{O_2}^{VB})$ and $\dot{V}_* = \dot{V}/501/\text{min}$.

Now, let us look at the $P_{CO_2}^{al}$ expression:

$$P_{CO_2}^{al} = k_3 e^{-k_4 \left( \frac{\dot{V}_{CO_2}}{\dot{V}_m} \right)} = k_3 e^{-k_4 \left( \frac{\dot{V}_*}{\dot{V}_{CO_2}} \right)}.$$

We note from Fig. 4 that for $\dot{V}_{CO_2} = 0.2 \text{ l/min}$ and $\dot{V}_m = 0.2$, $P_{CO_2}^{al} = 12$. Hence, from the above equation, we get:

$$12 = k_3 e^{-k_4} \quad (15)$$

Also, for $\dot{V}_{O_2} = 0.8 \text{ l/min}$ and $\dot{V}_m = 0.2$, $P_{CO_2}^{al} = 62 \text{ mmHg}$. Hence

$$62 = k_3 e^{-k_4 \left[ \frac{0.20}{0.80} \right]} = k_3 e^{-k_4 \left[ \frac{1}{4} \right]} \quad (16)$$

From eqns. (15) and (16), we get:

$$\frac{12}{62} = \frac{e^{-k_4}}{e^{-k_4 / 4}} = e^{\frac{3}{4} k_4}$$

$$\ln \left( \frac{12}{62} \right) = -\frac{2}{3} k_4, \quad \text{so that} \quad k_4 = 2.46. \quad (17)$$

Substituting $k_4 = 2.46$ into eqn. (16), we obtain:

$$62 = k_3 e^{-2.46 / 4}, \quad \therefore \quad k_3 = 114.68. \quad (18)$$

Hence, the $P_{CO_2}^{al}$ curve can be represented as

$$P_{CO_2}^{al} = 114.68 e^{-2.46 \left( \frac{\dot{V}_{CO_2}}{\dot{V}_m} \right)} \left( \frac{\dot{V}_*}{\dot{V}_{CO_2}} \right), \quad (19)$$

where $\dot{V}_* = \dot{V}/501/\text{min}$ and $\dot{V}_{CO_2} = Q(C_{CO_2}^{VB} - C_{CO_2}^{AB}).$

3.3 Arterial and venous $O_2$ and $CO_2$ partial-pressure expressions

We now need to express $P_{O_2}^{AB}$ and $P_{CO_2}^{VB}$ in terms of $C_{O_2}^{AB}$ and $C_{CO_2}^{VB}$.
So that let us look at the O₂ disassociation curve, as shown in Fig. 5.

\[
C_{O₂} = C_{O₂|\text{max}} \left[ 1 - e^{-k₅P_{O₂}^*} \right],
\]

or,

\[
C_{O₂}^* = 1 - e^{-k₅P_{O₂}^*},
\]

where \( C_{O₂}^* = \frac{C_{O₂}}{C_{O₂|\text{max}}} \), \( P_{O₂}^* = \frac{P_{O₂}}{P_{O₂|\text{max}}} \). \quad (20)

From Fig. 5, at \( P_{O₂}^* = \frac{40 \text{ mmHg}}{140 \text{ mmHg}} = 0.29 \) (for normal venous blood), and

\[
C_{O₂}^* = \frac{15}{20} = 0.75.
\]

Hence from eqn. (20):

\[
0.75 = 1 - e^{-0.29k₅} \quad \therefore \quad k₅ = 4.78.
\]

Also, \( P_{O₂}^* = \frac{95 \text{ mmHg}}{140 \text{ mmHg}} = 0.68 \) (for normal arterial blood), and

\[
C_{O₂}^* = \frac{19}{20} = 0.95.
\]

Hence from eqn. (20):

\[
0.95 = 1 - e^{-0.68k₅}, \quad \text{or} \quad k₅ = 4.4. \quad (22)
\]

So, we take the average value of \( k₅ \):

\[
\therefore \quad k₅ = \frac{(4.78 + 4.4)}{2} = 4.59. \quad (23)
\]

Then the O₂ disassociation curve is given by:

\[
C_{O₂} = C_{O₂}^B = 0.2 \left[ 1 - e^{-4.59 \left( \frac{P_{O₂}}{140} \right)} \right], \quad (24)
\]

and

\[
P_{O₂} = \frac{140}{4.59} \ln \left[ \frac{0.2}{0.2 - C_{O₂}^B} \right] = 30.5 \ln \left[ \frac{0.2}{0.2 - C_{O₂}^B} \right]. \quad (25)
\]

Finally, we look at the CO₂ disassociation curve

\[
C_{CO₂} = C_{CO₂|\text{max}} \left( 1 - e^{-k₆\frac{P_{CO₂}}{P_{CO₂|\text{max}}}} \right),
\]

or,

\[
C_{CO₂}^* = 1 - e^{-k₆\frac{P_{CO₂}}{P_{CO₂|\text{max}}}} = 1 - e^{-k₆P_{CO₂}^*}. \quad (26)
\]
Based on Fig. 6, when \( P_{CO_2}^* = \frac{20 \text{ mmHg}}{140 \text{ mmHg}} = 0.14 \), \( C_{CO_2}^* = \frac{38}{80} = 0.475 \), so that

\[
0.475 = 1 - e^{-0.14k_6}, \quad k_6 = 4.60,
\]

when \( P_{CO_2}^* = \frac{70 \text{ mmHg}}{140 \text{ mmHg}} = 0.5 \), \( C_{CO_2}^* = \frac{60}{80} = 0.75 \), so that

\[
0.75 = 1 - e^{-0.5k_6}, \quad k_6 = 2.77.
\]

So, we take the average value of \( k_6 \):

\[
k_6 = \frac{(4.60 + 2.77)}{2} = 3.69.
\]

Then the \( CO_2 \) concentration is given (from eqns. (26–29) by:

\[
C_{CO_2} = C_{CO_2}^B = 0.8 \left[ 1 - e^{-4.71 \left( \frac{P_{CO_2}}{140} \right)} \right]
\]

and

\[
P_{CO_2} = 29.72 \ln \left[ \frac{0.8}{0.8 - C_{CO_2}^B} \right].
\]

### 3.4 Sequential procedure to compute \( D_{O_2} \) and \( D_{CO_2} \)

1. We first monitor: \( V(t) \), \( \dot{V}(t) \), \( SV \) (stroke volume), \( EP \) (cardiac ejection period), \( C_{O_2}^B \), \( C_{O_2}^A \), \( C_{CO_2}^B \) and \( C_{CO_2}^A \) (\( O_2 \) and \( CO_2 \) concentrations in pre oxygenated and post oxygenated blood).

2. We substitute the values of \( C_{O_2}^A (= C_{O_2}^E) \) and \( C_{O_2}^B (= C_{O_2}^E) \) into eqn. (3), and the values of \( C_{CO_2}^A (= C_{CO_2}^E) \) and \( C_{CO_2}^B (= C_{CO_2}^E) \) into eqn. (4).

3. We next determine:

\[
Q = SV/ejection period,
\]

\[
\dot{V}_{O_2}(t) = Q(C_{O_2}^A - C_{O_2}^B),
\]

\[
\dot{V}_{CO_2}(t) = Q(C_{CO_2}^B - C_{CO_2}^A).
\]

4. We then substitute the expressions for \( \dot{V}_{O_2}(t) \) and \( \dot{V}_{CO_2}(t) \) into the equations for \( P_{O_2}^E \) (eqn. (14)) and \( P_{CO_2}^E \) (eqn. (19)).

5. We substitute the monitored values of \( C_{O_2}^B (= C_{O_2}^E) \) and \( C_{CO_2}^B (= C_{CO_2}^E) \) into eqns. (25) and (31), to obtain the values of \( P_{O_2}^E \) and \( P_{CO_2}^E \).

6. Now, in order to determine the values of the lung gas-exchange parameters \( D_{O_2} \) and \( D_{CO_2} \), we substitute into eqns. (3) and (4) for \( Q \) from eqn. (32), \( P_{O_2}^E \) from eqn. (14), \( P_{CO_2}^E \) from eqn. (19), \( P_{O_2}^B \) from eqn. (26), and \( P_{CO_2}^B \) from eqn. (31).
3.5 Determining $D_{O_2}$ and $D_{CO_2}$

Figure 7 illustrates the variation of $\Delta P^{O_2}$ ($= P^{al}_{O_2} - P^{cap}_{O_2} = P^{al}_{O_2} - P^{AB}_{O_2}$) along the length ($l$) of the capillary bed.

Let $l^* = l / l_m$.

Then we can express:

$$\Delta P^{O_2} = \Delta P^{O_2}_{\text{max}} f_{O_2}(l^*).$$

(35)

Then,

$$\Delta P^{O_2}_{\text{av}} = \Delta P^{O_2}_{\text{max}} \left( \int_0^1 f_{O_2}(l^*) \, dl^* \right) = \Delta P^{O_2}_{\text{max}} (F_{O_2}).$$

(36)

Based on data [3], since $\Delta P^{O_2}_{\text{av}} = 12$ mmHg for $\Delta P^{O_2}_{\text{max}} = 65$ mmHg, we have $F_{O_2} = 0.185$.

We can similarly determine the average value of $\Delta P^{CO_2}$ from Fig. 8 as:

Let $l^* = l / l_m$.

Then, we can represent Fig. 8 as:

$$\Delta P^{CO_2} = \Delta P^{CO_2}_{\text{max}} f_{O_2}(l^*).$$

(37)

Then,

$$\Delta P^{CO_2}_{\text{av}} = \Delta P^{O_2}_{\text{max}} \left( \int_0^1 f_{CO_2}(l^*) \, dl^* \right) = \Delta P^{CO_2}_{\text{max}} (F_{CO_2}).$$

(38)

Figure 7: Uptake of oxygen by the pulmonary capillary blood. (The curve in this figure was constructed from data in Mihorn and Pulley: Biophys. J., 8: 337, 1968). [from Guyton (1971), p. 434.]
Figure 8: Diffusion of carbon dioxide from the pulmonary blood into the alveolus. (The curve in this figure was constructed from data in Mihorn and Pulley: Biophys. J., 8: 337, 1968). [from Guyton (1971), p. 435.]

Based on data [3], since $\Delta P_{av}^{CO_2} = 0.5 \text{ mmHg}$ for $\Delta P_{max}^{CO_2} = 5 \text{ mmHg}$, we have $F_{CO_2} = 0.1$.

From the $\Delta P_{av}^{O_2}$ and $\Delta P_{av}^{CO_2}$ expressions, we can determine the $O_2$ consumption and the $CO_2$ production rates, as follows:

$$D_{O_2} = \frac{\text{Total } O_2 \text{ consumed}}{\Delta P_{av}^{O_2}} = \frac{\dot{V}_{O_2}}{\Delta P_{av}^{O_2}} = \frac{Q \left( C_{O_2}^{AB} - C_{O_2}^{VB} \right)}{\Delta P_{av}^{O_2}}$$  \hspace{1cm} (39)

$$D_{CO_2} = \frac{\text{Total } CO_2 \text{ produced}}{\Delta P_{av}^{CO_2}} = \frac{\dot{V}_{CO_2}}{\Delta P_{av}^{CO_2}} = \frac{Q \left( C_{CO_2}^{VB} - C_{CO_2}^{AB} \right)}{\Delta P_{av}^{CO_2}}.$$  \hspace{1cm} (40)

4 Case studies

(A) We monitor the partial pressures blood concentrations of $O_2$ and $CO_2$ as:

$$C_{O_2}^{AE} = C_{O_2}^{VB} = 0.13, \quad C_{O_2}^{VE} = C_{O_2}^{AB} = 0.18, \quad C_{CO_2}^{AE} = C_{CO_2}^{VB} = 0.525,$$

$$C_{CO_2}^{VE} = C_{CO_2}^{AB} = 0.485.$$

From eqn. (26), we obtain:

$$p_{O_2}^{VB} = 30.5 \ln \left[ \frac{0.2}{0.2 - C_{O_2}^{VB}} \right] = 29.72 \ln \left[ \frac{0.2}{0.2 - 0.13} \right]$$

$$= 32.02 \text{ mmHg}. \hspace{1cm} (41)$$
From eqn. (31), we obtain:

\[
P_{\text{CO}_2}^{\text{VB}} = 37.94 \ln \left[ \frac{0.8}{0.8 - C_{\text{CO}_2}^{\text{VB}}} \right] = 37.94 \ln \left[ \frac{0.8}{0.8 - 0.525} \right] = 40.51 \text{ mmHg.} \tag{42}
\]

We now also monitor \(Q = 51/\text{min}, \dot{V}^* = 0.1\) and \(\dot{V} = 51/\text{min}\).

Then, from eqn. (33):

\[
\dot{V}_{\text{O}_2}(t) = Q \left( C_{\text{O}_2}^{\text{AB}} - C_{\text{O}_2}^{\text{VB}} \right),
\]

so that from the above data,

\[
\dot{V}_{\text{O}_2}(t) = 5000 \times 0.05 = 250 \text{ ml O}_2/\text{min Consumption rate} \tag{43}
\]

From eqn. (34):

\[
\dot{V}_{\text{CO}_2}(t) = Q \left( C_{\text{CO}_2}^{\text{VB}} - C_{\text{CO}_2}^{\text{AB}} \right) = 5000(0.04)
= 200 \text{ ml CO}_2/\text{min production rate.} \tag{44}
\]

Now, from eqn. (14).

For \(\dot{V}^* = 0.1\) and \(\dot{V}_{\text{O}_2} = 0.251\), we obtain \(P_{\text{O}_2}^{\text{al}}\):

\[
P_{\text{O}_2}^{\text{al}} = 140 \left[ 1 - e^{-4.18 \left( \dot{V}^* / \dot{V}_{\text{O}_2} \right)} \right],
= 140 \left[ 1 - e^{-4.18[0.1/0.25]} \right] = 113.7 \text{ mmHg.} \tag{45}
\]

From eqn. (19), for \(\dot{V}^* = 0.1\) and \(\dot{V}_{\text{CO}_2} = 0.20 l\), we obtain \(P_{\text{CO}_2}^{\text{al}}\):

\[
P_{\text{O}_2}^{\text{al}} = 107.18e^{-2.19 \left( \dot{V}^* / \dot{V}_{\text{CO}_2} \right)}
= 107.18e^{-2.19[0.1/0.2]} = 35.86 \text{ mmHg.} \tag{46}
\]

Now, we can evaluate the diffusion coefficients:

From eqns. (3), (36), (41), and (45):

\[
D_{\text{O}_2} = \frac{Q(C_{\text{O}_2}^{\text{AB}} - C_{\text{O}_2}^{\text{VB}})}{\Delta P_{\text{O}_2}^{\text{al}}}
= \frac{5000(0.18 - 0.13)}{(113.7 - 31.2) \times 0.18} = 16.84 \text{ ml O}_2/\text{min/mmHg.} \tag{47}
\]
From eqn. (4):

\[ D_{CO_2} = \frac{Q(C_{CO_2}^{VB} - C_{CO_2}^{AB})}{\Delta P_{av}^{CO_2}} = \frac{5000(0.04)}{(40.51 - 35.86) \times 0.1} = 430.11 \text{ ml CO}_2/\text{min/mmHg}. \] \hspace{1cm} (48)

(B) Alternately, we derive data from:

(i) the inspired and expired air analysis (such as that carried out in Section 2.3):

O\textsubscript{2} consumption rate = 283.2 ml/min,
CO\textsubscript{2} production rate = 226.8 ml/min,
P^{al}_{O_2} = 103.03 \text{ mmHg and } P^{al}_{CO_2} = 38.41 \text{ mmHg}

and (ii) venous blood gas analysis:

\[ C_{O_2}^{VB} = 0.13, C_{CO_2}^{VB} = 0.548. \]

Then, as per eqn. (41),

\[ P_{O_2}^{VB} = 31.2 \text{ mmHg}, \] \hspace{1cm} (49)

corresponding to \( C_{O_2}^{VB} = 0.13 \) and, as per eqn. (42):

\[ P_{CO_2}^{VB} = 37.94 \ln \left( \frac{0.8}{0.8 - C_{CO_2}^{VB}} \right) = 37.94 \ln \left( \frac{0.8}{0.8 - 0.548} \right) = 43.84 \text{ mmHg}. \] \hspace{1cm} (50)

We obtain, from air-composition analysis, that \( \dot{V}_{O_2}(t) = 283.3 \text{ ml/min} \) \hspace{1cm} (51)

and \( \dot{V}_{CO_2}(t) = 226.8 \text{ ml/min}. \) \hspace{1cm} (52)

Hence,

\[ D_{O_2} = \frac{\dot{V}_{O_2}}{\Delta P_{av}^{O_2}} = \frac{283.2}{(103.03 - 31.2) \times 0.18} = 21.90 \text{ mlO}_2/\text{min/mmHg}, \] \hspace{1cm} (53)

and

\[ D_{CO_2} = \frac{\dot{V}_{CO_2}}{\Delta P_{av}^{CO_2}} = \frac{226.8}{(43.84 - 38.41) \times 0.1} = 417.68 \text{ mlCO}_2/\text{min/mmHg}. \] \hspace{1cm} (54)

The advantage of this method (B) over (A) is that it does not require monitoring of the cardiac output, and is hence simpler to implement clinically.
References


Dear Colleagues:

I would like to cordially thank all of you for your contributions.

According to the review received on our book: *Human Respiration: Anatomy and Physiology, Mathematical Modeling, Numerical Simulation and Applications*, all the chapters submitted by us are accepted for publication. Congratulations!!!

However, we need to make some minor additions and amendments.

The reviewer's comment is attached to this message (see below). In summary, we need to take the following steps:

1. All equations are to be numbered and typed by means of MS Word Equation Editor. Each equation should be a single object but not a mixture of text symbols and equations in one line.
2. All symbols that are used in equations and appear in text must be typed by means of MS Word Equation Editor within the text.
3. All repetitions among the chapters contributed by the same principal author should be removed.
4. Each principal author has to provide me with *nomenclature* (in a separate MS Word file), so that the same symbols were used by one principal author in all his/her chapters.
5. Each principal author has to provide me with *key words* to be included into *Subject Index* that will follow our book.
6. Each principal author has to send me the amended version of his/her contribution(s) in MS Word format together with the nomenclature and key words file by e-mail: mvvkulish@ntu.edu.sg. Please ensure that each chapter is formatted according to the template that was sent to you previously [otherwise, the production of the book can be delayed].

The deadline set by the publisher (WIT Press) is September 20, 2004. Hence, I have to receive all your amended

I am looking forward to hearing from you.

With kindest regards,

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'Relevance

The bio-engineering discipline is now recognised as being of substantial importance. Human respiration is a significant, challenging and rewarding field: significant because of the increase in airborne pollutants and congenital respiratory diseases; challenging because of the wide range of scales in the pulmonary system, which span about three orders of magnitude (or five, if the thickness of the alveolar membrane is included); and rewarding

because of the marvellous ingenuity that characterises the system. A text that covers highlights of the application of bio-engineering techniques to the study of human respiration is to be welcomed.
This text comprises twelve chapters dealing with various topics in human respiration, from fundamental aspects of anatomy and physiology through to numerical modelling of processes such as gas diffusion and practical applications in the field of respiratory physiotherapy. As such, there is material here that will be of interest to seasoned bio-engineers and clinical practitioners, as well as novices to the study of human respiration. **There should be a good market for the text** – WIT should use the success of their publication “Medical Application of Computer Modelling – the Respiratory System” as a guide.

Technical Correctness

The text encompasses such a wide range of material that I cannot comment on all of it. Nevertheless, I am satisfied that in the field that I do have some knowledge (fluid mechanics) the material presented is correct. Moreover, each chapter appears to be a distillation of a large body of work which has been presented and reviewed for publication in technical journals, and this gives me confidence that the whole work is accurate and reliable. There are several papers that deal with modelling of gas transfer across that alveolar lumen. **The nomenclature employed in each paper (or group of papers, where a group is characterised by having the same principal author) is slightly different. It would be very helpful if a common nomenclature could be employed. A formal definition of nomenclature after the Table of Contents would be useful.**

There are instances where relatively complex equations have been poorly constructed. For example, dots above symbols to represent differentiation with respect to time (e.g. _) have been replaced by small “o”s (e.g. _); in some instances the “o”s have been badly misplaced. This is not correct, and is unnecessary – the text appears to have been written using Microsoft Word, and Word includes an equation editor that has all the functionality required to produce neat equations employing standard notation. The final text should not contain any ambiguities in its formulae.

Quality of Text

The text is written in generally good English. While I am not sure whether it is the reviewer’s role to flag (what he thinks may be) grammatical errors, I have annotated the text where I think it might be improved. I offer these corrections not critically (they are few in number), but in the hope that through such minor corrections to the text, I might contribute to its acceptance in the academic community.

There are some instances of repetition of material between chapters by the same principal authors; there is also duplication of introductory material on respiratory anatomy between different authors. It would be beneficial to the ease with which the text can be used if (a) the repetitions were removed, (b) the duplication was minimised, and (c) the introductory material was brought forward to the first and second chapters (see below for more detail).

Order of Chapters
If the original 12 chapters are to be retained as they are, then I would suggest the following re-ordering of the text:

Anatomy and Physiology

1. Anatomy and Physiology of the Human Respiratory System
2. Fundamentals of Alveolar Gas Diffusion Mathematical Modelling and Numerical Simulation
3. Lung Gas Composition and Transfer Analysis: O2 and CO2 Diffusion Coefficients and Metabolic Rates
4. Lung Ventilation Modelling and Assessment
5. Visualisation of Alveolar Diffusion
6. Modelling of Two-Phase Flow in the Human Respiratory System
7. Impact of Microscopic Solid Particles on Alveolar Diffusion
8. Quantification of Human Physiological Response to Toxic Substances
9. Anatomically-based Modelling of Pulmonary Structure Applications
10. Applied Chest-Wall Vibration Therapy for Patients with Obstructive Lung Disease
11. Indicator for Lung Status in a Mechanically Ventilated COPD Patient using Lung Ventilation Modelling and Assessment
12. Mechanics of Proportional Assist Ventilation

I have suggested that “Anatomy and Physiology of the Human Respiratory System” should come before “Fundamentals of Alveolar Gas Diffusion”, and that “Lung Gas Composition and Transfer Analysis” and “Lung Ventilation Modelling and Assessment” should precede “Visualisation of Alveolar Diffusion”, “Modelling of Two-Phase Flow in the Human Respiratory System” and “Impact of Microscopic Solid Particles on Alveolar Diffusion”. This is because it may be easier for the reader to deal with the more general issue of lung respiration before approaching the topic of alveolar respiration. However, if some reordering of the material in chapters 2 and 5 can be allowed, then I would recommend the following titles for these chapters: 2. Fundamentals of Alveolar Gas Diffusion – Physiological Aspects 5. Alveolar Gas Diffusion – Numerical Modelling and Visualisation Here, chapter 2 would deal with the physiology of alveolar gas diffusion, and the modelling aspects would be placed in chapter 5. This would have the advantages that: (a) the first section is a relatively easy introduction of the topic of human respiration; and (b) the visualisation of the calculations by Kulish et al is presented in the best context.

It should also be possible to combine the chapters “Modelling of Two-Phase Flow in the Human Respiratory System” and “Impact of Microscopic Solid Particles on Alveolar Diffusion” into a single chapter, e.g. “Modelling the Impact of Microscopic Solid Particles on Alveolar Diffusion”. Certainly,
the material in “Impact of Microscopic Solid Particles on Alveolar Diffusion” which is a repetition of material in “Visualisation of Alveolar Diffusion” should be deleted.

I cannot decide whether the chapter entitled “Quantification of Human Physiological Response to Toxic Substances” should be left in the section on “Mathematical Modelling and Numerical Simulation” or placed in the section on “Applications”. Perhaps Kulish as the author is the deciding factor, and it should remain where it is in proximity to Kulish’s other papers. Thus, the chapter order becomes:

1. Anatomy and Physiology of the Human Respiratory System
2. Fundamentals of Alveolar Gas Diffusion – Physiological Aspects Mathematical Modelling and Numerical Simulation
3. Lung Gas Composition and Transfer Analysis: O2 and CO2 Diffusion Coefficients and Metabolic Rates
4. Lung Ventilation Modelling and Assessment
5. Alveolar Gas Diffusion – Numerical Modelling and Visualisation
6. Impact of Microscopic Solid Particles on Alveolar Diffusion
7. Quantification of Human Physiological Response to Toxic Substances
8. Anatomically-based Modelling of Pulmonary Structure Applications
9. Applied Chest-Wall Vibration Therapy for Patients with Obstructive Lung Disease
10. Indicator for Lung Status in a Mechanically Ventilated COPD Patient using Lung Ventilation Modelling and Assessment
11. Mechanics of Proportional Assist Ventilation
Human Respiration
Anatomy and Physiology, Mathematical Modeling, Numerical Simulation and Applications

Editor: V. Kulish
Human Respiration
Anatomy and Physiology, Mathematical Modeling, Numerical Simulation and Applications

Series: Advances in Bioengineering Volume 3

Even in ancient times, breathing was believed to be the most important feature of life itself. The very Universe was viewed as a huge breathing organism, within which every part was related to everything else through a process of vibration— or breath. Nowadays, our understanding of the laws governing the Universe and life has advanced tremendously. Yet this has not changed our perception of breathing as one of the most important mechanisms of life support.

Books on human respiration are usually written either only by physicians or engineers. This book became possible as a result of a decade of research collaboration between physicians, engineers, physicists and applied mathematicians. Consequently, this volume presents the latest developments and major challenges in the area of biomedical engineering concerned with studies of the human respiratory system.

The contributors cover the anatomy and physiology of human respiration, some of the newest macro- and microscopic models of the respiratory system, numerical simulation and computer visualisation of gas transport phenomena, and applications of these models to medical diagnostics, treatment and safety.

Titles of related interest:

Modelling and Medicine in Biology VI
Editors: M. URSINO, C. A. BREBBIA, G. PONTRELLI & E. MAGOSSO
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Haemodynamics of Arterial Organs:Comparisons of Computational Predictions with In Vitro and In Vivo Data
Editors: X. Y. XU & M. W. COLLINS
Series: Advances in Computational Bioengineering, Volume 1

ISSN: 1464-9292
Chapter 3
Lung-gas composition and transfer analysis: O₂ and CO₂ diffusion coefficients and metabolic rates ........................................ 77
D.N. Ghista, K.M. Loh & D. Ng

1 Introduction .............................................................................. 77
2 Lung-air composition analysis (and O₂ consumption and CO₂ production rates) .......................................................... 78
  2.1 Calculation of O₂ consumption rate and CO₂ production rate ...... 78
  2.2 Dead-space air composition ................................................. 79
  2.3 Alveolar air composition and partial pressures ......................... 80
3 Lung gas-exchange model and parametric analysis ....................... 81
  3.1 Expressions for \(D_{O_2}\) and \(D_{CO_2}\) ........................................ 81
  3.2 Alveolar O₂ and CO₂ partial-pressure expressions ..................... 85
  3.3 Arterial and venous O₂ and CO₂ partial-pressure expressions ...... 86
  3.4 Sequential procedure to compute \(D_{O_2}\) and \(D_{CO_2}\) .................. 88
  3.5 Determining \(D_{O_2}\) and \(D_{CO_2}\) ............................................. 89
4 Case studies .............................................................................. 90

Chapter 4
Lung ventilation modeling and assessment ..................................... 95
D.N. Ghista, K.M. Loh & M. Damodaran

1 Introduction .............................................................................. 95
  1.1 Role of lung ventilation ....................................................... 95
2 Lung ventilation performance using a linear first-order model ......... 96
3 Ventilatory Index ..................................................................... 101
  3.1 Noninvasively determinable ventilatory index ......................... 101
4 Variations in \(R\) and \(C\) during a respiratory cycle (towards nonlinear) .......................................................... 103
  4.1 Nonlinear compliance ...................................................... 104
5 Work of breathing (WOB) ........................................................ 106
6 Second-order model for single-compartment lung model ............... 108
7 Two-compartmental linear model .............................................. 110
  7.1 Two compartmental model using first order ventilatory model .......... 112
     7.1.1 Stiff right lung (with compliance problems) ..................... 115
     7.1.2 Right lung with \(R\) problems ........................................ 115

Chapter 5
Modeling of two-phase flow in the human respiratory system ........... 117
V.V. Kulish, B. Wijayanto & C.S. Lim

1 Introduction .............................................................................. 117
2 Methodology ........................................................................... 118
  2.1 Geometry of the human respiratory duct ............................... 118
CHAPTER 3

Lung-gas composition and transfer analysis: 
O₂ and CO₂ diffusion coefficients and 
metabolic rates

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Abstract

The primary function of the lung is to (i) oxygenate the blood and thereby provide oxygen to the cells for metabolism purposes, and (ii) to remove the collected CO₂ from the pulmonary blood. Herein, we will analyze the compositions of the inspired and expired air per breath, and from there compute the O₂ consumption and CO₂ production rates. Next, we derive expressions for diffusion coefficients \( D_{O₂} \) and \( D_{CO₂} \) in terms of the evaluated cardiac output, O₂ and CO₂ concentrations in arterial and venous blood, alveolar and blood O₂ and CO₂ partial pressures. We then take up a typical case study, and demonstrate the computation of \( D_{O₂} \) and \( D_{CO₂} \), to represent the lung-performance capability to oxygenate the blood.

1 Introduction

The lung-functional performance is characterized by (i) its ventilatory capacity, to bring air (and hence O₂) into the alveoli, and (ii) its capacity to transfer O₂ and CO₂ into and from the pulmonary capillary bed. Hence, the O₂ and CO₂ diffusion coefficients as well as the O₂ consumption rate and the CO₂ production rate represent the lung-performance indices.
2 Lung-air composition analysis (and O₂ consumption and CO₂ production rates)

We carry out a mass-balance analysis, involving:

(i) compositions of air breathed in and out
(ii) consumption or losses of O₂, CO₂ and H₂O.

Table 1 provides clinical data on partial pressures and volumes of N₂, O₂, CO₂ and H₂O of atmospheric air breathed in and expired out, one breath cycle. The monitored breathing rate (BR) = 12 breaths/min, and we assume $P_{H₂O}$ at 37°C = 47 mmHg.

It can be noted that the expired air volume exceeds the inspired air volume for this particular breath cycle. The H₂O loss of 30.1 ml (=32.6–2.5 ml) contributes the major portion of this difference.

2.1 Calculation of O₂ consumption rate and CO₂ production rate

We now determine the O₂ consumption rate and CO₂ production rates from the inspired and expired gases.

Assuming the patient breathes at 12 times per minute we have

\[
O₂ \text{ Consumption Rate} = (\text{Inspired O₂} - \text{Expired O₂}) \times 12
\]

\[= (104.2 - 80.6) \times 12\]

\[= 283.2 \text{ ml/min}\]

<table>
<thead>
<tr>
<th>Respiratory gases</th>
<th>Atmospheric air</th>
<th>Expired air</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmHg</td>
<td>ml/%</td>
</tr>
<tr>
<td>N₂</td>
<td>597</td>
<td>393.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>78.55%</td>
</tr>
<tr>
<td>O₂</td>
<td>159</td>
<td>104.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20.84%</td>
</tr>
<tr>
<td>CO₂</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.04%</td>
</tr>
<tr>
<td>H₂O</td>
<td>3.7</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.49%</td>
</tr>
<tr>
<td>Total</td>
<td>760</td>
<td>500</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100%</td>
</tr>
</tbody>
</table>
CO$_2$ Production Rate = (Expired CO$_2$ – Inspired CO$_2$) × 12
= (19.1 – 0.2) × 12
= 226.8 ml/min

The amount of water vapor in the humidified expired air amounts to 6.2% of the expired air (compared to 0.49% of the dry inspired air) corresponding to the partial-pressure ratio of water vapor in the expired air (= 47/760). The volume of the dry expired air = (525.3 – 32.6) ml = 492.7 ml.

Now, assume that out of 500 ml of inspired air, the dead-space air volume (not taking part in the gas-transfer process) is 150 ml and the alveolar air volume is 350 ml. We next compute the dead-space air volume composition.

2.2 Dead-space air composition

The clinical data of expired air composition is:

N$_2$ = 393.1 ml
O$_2$ = 83.36 ml
CO$_2$ = 16.87 ml
H$_2$O = 34.15 ml
Total = 527.49 ml

Now, the dead-space air will be made up of (i) a dry air portion from the inspired air (assumed to be = 141 ml), plus (ii) the water vapor taken up by the dry air
(estimated to be \( = 9 \) ml) since the expired air portion of 141 ml will not have undergone \( \text{O}_2 \) and \( \text{CO}_2 \) transfer, its composition is the same as that of the inspired air:

\[
\text{N}_2 = 111 \text{ ml (78.55\%), } \text{O}_2 = 29.40 \text{ ml (20.84\%), } \text{CO}_2 = 0.06 \text{ ml (0.04\%), } \text{H}_2\text{O} = 0.69 \text{ ml (0.49\%)}.
\]

When this inspired air (in the dead space) of 141 ml is fully humidified, it will take up a further \( X \) ml of \( \text{H}_2\text{O} \) vapor, in the ratio of the partial pressures, as:

\[
\frac{X}{141} = \frac{47}{713} = 0.0659
\]

\[
\therefore X = 0.0659 \times 141 = 9.29 \text{ ml of } \text{H}_2\text{O} \text{ vapor (which is close to our estimate).}
\]

So, by adding 9.29 ml of \( \text{H}_2\text{O} \) vapor to 0.69 ml of water vapor in the inspired air volume of 141 ml, the total water vapor in the dead-space air is 9.98 ml. The humidified dead-space air composition will be:

\[
\begin{align*}
\text{N}_2 &= 111.00 \text{ ml (73.78\%)} \\
\text{O}_2 &= 29.40 \text{ ml (19.55\%)} \\
\text{CO}_2 &= 0.06 \text{ ml (0.04\%)} \\
\text{H}_2\text{O} &= 9.98 \text{ ml (6.63\%)} \\
\text{Total} &= 150.44 \text{ ml}
\end{align*}
\]

### 2.3 Alveolar-air composition and partial pressures

We can now compute the alveolar air composition, by subtracting the dead-space air from the expired air. These values are tabulated in column 4 of the table below.

Finally, we compute the partial pressure of \( \text{O}_2 \) and \( \text{CO}_2 \) (as well as of \( \text{N}_2 \) and \( \text{H}_2\text{O} \)), so that we can determine next the diffusion coefficients of \( \text{O}_2 \) and \( \text{CO}_2 \) based on the monitoring of arterial and venous blood concentrations. These values are tabulated in column 5 of the below table.

<table>
<thead>
<tr>
<th></th>
<th>Expired air (ml)</th>
<th>Dead-space air (ml)</th>
<th>Alveolar air (ml)</th>
<th>Alveolar-air partial pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{N}_2 )</td>
<td>393.1</td>
<td>111.00</td>
<td>282.1</td>
<td>569.41</td>
</tr>
<tr>
<td>( \text{O}_2 )</td>
<td>80.53</td>
<td>29.40</td>
<td>51.13</td>
<td>103.21</td>
</tr>
<tr>
<td>( \text{CO}_2 )</td>
<td>19.12</td>
<td>0.06</td>
<td>19.06</td>
<td>38.47</td>
</tr>
<tr>
<td>( \text{H}_2\text{O} )</td>
<td>34.21</td>
<td>9.98</td>
<td>24.23</td>
<td>48.91</td>
</tr>
<tr>
<td>Total</td>
<td>526.96</td>
<td>150.44</td>
<td>376.52</td>
<td>760</td>
</tr>
</tbody>
</table>
3 Lung gas-exchange model and parametric analysis

3.1 Expressions for \( D_{O_2} \) and \( D_{CO_2} \)

The gas exchange between the alveolar air and pulmonary capillary blood is represented by the following \( O_2 \) and \( CO_2 \) conservation equations (Fig. 2):

\[
Q^{VE} C^{VE}_{O_2} = Q^{AE} C^{AE}_{O_2} + \dot{V} O_2 \quad \text{(from the alveolar air to capillary blood)}
\]

\[
= Q^{AE} C^{AE}_{O_2} + (\Delta P^{O_2}_{av}) D_{O_2}; \quad P_{O_2}^{cap} = P^{AE}_{O_2},
\]

in which \( P_{O_2}^{cap} = P^{PBB}_{O_2} \) (\( O_2 \) concentration of the preoxygenated blood)

\[
Q^{VE} C^{VE}_{CO_2} = Q^{AE} C^{AE}_{CO_2} - \dot{V} CO_2
\]

\[
= Q^{AE} C^{AE}_{CO_2} - (\Delta P^{CO_2}_{av}) D_{CO_2}; \quad P_{CO_2}^{cap} = P^{VE}_{CO_2},
\]

in which \( P_{CO_2}^{cap} = P^{PBB}_{CO_2} \) (\( CO_2 \) concentration of the preoxygenated blood).

wherein

(i) \( Q^{AB} \) and \( Q^{VB} \) are arterial and venous blood flow-rates;

(ii) \( P^{al}_{O_2} \) and \( P^{cap}_{O_2} \) are the alveolar and capillary \( O_2 \) partial pressures

(iii) \( P^{al}_{CO_2} \) and \( P^{cap}_{CO_2} \) are the alveolar and capillary \( CO_2 \) partial pressures

(iv) \( D_{O_2} \) and \( D_{CO_2} \) are the \( O_2 \) and \( CO_2 \) diffusion coefficients

(v) \( \Delta P^{O_2}_{av} \) = average of \( (P^{al}_{O_2} - P^{cap}_{O_2}) \) over the capillary length;

\( \Delta P^{CO_2}_{av} \) = average of \( (P^{al}_{CO_2} - P^{cap}_{CO_2}) \) over the capillary length.

Now we can equate the arterial and venous blood flow rates, as

\[
Q^{AB} - Q^{VB} = Q - (SV)/(EP) \simeq CO/60,
\]

\( SV, EP \) and \( CO \) being the stroke volume, ejection period and cardiac output, respectively. Hence the above equations can be rewritten as:

(vi) \( \dot{V} O_2 \) is the \( O_2 \) transfer rate from alveolar air to capillary blood (= \( O_2 \) consumption rate), \( \dot{V} CO_2 \) is the \( CO_2 \) transfer rate from capillary blood to alveolar air.

![Figure 2: Schematic of blood-gas concentration in the pulmonary capillary.](image-url)
From eqn. (1):

\[ Q^{VE} C^{VE}_{O_2} = Q^{AB} C^{AB}_{O_2} + (\Delta P^{O_2}_{av})D_{O_2}; \quad P^{cap}_{O_2} = P^{AE}_{O_2} = P_{O_2} \]

\[ Q^{VE} C^{VE}_{O_2} = Q^{AB} C^{AB}_{O_2} + (\Delta P^{O_2}_{av})D_{O_2} \]

\[ D_{O_2} = \frac{Q(C^{VE}_{O_2} - C^{AE}_{O_2})}{(\Delta P^{O_2}_{av})} = \frac{Q(C^{AB}_{O_2} - C^{VB}_{O_2})}{(\Delta P^{O_2}_{av})}. \]  

From eqn. (2):

\[ Q^{VE} C^{VE}_{CO_2} = Q^{AE} C^{AE}_{CO_2} - (\Delta P^{CO_2}_{av})D_{CO_2}; \quad P^{cap}_{CO_2} = P^{AE}_{CO_2} = P^{VB}_{CO_2} \]

\[ Q^{VE} C^{VE}_{CO_2} = Q^{AE} C^{AE}_{CO_2} - (\Delta P^{CO_2}_{av})D_{CO_2} \]

\[ D_{CO_2} = \frac{Q(C^{VE}_{CO_2} - C^{AB}_{CO_2})}{(\Delta P^{CO_2}_{av})}. \]  

wherein

(i) \( Q \), \( C^{VE}_{O_2} \) and \( C^{AE}_{O_2} \), \( C^{VE}_{CO_2} \) and \( C^{AE}_{CO_2} \) can be monitored because

\( C^{VE}_{O_2} \) and \( C^{VE}_{CO_2} \) = \( C^{AB}_{O_2} \) and \( C^{AB}_{CO_2} \) and \( C^{AE}_{O_2} \) and \( C^{AE}_{CO_2} \) = \( C^{VB}_{O_2} \) and \( C^{VB}_{CO_2} \)

(ii) \( D_{O_2} \) and \( D_{CO_2} \) (eqns. (3) and (4)) represent the lung gas-exchange parameters.

Now from eqns. (3) and (4), if we want to evaluate the diffusion coefficients \( D_{O_2} \) and \( D_{CO_2} \), we need to also express \( P_{O_2}^{al} \), \( P_{O_2}^{cap} \) and \( P_{CO_2}^{al} \), \( P_{CO_2}^{cap} \) in terms of monitorable quantities. In this regard,

(i) Alveolar \( P_{O_2}^{al} \) can be expressed in terms of \( \hat{V} \) (the ventilation rate) and \( \hat{V}_{O_2} \) (the \( O_2 \) consumption rate) as Fig. 3:

\[ P_{O_2}^{al} = k_1 \left[ 1 - e^{-k_2 \left( \frac{\hat{V}}{\hat{V}_m} / \hat{V}_{O_2} \right)} \right], \]  

where \( \hat{V}_m \) is the maximum ventilation rate and \( \hat{V}_{O_2} \) (the \( O_2 \) consumption rate or absorption rate from the alveoli) = \( Q(C^{AB}_{O_2} - C^{VB}_{O_2}) \). Equation (5) implies that as \( (\hat{V} / \hat{V}_m) \) increases, (the exponential term decreases, and) \( P_{O_2}^{al} \) increases (as in Fig. 3), and as \( \hat{V}_{O_2} \) increases \( P_{O_2}^{al} \) decreases (as in Fig. 3).

(ii) Alveolar \( P_{CO_2}^{al} \) can be expressed in terms of \( \hat{V} \) and \( \hat{V}_{O_2} \) as in Fig. 4.

\[ P_{CO_2}^{al} = k_3 e^{-k_4 \left( \frac{\hat{V}}{\hat{V}_m} / \hat{V}_{CO_2} \right)}, \]  

where \( \hat{V}_{CO_2} \) (the \( CO_2 \) production rate or excretion rate from the blood) = \( Q(C^{VB}_{CO_2} - C^{AB}_{CO_2}) \). This equation implies that as \( \hat{V} / \hat{V}_m \) increases, \( P_{CO_2}^{al} \) decreases; also, as \( \hat{V}_{CO_2} \) increases (the exponential term decreases, and hence) \( P_{CO_2}^{al} \) increases.
Figure 3: Effect on alveolar $P_{O_2}$ of (i) alveolar ventilation, and (ii) rate of oxygen absorption from alveolar $P_{O_2}$ or $O_2$ consumption rate [from Guyton (1971), p. 476].

Figure 4: Effect on alveolar $P_{CO_2}$ of alveolar ventilation and rate of carbon dioxide excretion from the blood or CO$_2$ production rate [from Guyton (1971), p. 476].

(iii) Blood $P_{O_2}$ can be obtained in terms of blood CO$_2$, from the $O_2$ disassociation curve (providing concentrations in arterial and venous blood), is represented in Fig. 5 as:

$$C_{O_2} = C_{O_2}^m \left(1 - e^{-k_{P_{O_2}} P_{O_2}}\right), \quad \text{or} \quad C_{O_2}^v = 1 - e^{-k_{P_{O_2}} P_{O_2}},$$  \hspace{1cm} (7)
Figure 5: $O_2$ dissociation curves, showing the total oxygen in each 100 ml of normal blood, the portion dissolved in the water of the blood [from Guyton [2], p. 485].

Figure 6: The carbon dioxide dissociation curve [from Guyton [2], p. 491].

where
- $C_{O_2}^m$ and $P_{O_2}^m$ are the maximum values of blood $O_2$ partial pressure
- $CO_2^* = CO_2/C_2^m$
- $P_{O_2}^* = P_{O_2}/P_{O_2}^m$.

(iv) Blood $P_{CO_2}$ can be obtained in terms of $C_{CO_2}$, from the $CO_2$ disassociation curve or $CO_2$ concentration in arterial and venous blood can be represented.
as per Fig. 6 as:

\[ C_{\text{CO}_2} = C_{\text{O}_2}^m \left( 1 - e^{-k_2 P_{\text{CO}_2}/P_{\text{CO}_2}^m} \right) \]

or, \[ C_{\text{CO}_2}^* = 1 - e^{-k_2 P_{\text{CO}_2}/P_{\text{CO}_2}^m} = 1 - e^{-k_2 P_{\text{CO}_2}^m}. \] (8)

3.2 Alveolar \( \text{O}_2 \) and \( \text{CO}_2 \) partial-pressure expressions

Now, let us refer eqn. (4) for the \( P_{\text{O}_2}^a \) partial pressure curve (Fig. 3), represented by the equation:

\[
P_{\text{O}_2}^a = k_1 \left[ 1 - e^{-k_2 \left( \frac{\hat{V}}{V_m} \right)} \right]
\]

\[
= k_1 \left[ 1 - e^{-k_2 \left( \frac{\hat{V}^*}{V_m} \right)} \right], \quad \text{where} \quad \hat{V}^* = \frac{\hat{V}}{V_m}
\] (9)

where \( \hat{V} \) is the alveolar ventilation rate (in liters/min), \( V_m \) is the maximum ventilation rate (= 50 l/min) and \( \hat{V}_{\text{O}_2} \) is the \( \text{O}_2 \) consumption rate (in liters/min). Herein, the coefficients \( k_1 \) and \( k_2 \) can be determined by having this equation match the Fig. 3 data. Note, in this equation, when \( \hat{V} = 0, P_{\text{O}_2}^a = 0 \) from the equation, which satisfies the data.

Now for \( \hat{V}_{\text{O}_2} = 0.25 \text{ l/min} \), when \( \hat{V}^* = \frac{\hat{V}}{V_m} = 0.5 \), \( P_{\text{O}_2}^a = 140 \text{ mmHg} \). Hence,

\[
140 = k_1 \left[ 1 - e^{-k_2 \left( \frac{0.5}{0.5} \right)} \right] = k_1 (1 - e^{-2k_2}).
\] (10)

Also, when \( \hat{V}_{\text{O}_2} = 1 \text{ l/min}, \hat{V}^* = 0.3 \text{ l/min}, P_{\text{O}_2}^a = 100 \text{ mmHg} \). Hence

\[
100 = k_1 \left[ 1 - e^{-k_2 \left( \frac{0.3}{0.5} \right)} \right] = k_1 (1 - e^{-0.3k_2}).
\] (11)

From eqns. (10) and (11), we get:

\[
\frac{140}{100} = \frac{k_1 (1 - e^{-2k_2})}{k_1 (1 - e^{-0.3k_2})} = \frac{1 - e^{-2k_2}}{1 - e^{-0.3k_2}}
\]

\[
\therefore \quad 140 - 140e^{-0.3k_2} = 100 - 100e^{-2k_2}
\]
or, \[ 40 = 100e^{-2k_2} + 140e^{-0.3k_2} \], so that \( k_2 = 4.18 \text{ min/l} \). (12)

Upon substituting \( k_2 = 4.18 \text{ min/l} \) into eqn. (10) we obtain:

\[
140 = k_1 (1 - e^{(-2 \times 4.18)}), \quad \text{so that} \quad k_1 \approx 140 \text{ mmHg}.
\] (13)
Hence, the $P^\text{al}_{O_2}$ curve can be represented by:

$$P^\text{al}_{O_2} = 140 \left[ 1 - e^{-4.18 \left( \frac{\tilde{V}^*}{\tilde{V}_{O_2}} \right)} \right], \quad (14)$$

where, $\tilde{V}_{O_2} = Q(C^\text{AB}_{O_2} - C^\text{VB}_{O_2})$ and $\tilde{V}^* = \tilde{V}/501/\text{min}$.

Now, let us look at the $P^\text{al}_{CO_2}$ expression:

$$P^\text{al}_{CO_2} = k_3 e^{-k_4 \left[ \frac{\tilde{V}^*}{\tilde{V}_{m}} \right] \left/ \tilde{V}_{CO_2} \right.} = k_3 e^{-k_4 \left[ \frac{\tilde{V}^*}{\tilde{V}_{CO_2}} \right]}.$$  

We note from Fig. 4 that for $\tilde{V}_{CO_2} = 0.2 \text{l/min}$ and $\tilde{V}_{m} = 0.2$, $P^\text{al}_{CO_2} = 12$. Hence, from the above equation, we get:

$$12 = k_3 e^{-k_4} \quad (15)$$

Also, for $\tilde{V}_{O_2} = 0.8 \text{l/min}$ and $\tilde{V}_{m} = 0.2$, $P^\text{al}_{CO_2} = 62 \text{mmHg}$. Hence

$$62 = k_3 e^{-k_4 \left[ \frac{\tilde{V}^*}{\tilde{V}_{CO_2}} \right]} = k_3 e^{-\frac{k_4}{4}}. \quad (16)$$

From eqns. (15) and (16), we get:

$$\frac{12}{62} = \frac{e^{-k_4}}{e^{-\frac{k_4}{4}}} = e^{-\frac{1}{2}k_4}$$

$$\ln \left( \frac{12}{62} \right) = -\frac{2}{3}k_4, \quad \text{so that} \quad k_4 = 2.46. \quad (17)$$

Substituting $k_4 = 2.46$ into eqn. (16), we obtain:

$$62 = k_3 e^{-\frac{2.46}{4}}, \quad \therefore \quad k_3 = 114.68. \quad (18)$$

Hence, the $P^\text{al}_{CO_2}$ curve can be represented as

$$P^\text{al}_{CO_2} = 114.68 e^{-2.46 \left[ \frac{\tilde{V}^*}{\tilde{V}_{m}} \right] \left/ \tilde{V}_{CO_2} \right.}, \quad (19)$$

where $\tilde{V}^* = \tilde{V}/501/\text{min}$ and $\tilde{V}_{CO_2} = Q(C^\text{VB}_{CO_2} - C^\text{AB}_{CO_2})$.

### 3.3 Arterial and venous $O_2$ and $CO_2$ partial-pressure expressions

We now need to express $P^\text{AB}_{O_2}$ and $P^\text{VB}_{CO_2}$ in terms of $C^\text{AB}_{O_2}$ and $C^\text{VB}_{CO_2}$. 


So that let us look at the $O_2$ disassociation curve, as shown in Fig. 5.

$$C_{O_2} = C_{O_2,\text{max}} \left[ 1 - e^{-k_S P_{O_2}/P_{O_2,\text{max}}} \right],$$

or,

$$C_{O_2}^* = 1 - e^{-k_S P_{O_2}^*},$$

where $C_{O_2}^* = \frac{C_{O_2}}{C_{O_2,\text{max}}}$, $P_{O_2}^* = \frac{P_{O_2}}{P_{O_2,\text{max}}}$.

From Fig. 5, at $P_{O_2}^* = \frac{40 \text{ mmHg}}{140 \text{ mmHg}} = 0.29$ (for normal venous blood), and

$$C_{O_2}^* = \frac{15}{20} = 0.75.$$

Hence from eqn. (20):

$$0.75 = 1 - e^{-0.29k_S}$$

$$\therefore k_S = 4.78.$$  \hspace{1cm} (21)

Also, $P_{O_2}^* = \frac{95 \text{ mmHg}}{140 \text{ mmHg}} = 0.68$ (for normal arterial blood), and

$$C_{O_2}^* = \frac{19}{20} = 0.95.$$

Hence from eqn. (20):

$$0.95 = 1 - e^{-0.68k_S}, \text{ or } k_S = 4.4.$$  \hspace{1cm} (22)

So, we take the average value of $k_S$:

$$\therefore k_S = \frac{(4.78 + 4.4)}{2} = 4.59.$$  \hspace{1cm} (23)

Then the $O_2$ disassociation curve is given by:

$$C_{O_2} = C_{O_2}^B = 0.2 \left[ 1 - e^{-4.59 \left( \frac{P_{O_2}}{140} \right)} \right],$$  \hspace{1cm} (24)

and

$$P_{O_2} = \frac{140}{4.59} \ln \left[ \frac{0.2}{0.2 - C_{O_2}^B} \right] = 30.5 \ln \left[ \frac{0.2}{0.2 - C_{O_2}^B} \right].$$  \hspace{1cm} (25)

Finally, we look at the $CO_2$ disassociation curve

$$C_{CO_2} = C_{CO_2,\text{max}} \left( 1 - e^{-k_6 P_{CO_2}/P_{CO_2,\text{max}}} \right),$$

or,

$$C_{CO_2}^* = 1 - e^{-k_6 P_{CO_2}^*} = 1 - e^{-k_6 P_{CO_2,\text{max}}}.$$  \hspace{1cm} (26)
Based on Fig. 6, when \( P_{\text{CO}_2}^* = \frac{20 \text{ mmHg}}{140 \text{ mmHg}} = 0.14, \ C_{\text{CO}_2}^* = \frac{38}{80} = 0.475 \), so that
\[
0.475 = 1 - e^{-0.14k_6}, \quad k_6 = 4.60, \tag{27}
\]
when \( P_{\text{CO}_2}^* = \frac{70 \text{ mmHg}}{140 \text{ mmHg}} = 0.5, \ C_{\text{CO}_2}^* = \frac{60}{80} = 0.75 \), so that
\[
0.75 = 1 - e^{-0.5k_6}, \quad k_6 = 2.77. \tag{28}
\]
So, we take the average value of \( k_6 \):
\[
k_6 = \frac{(4.60 + 2.77)}{2} = 3.69. \tag{29}
\]
Then the CO\(_2\) concentration is given (from eqns. (26–29) by:
\[
C_{\text{CO}_2} = C_{\text{CO}_2}^B = 0.8 \left[ 1 - e^{-4.71 \left( \frac{P_{\text{CO}_2}}{140} \right)} \right] \tag{30}
\]
and
\[
P_{\text{CO}_2} = 29.72 \ln \left[ \frac{0.8}{0.8 - C_{\text{CO}_2}^B} \right]. \tag{31}
\]

### 3.4 Sequential procedure to compute \( D_{\text{O}_2} \) and \( D_{\text{CO}_2} \)

1. We first monitor: \( V(t) \), \( \dot{V}(t) \), \( \text{SV} \) (stroke volume), \( \text{EP} \) (cardiac ejection period), \( C_{\text{O}_2}^V \), \( C_{\text{O}_2}^A \), \( C_{\text{O}_2}^B \), \( C_{\text{O}_2}^C \), \( C_{\text{CO}_2}^A \) (O\(_2\) and CO\(_2\) concentrations in pre oxygenated and post oxygenated blood).
2. We substitute the values of \( C_{\text{O}_2}^{AB} (=C_{\text{O}_2}^{VE}) \) and \( C_{\text{O}_2}^{VB} (=C_{\text{O}_2}^{AE}) \) into eqn. (3), and
   the values of \( C_{\text{CO}_2}^{AB} (=C_{\text{CO}_2}^{VE}) \) and \( C_{\text{CO}_2}^{VB} (=C_{\text{CO}_2}^{AE}) \) into eqn. (4).
3. We next determine:
   \[
   Q = \text{SV/ejection period}, \tag{32}
   \]
   \[
   \dot{V}_{\text{O}_2}(t) = Q(C_{\text{O}_2}^{AB} - C_{\text{O}_2}^B). \tag{33}
   \]
   \[
   \dot{V}_{\text{CO}_2}(t) = Q(C_{\text{CO}_2}^{VB} - C_{\text{CO}_2}^{AB}). \tag{34}
   \]
4. We then substitute the expressions for \( \dot{V}_{\text{O}_2}(t) \) and \( \dot{V}_{\text{CO}_2}(t) \) into the equations for \( P_{\text{O}_2}^{\text{al}} \) (eqn. (14)) and \( P_{\text{CO}_2}^{\text{al}} \) (eqn. (19)).
5. We substitute the monitored values of \( C_{\text{O}_2}^{VB} (=C_{\text{O}_2}^{AE}) \) and \( C_{\text{CO}_2}^{VB} (=C_{\text{CO}_2}^{AE}) \) into eqns. (25) and (31), to obtain the values of \( P_{\text{O}_2}^{AE} \) and \( P_{\text{CO}_2}^{AE} \).
6. Now, in order to determine the values of the lung gas-exchange parameters \( D_{\text{O}_2} \) and \( D_{\text{CO}_2} \), we substitute into eqns. (3) and (4) for \( Q \) from eqn. (32), \( P_{\text{O}_2}^{\text{al}} \) from eqn. (14), \( P_{\text{CO}_2}^{\text{al}} \) from eqn. (19), \( P_{\text{O}_2}^{\text{VE}} \) from eqn. (26), and \( P_{\text{CO}_2}^{\text{VE}} \) from eqn. (31).
3.5 Determining $D_{O_2}$ and $D_{CO_2}$

Figure 7 illustrates the variation of $\Delta P^O_2 (= P^al_{O_2} - P^{cap}_{O_2} = P^al_{O_2} - P^{AB}_{O_2})$ along the length ($l$) of the capillary bed.

Let $l^* = l/l_m$.

Then we can express:

$$\Delta P^O_2 = \Delta P^O_{\text{max}} f_{O_2}(l^*) .$$  \hspace{1cm} (35)

Then,

$$\Delta P^{O_2}_{\text{av}} = \Delta P^O_{\text{max}} \left( \int_0^1 f_{O_2}(l^*) \, dl^* \right) = \Delta P^O_{\text{max}} (F_{O_2}) .$$  \hspace{1cm} (36)

Based on data [3], since $\Delta P^{O_2}_{\text{av}} = 12 \text{ mmHg}$ for $\Delta P^O_{\text{max}} = 65 \text{ mmHg}$, we have $F_{O_2} = 0.185$.

We can similarly determine the average value of $\Delta P^{CO_2}_{\text{av}}$ from Fig. 8 as:

Let $l^* = l/l_m$.

Then, we can represent Fig. 8 as:

$$\Delta P^{CO_2} = \Delta P^{CO_2}_{\text{max}} f_{O_2}(l^*) .$$  \hspace{1cm} (37)

Then,

$$\Delta P^{CO_2}_{\text{av}} = \Delta P^{CO_2}_{\text{max}} \left( \int_0^1 f_{CO_2}(l^*) \, dl^* \right) = \Delta P^{CO_2}_{\text{max}} (F_{CO_2}) .$$  \hspace{1cm} (38)

![Diagram of lung gas composition and transfer analysis](image)

Figure 7: Uptake of oxygen by the pulmonary capillary blood. (The curve in this figure was constructed from data in Mihorn and Pulley: Biophys. J., 8: 337,1968). [from Guyton (1971), p. 434.]
Based on data [3], since $\Delta P_{av}^{CO_2} = 0.5 \text{ mmHg}$ for $\Delta P_{max}^{CO_2} = 5 \text{ mmHg}$, we have $F_{CO_2} = 0.1$.

From the $\Delta P_{av}^{O_2}$ and $\Delta P_{av}^{CO_2}$ expressions, we can determine the $O_2$ consumption and the $CO_2$ production rates, as follows:

$$D_{O_2} = \frac{\text{Total } O_2 \text{ consumed}}{\Delta P_{av}^{O_2}} = \frac{\bar{V}_{O_2}}{\Delta P_{av}^{O_2}} = \frac{Q (c_{O_2}^{AB} - c_{O_2}^{VB})}{\Delta P_{av}^{O_2}} \tag{39}$$

$$D_{CO_2} = \frac{\text{Total } CO_2 \text{ produced}}{\Delta P_{av}^{CO_2}} = \frac{\bar{V}_{CO_2}}{\Delta P_{av}^{CO_2}} = \frac{Q (c_{CO_2}^{VB} - c_{CO_2}^{AB})}{\Delta P_{av}^{CO_2}} \tag{40}$$

4 Case studies

(A) We monitor the partial pressures blood concentrations of $O_2$ and $CO_2$ as:

$$c_{O_2}^{AE} = c_{O_2}^{VE} = 0.13, \quad c_{O_2}^{AB} = c_{O_2}^{VB} = 0.18, \quad c_{O_2}^{AE} = c_{CO_2}^{VB} = 0.525, \quad c_{CO_2}^{AE} = c_{CO_2}^{AB} = 0.485.$$

From eqn. (26), we obtain:

$$P_{O_2}^{VB} = 30.5 \ln \left[ \frac{0.2}{0.2 - c_{O_2}^{VB}} \right] = 29.72 \ln \left[ \frac{0.2}{0.2 - 0.13} \right]$$

$$= 32.02 \text{ mmHg}. \tag{41}$$
From eqn. (31), we obtain:

\[
P^\text{VB}_{\text{CO}_2} = 37.94 \ln \left[ \frac{0.8}{0.8 - C^\text{VB}_{\text{CO}_2}} \right] = 37.94 \ln \left[ \frac{0.8}{0.8 - 0.525} \right] = 40.51 \text{ mmHg.} \quad (42)
\]

We now also monitor \( Q = 51/\text{min}, \ \hat{V}^* = 0.1 \) and \( \hat{V} = 51/\text{min} \).

Then, from eqn. (33):

\[
\hat{V}_{\text{O}_2}(t) = Q \left( C^\text{AB}_{\text{O}_2} - C^\text{VB}_{\text{O}_2} \right),
\]

so that from the above data,

\[
\hat{V}_{\text{O}_2}(t) = 5000 \times 0.05 = 250 \text{ ml O}_2/\text{min Consumption rate} \quad (43)
\]

From eqn. (34):

\[
\hat{V}_{\text{CO}_2}(t) = Q \left( C^\text{VB}_{\text{CO}_2} - C^\text{AB}_{\text{CO}_2} \right) = 5000(0.04) = 200 \text{ ml CO}_2/\text{min production rate.} \quad (44)
\]

Now, from eqn. (14).

For \( \hat{V}^* = 0.1 \) and \( \hat{V}_{\text{O}_2} = 0.25 \), we obtain \( P^\text{al}_{\text{O}_2} \):

\[
P^\text{al}_{\text{O}_2} = 140 \left[ 1 - e^{-4.18 \left( \hat{V}^*/\hat{V}_{\text{O}_2} \right)} \right],
\]

\[
= 140 \left[ 1 - e^{-4.18[0.1/0.25]} \right] = 113.7 \text{ mmHg.} \quad (45)
\]

From eqn. (19), for \( \hat{V}^* = 0.1 \) and \( \hat{V}_{\text{CO}_2} = 0.20 \), we obtain \( P^\text{al}_{\text{CO}_2} \):

\[
P^\text{al}_{\text{CO}_2} = 107.18e^{-2.19 \left( \hat{V}^*/\hat{V}_{\text{CO}_2} \right)} = 107.18e^{-2.19[0.1/0.2]} = 35.86 \text{ mmHg.} \quad (46)
\]

Now, we can evaluate the diffusion coefficients:

From eqns. (3), (36), (41), and (45):

\[
D_{\text{O}_2} = \frac{Q(C^\text{AB}_{\text{O}_2} - C^\text{VB}_{\text{O}_2})}{\Delta P^\text{al}_{\text{O}_2}}
= \frac{5000(0.18 - 0.13)}{(113.7 - 31.2) \times 0.18} = 16.84 \text{ ml O}_2/\text{min/mmHg.} \quad (47)
\]
From eqn. (4):

\[ D_{CO2} = \frac{Q(C_{CO2}^{VB} - C_{CO2}^{AB})}{\Delta P_{av}^{CO2}} = \frac{5000(0.04)}{(40.51 - 35.86) \times 0.1} = 430.11 \text{ ml} CO_2/\text{min/mmHg}. \]  

(48)

(B) Alternately, we derive data from:

(i) the inspired and expired air analysis (such as that carried out in Section 2.3):

O2 consumption rate = 283.2 ml/min,
CO2 production rate = 226.8 ml/min,
\[ P^{al}_{O2} = 103.03 \text{ mmHg and } P^{al}_{CO2} = 38.41 \text{ mmHg} \]

and

(ii) venous blood gas analysis:

\[ C_{O2}^{VB} = 0.13, C_{CO2}^{VB} = 0.548. \]

Then, as per eqn. (41),

\[ P_{O2}^{VB} = 31.2 \text{ mmHg}, \]

(49)

corresponding to \( C_{O2}^{VB} = 0.13 \) and, as per eqn. (42):

\[ P_{CO2}^{VB} = 37.94 \ln \left( \frac{0.8}{0.8 - C_{CO2}^{VB}} \right) = 37.94 \ln \left( \frac{0.8}{0.8 - 0.548} \right) = 43.84 \text{ mmHg}. \]

(50)

We obtain, from air-composition analysis, that \( \dot{V}_{O2}(t) = 283.3 \text{ ml/min} \)  

(51)

and \( \dot{V}_{CO2}(t) = 226.8 \text{ ml/min} \).

(52)

Hence,

\[ DO2 = \frac{\dot{V}_{O2}}{\Delta P_{av}^{O2}} = \frac{283.2}{(103.03 - 31.2) \times 0.18} = 21.90 \text{ mlO2/min/mmHg}, \]

(53)

and

\[ DCO2 = \frac{\dot{V}_{CO2}}{\Delta P_{av}^{CO2}} = \frac{226.8}{(43.84 - 38.41) \times 0.1} = 417.68 \text{ mlCO2/min/mmHg}. \]

(54)

The advantage of this method (B) over (A) is that it does not require monitoring of the cardiac output, and is hence simpler to implement clinically.
References


$O_2$ consumption
rate

$CO_2$ production
rate

Concentration
$C_{O_2}$
$C_{CO_2}$

Lung Air Composition
Dead Space Air

$D_{O_2}$

$D_{CO_2}$

Partial Pressure
$P_{O_2}^{al}$
$P_{CO_2}^{al}$
### TABLE – 1: Nomenclature

<table>
<thead>
<tr>
<th>SYMBOL</th>
<th>MEANING</th>
<th>UNITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C$</td>
<td>Lung Compliance</td>
<td>$(cmH_2O)^{-1}$</td>
</tr>
<tr>
<td>$C_a$</td>
<td>Average Lung Compliance</td>
<td>$(cmH_2O)^{-1}$</td>
</tr>
<tr>
<td>$R$</td>
<td>Lung air-flow resistance</td>
<td>$cmH_2Osl^{-1}$</td>
</tr>
<tr>
<td>$R_a$</td>
<td>Average Lung air-flow resistance</td>
<td>$cmH_2Osl^{-1}$</td>
</tr>
</tbody>
</table>

### TABLE 2: ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTI</td>
<td>Lung-Ventilatory Index</td>
</tr>
<tr>
<td>WOB</td>
<td>Work of Breathing</td>
</tr>
</tbody>
</table>
Human Respiration
Anatomy and Physiology, Mathematical Modeling, Numerical Simulation and Applications
Series: Advances in Bioengineering Volume 3

Even in ancient times, breathing was believed to be the most important feature of life itself. The very Universe was viewed as a huge breathing organism, within which every part was related to every other through a process of vibration – or breath. Nowadays, our understanding of the laws governing the Universe and life has advanced tremendously. Yet this has not changed our perception of breathing as one of the most important mechanisms of life support.

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ISSN: 1464-9292
Chapter 3
Lung-gas composition and transfer analysis: \( O_2 \) and \( CO_2 \) diffusion coefficients and metabolic rates .................................................. 77
*D.N. Ghista, K.M. Loh & D. Ng*

1 Introduction .................................................................................................................. 77
2 Lung-air composition analysis (and \( O_2 \) consumption and \( CO_2 \) production rates) ......................................................................................................................... 78
   2.1 Calculation of \( O_2 \) consumption rate and \( CO_2 \) production rate .......... 78
   2.2 Dead-space air composition ................................................................. 79
   2.3 Alveolar air composition and partial pressures ................................. 80
3 Lung gas-exchange model and parametric analysis ............................................. 81
   3.1 Expressions for \( D_{O_2} \) and \( D_{CO_2} \) .................................................. 81
   3.2 Alveolar \( O_2 \) and \( CO_2 \) partial-pressure expressions .......................... 85
   3.3 Arterial and venous \( O_2 \) and \( CO_2 \) partial-pressure expressions ............... 86
   3.4 Sequential procedure to compute \( D_{O_2} \) and \( D_{CO_2} \) ...................... 88
   3.5 Determining \( D_{O_2} \) and \( D_{CO_2} \) ........................................ 89
4 Case studies ............................................................................................................... 90

Chapter 4
Lung ventilation modeling and assessment............................................................... 95
*D.N. Ghista, K.M. Loh & M. Damodaran*

1 Introduction .................................................................................................................. 95
   1.1 Role of lung ventilation ................................................................. 95
2 Lung ventilation performance using a linear first-order model ........................................ 96
3 Ventilatory Index ................................................................................................. 101
   3.1 Noninvasively determinable ventilatory index ................................. 101
4 Variations in \( R \) and \( C \) during a respiratory cycle (towards nonlinear) ............ 103
   4.1 Nonlinear compliance: ....................................................................... 104
5 Work of breathing (WOB) .................................................................................... 106
6 Second-order model for single-compartment lung model ....................................... 108
7 Two-compartmental linear model ......................................................................... 110
   7.1 Two compartmental model using first order ventilatory model .......... 112
      7.1.1 Stiff right lung (with compliance problems) ............................... 115
      7.1.2 Right lung with \( R \) problems ............................................. 115

Chapter 5
Modeling of two-phase flow in the human respiratory system .................................. 117
*Y.V. Kulish, B. Wijayanto & C.S. Lim*

1 Introduction ............................................................................................................... 117
2 Methodology .......................................................................................................... 118
   2.1 Geometry of the human respiratory duct ............................................. 118
CHAPTER 4

Lung ventilation modeling and assessment

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Abstract

We have developed a lung-ventilation model by modeling the lung-volume response to mouth minus pleural driving pressure (by means of first- and second-order differential equations) in terms of resistance to airflow \( R \) and the lung compliance \( C \). The lung-volume solution of the differential equation is matched with the clinical-volume data, to evaluate the parameters, \( R \) and \( C \). These parameter values can help us to distinguish an obstructive lung and a lung with stiffened parenchyma from a normal lung, and hence diagnose lung diseases such as asthma and emphysema.

We have also formulated a nonlinear compliance lung model, and demonstrated deceased lung compliance with filling volume. We then formulated a nondimensional lung-ventilatory index \( VTI \), incorporating the parameters \( R \) and \( C \) as well as the lung-breathing rate. When the \( VTI \) is evaluated for various lung diseases, it will conveniently enable us to diagnose lung diseases in terms of just one \( VTI \) number. Finally, we have shown how to model a two-lobe lung, and differentiate between normal and diseased lobes.

1 Introduction

1.1 Role of lung ventilation

Lung ventilation constitutes inhalation of an appropriate air volume under driving pressure (=mouth pressure – pleural pressure), so as to: (i) provide an adequate alveolar \( O_2 \) amount at an appropriate partial pressure, (ii) oxygenate the pulmonary blood, and (iii) thereby provide adequate metabolic oxygen to the cells.
Hence, ventilatory function and performance assessment entails determining how much air volume is provided to the alveoli, to make available adequate alveolar oxygen for blood oxygenation and cellular respiration.

Based on Fig. 1, we get:
(i) \( (P_a - P_p) - P_{el} = 0 \)
(ii) \( P_{el} = \frac{2a h}{R r} = 2 T / r = V / C + P_{e10} \)
(iii) \( (P_m - P_a) = R(dV/dt) \)
(iv) \( P_L = P_m - P_p \)
(v) \( R(dV/dt) + V/C = P_L - P_{e10} \) (lung elastic recoil pressure at end of expiration)

2 Lung-ventilation performance using a linear first-order model

We first analyze the lung-ventilation function by means of a very simple model represented by a first-order differential equation \( (Deq) \) in lung-volume \( (V) \) dynamics in response to the driving pressure \( (P_L = \text{atmospheric pressure} - \text{pleural pressure}) \), as displayed in Fig. 1. The clinical pressure-volume data is in Fig. 2.

The model-governing equation (shown derived in Fig. 1) is as follows:

\[
R \ddot{V} + \frac{V}{C} = P_L(t) - P_{e10} = P_N(t),
\]

wherein:
(i) the values of pressure are obtained from the given \( P_L (= P_m - P_p) \) data
(ii) the parameters of this governing \( Deq \) are lung compliance \( (C) \) and airflow resistance \( (R) \); in the equation both \( R \) and \( C \) are instantaneous values
(iii) \( V = V(t) - V_o \) (the lung volume at the end of expiration
(iv) \( P_{e10} \) is the lung elastic-recoil pressure at the end of expiration, and

\[
P_{e10} = P_{el} - \frac{V}{C}.
\]
Figure 2: Lung-ventilatory model and lung-volume and pleural-pressure data. Curve 1 on the curve represents $P_{el}$, the pressure required to overcome lung elastance ($= V/C$). Curve 2 curve represents $P_{pl}$, the summation of $P_{el}$ and $P_{a}$. The pressure $P_{N}(t)$ in eqn. (1a) equals $P_{p}$ minus $P_{el}$ at end of expiration.

At the end of expiration when $\omega t = \omega T, P_{L} = P_{e0} = P_{N}(t)$, which is represented by

$$P_{N}(t) = \sum_{i=1}^{3} P_i \sin (\omega_{i} t + c_i),$$

and the governing eqn. (1a) becomes:

$$RV' + \frac{V}{C} = P_{N}(t) = \sum_{i=1}^{3} P_i \sin (\omega_{i} t + c_i), \quad (2a)$$

where the right-hand side represents the net driving pressure minus pleural pressure $P_{N} = (P_{m} - P_{p}) - P_{e0}$. This $P_{N}$ is, in fact, the driving pressure $(P_{m} - P_{p})$ normalized with respect to its value at end of expiration. Equation (2a) can be rewritten as follows:

$$\frac{\dot{V}}{R} + \frac{V}{RC} = \frac{1}{R} \sum_{i=1}^{3} P_{i} \sin (\omega_{i} t + c_{i}), \quad (2b)$$
wherein the $P(t)$ clinical data (displayed in Fig. 2) is assumed to be represented by:

$$P(t) = \sum_{i=1}^{3} P_i \sin(\omega_i t + c_i).$$  \hspace{1cm} (3)

$$P_1 = 1.581 \text{ cmH}_2\text{O} \hspace{1cm} P_2 = -5.534 \text{ cmH}_2\text{O} \hspace{1cm} P_3 = 0.5523 \text{ cmH}_2\text{O}$$

$$\omega_1 = 1.214 \text{ rad/s} \hspace{1cm} \omega_2 = 0.001414 \text{ rad/s} \hspace{1cm} \omega_3 = 2.401 \text{ rad/s}$$

$$c_1 = -0.3132 \text{ rad} \hspace{1cm} c_2 = 3.297 \text{ rad} \hspace{1cm} c_3 = -2.381 \text{ rad}.$$

The pressure curve (in Fig. 3A) represented by the above eqn. (3) closely matches the pressure data of Fig. 2. If, in eqn. (1), we designate $R_a$ and $C_a$ as the average values (R and C) for the ventilatory cycle, then the solution of eqn. (1) is given by:

$$V(t) = \sum_{i=1}^{3} \frac{P_i C_a [\sin(\omega_i t + c_i) - b_i R_a C_a \cos(\omega_i t + c_i)]}{(1 + \omega_i^2 (R_a C_a)^2)} - H e^{-\frac{t}{\tau_a}}.$$  \hspace{1cm} (4)

wherein the term $(R_a C_a)$ is denoted by $\tau_a$. We need to have $V = 0$ at $t = 0$. Hence, putting $V$ (at $t = 0$) = 0, gives us:

$$H = \sum_{i=1}^{3} \frac{P_i C_a [\sin(\omega_i t + c_i) - b_i R_a C_a \cos(\omega_i t + c_i)]}{(1 + \omega_i^2 (R_a C_a)^2)}.$$  \hspace{1cm} (5)

Then from eqns. (4) and (5), the overall expressions for $V(t)$ becomes

$$V(t) = \sum_{i=1}^{3} \frac{P_i C_a [\sin(\omega_i t + c_i) - \omega_i^2 \tau_a^2 \cos(\omega_i t + c_i)]}{(1 + \omega_i^2 \tau_a^2)}$$

$$- \sum_{i=1}^{3} \frac{P_i C_a [\sin(\omega_i t + c_i) - \omega_i \tau_a \cos(\omega_i t + c_i)]}{(1 + \omega_i^2 \tau_a^2)} e^{-\frac{t}{\tau_a}}$$

$$= \sum_{i=1}^{3} \frac{P_i C_a [\sin(\omega_i t + c_i) - \omega_i \tau_a \cos(\omega_i t + c_i)]}{(1 + \omega_i^2 \tau_a^2)} \left[1 - e^{-\frac{t}{\tau_a}}\right].$$  \hspace{1cm} (6)

We also want that $dV/dt = 0$ at $t = 0$, implying no air-flow at the start of inspiration. So, by differentiating eqn. (6), we get:

$$\dot{V} = \sum_{i=1}^{3} \frac{P_i C_a [\omega_i \cos(\omega_i t + c_i) + \omega_i^2 \tau_a \sin(\omega_i t + c_i)]}{(1 + \omega_i^2 \tau_a^2)} \left[1 - e^{-\frac{t}{\tau_a}}\right]$$

$$+ \sum_{i=1}^{3} \frac{P_i C_a [\sin(\omega_i t + c_i) - \omega_i \tau_a \cos(\omega_i t + c_i)]}{(1 + \omega_i^2 \tau_a^2)} e^{-\frac{t}{\tau_a}}.$$  \hspace{1cm} (7)

From eqn. (7), we get $\dot{V} \neq 0$ at $t = 0$, thereby also satisfying this initial condition.
Figure 3: A The pressure curve represented by eqn. (3) matched against the pressure data (represented by dots). B The volume curve represented by eqn. (6), for from $C_a = 0.2132$ (cmH$_2$O)$^{-1}$ and $R_a = 2.275$ cmH$_2$Osl$^{-1}$ pp. 3 matched against the volume data represented by dots.
Now, by matching the above $V(t)$ expression (6) with the given $V(t)$ data in Fig. 2, and carrying out parameter identification, we can determine the in vivo values of $R_a$ and $C_a$, to be

$$C_a = 0.2132 \text{ (cmH}_2\text{O)}^{-1}, \quad R_a = 2.275 \text{ cmH}_2\text{Os}^{-1}$$

The computed $V(t)$ curve, represented by eqn. (6) for the above values of $C_a$ and $R_a$, is shown in Fig. 3B. We can however analytically evaluate $R_a$ and $C_a$ by satisfying some conditions. For this purpose, we first note that $V$ is maximum (= tidal volume, TV) at about $t = t_T = 2.02$ s. At $t = t_T$, the exponential term $e^{-\frac{t}{t_T}}$ in (6) becomes of the order of $e^{-10}$, and hence negligible. Then by putting $\dot{V}(t = 2.02) = 0$ in eqn. (7), without the exponential term we obtain:

$$\dot{V}_{t=2.02} = \sum_{i=1}^{3} \frac{P_i C_a [\omega_i \cos(\omega_i \times 2.02 + c_i) + \omega_i^2 \tau_a \sin(\omega_i \times 2.02 + c_i)]}{(1 + \omega_i^2 \tau_a^2)} = 0,$$

in which the values of $P_i$, $\omega_i$, and $c_i$ are given by eqn. (3). Then by solving eqn. (8), we get $\tau_a = 0.522$ s. We can also put $\dot{V} = 0$ at $t \simeq 1.81/2.87$ s and obtain a similar value for $\tau_a$.

Then, we also note that at $t_T = 2.02$ s (at which $dV/dt = 0$) and $V = 0.551$. Hence upon substituting into eqn. (6), and neglecting the exponential term, we get the following algebraic equation:

$$V(t)_{t=2.02} = \sum_{i=1}^{3} \frac{P_i C_a [\sin(\omega_i t + c_i) - \omega_i \tau_a \cos(\omega_i t + c_i)]}{(1 + \omega_i^2 \tau_a^2)} = 2.55C_a,$$

by employing the values of $P_i$, $\omega_i$ and $c_i$ from eqn. (3). Now since $V(t = 2.02) = 0.551$, we get

$$2.55C_a = 0.55 \quad \Rightarrow \quad C_a = 0.221 \text{ (cmH}_2\text{O)}^{-1}.$$

We can substitute, therein, the values of $P_1$ and $P_2$ from eqn. (3), and obtain the value of $C_a$ as: $C_a = 0.221 \text{ (cmH}_2\text{O)}^{-1}$. Since we have computed $\tau_a = 0.485$ s, therefore $R_a = 2.275 \text{ (cmH}_2\text{Os)}^{-1}$. These are the average values of resistance to airflow and lung compliance during the ventilatory cycle shown in Fig. 2.

Since lung disease will influence the values of $R$ and $C$, these parameters can be employed to diagnose lung diseases. For instance in the case of emphysema, the destruction of lung tissue between the alveoli produces a more compliant lung, and hence results in a larger value of $C$. In asthma, there is increased airway resistance $(R)$ due to contraction of the smooth muscle around the airways. In fibrosis of the lung, the membranes between the alveoli thicken and hence lung compliance $(C)$ decreases. Thus, by determining the normal and diseased ranges of the parameters $R$ and $C$, we can employ this simple lung-ventilation model for differential diagnosis.
3 Ventilatory index

Let us, however, formulate just one non dimensional number to serve as a ventilatory-performance index $VTI_1$ (to characterize ventilatory function), as:

$$VTI_1 = [(R_a C_a)(\text{Ventilatory rate in s}^{-1}) 60]^2 = \tau_a^2 (BR)^2 60^2,$$

(11)

where $BR$ is the breathing rate.

Now, let us obtain its order of magnitude by adopting representative values of $R_a$ and $C_a$ in normal and disease states. Let us take the above computed values of $R_a = 2.275 \text{ (cmH}_2\text{O)}\text{s}^{-1}$ and $C_a = 0.21321 \text{ (cmH}_2\text{O})^{-1}$ and $BR = 12 \text{ m}^{-1}$ or $0.25 \text{ s}^{-1}$, computed for the data of Fig. 2 and eqn. (3). Then, in a supposed normal situation, the value of $VTI_1$ is of the order of 33.88. In the case of obstructive lung disease, (with increased $R_a$), let us take $R_a = 5 \text{ (cmH}_2\text{O)}\text{s}^{-1}$, $C_a = 0.121 \text{ (cmH}_2\text{O})^{-1}$ and $BR = 0.3 \text{ s}^{-1}$; then we get $VTI_1 = 116.6$. For the case of emphysema (with enhanced $C_a$), let us take $R_a = 2.0 \text{ cmH}_2\text{O} \text{s}^{-1}$, $C_a = 0.51 \text{ (cmH}_2\text{O})^{-1}$ and $BR = 0.2 \text{ s}^{-1}$; then we obtain $VTI_1 = 144$. In the case of lung fibrosis (with decreased $C_a$), we take $R_a = 2.0 \text{ cmH}_2\text{O} \text{s}^{-1}$, $C_a = 0.081 \text{ (cmH}_2\text{O})^{-1}$ and $BR = 0.2 \text{ s}^{-1}$; then we obtain $VTI_1 = 3.7$. We can hence summarize that $VTI_1$ would be in the range of 2–5 in the case of fibrotic lung disease, 5–50 in normal persons, 50–150 in the case of obstructive lung disease and 150–200 for the case of emphysema. This would of course need verification by analyzing a big patient population.

Now, all of this analysis requires pleural-pressure data, for which the patient has to be intubated. If now we evaluate the patient in an outpatient clinic, in which we can only monitor lung volume and not the pleural pressure, then can we develop a non invasively obtainable ventilatory index?

3.1 Noninvasively determinable ventilatory index

In order to formulate a non-invasively determinable ventilatory index from eqn. (1), we need to recognize that in this case $P_X(t)$ (and hence $P_t$, $\omega$ and $C_t$) will be unknown and we need to redesignate the model parameters and indicate their identification procedure. So we make use of the following features from the volume–time data to facilitate evaluation of the following three parameters:

$(P_t, C_t), \omega_t, c_t$, and $\tau_a$.

At $t = t_v = 2.02 \text{ s}$, $V$ is max and $dV/dt = 0$; hence we rewrite eqn. (9) as:

$$\dot{V}_{t=2.02} = \sum_{i=1}^{3} \frac{(P_i C_a) [\omega_i \cos (2.02 \times \omega_i + c_i) + \omega_i^2 \tau_a \sin (2.02 \times \omega_i + c_i)]}{(1 + \omega_i^2 \tau_a^2)} = 0.$$

(12)
Also, at $t = t_m = 1.82/2.87 \text{ s}$, $\dot{V} = 0$. Hence by differentiating eqn. (7), without the exponential term, we obtain:

$$
\dot{V}(t) = \sum_{i=1}^{3} (P_i C_a) \left[ -\sin(\omega_i t_m + c_i) \omega_i^2 + \omega_i^3 \tau_a^2 \cos(\omega_i t_m + c_i) \right] \left[ 1 - e^{-\frac{t_m}{\tau_a}} \right] + 2 \sum_{i=1}^{3} \frac{(P_i C_a) [\omega_i \cos(\omega_i t_m + c_i) - \omega_i^2 \tau_a \sin(\omega_i t_m + c_i)]}{\tau_a (1 + \omega_i^2 \tau_a^2)} e^{-\frac{t_m}{\tau_a}} - \sum_{i=1}^{3} \frac{(P_i C_a) [\sin(\omega_i t_m + c_i) - \omega_i \tau_a^2 \cos(\omega_i t_m + c_i)]}{\tau_a^2 (1 + \omega_i^2 \tau_a^2)} e^{-\frac{t_m}{\tau_a}} = 0. \hspace{1cm} (13)
$$

Then, at $t = 1 \text{ s}$, $V_1 = 2.02l$. From eqn. (6), without the exponential term, this condition yields:

$$
V_1 = \sum_{i=1}^{3} \frac{(P_i C_a) [\sin(\omega_i t_m + c_i) \omega_i^2 + \omega_i^3 \tau_a^2 \cos(\omega_i t_m + c_i)]}{(1 + \omega_i^2 \tau_a^2)} = 2.02.
$$

In addition, we can utilize data information concerning $V_j$ at $t_j$ ($j = 1$ to 8), and put down:

$$
V_j = \sum_{i=1}^{3} \frac{(P_i C_a) [\sin(\omega_i t_j + c_i) \omega_i^2 + \omega_i^3 \tau_a^2 \cos(\omega_i t_j + c_i)]}{(1 + \omega_i^2 \tau_a^2)} ; \hspace{0.5cm} j = 1 \text{ to } 8. \hspace{1cm} (14)
$$

From eqns. (12)–(14), we can obtain the values of $P_i C_a$ (but not of $P_1$, $P_2$ and $P_3$ by themselves), $\omega_i$, $c_i$ and $\tau_a$. On the other hand, by also fitting eqn. (6), (without the exponential term) to the $V(t)$ data, we obtain:

$$
P_1 C = 0.3223 \hspace{1cm} P_2 C = 0.3143 \hspace{1cm} P_3 C = -0.02269 \hspace{1cm} (15)
$$

$$
\omega_1 = -1.178 \hspace{1cm} \omega_2 = 0.5067 \hspace{1cm} \omega_3 = 1.855 \hspace{1cm} (16)
$$

$$
c_1 = 90223 \hspace{1cm} c_2 = 0.2242 \hspace{1cm} c_3 = -3.961 \hspace{1cm} (17)
$$

$$
\tau_a = 0.5535.
$$

We can now also formulate another noninvasively determinable nondimensional ventilatory index ($VTI_2$) in terms of these parameters as follows:

$$
VTI_2 = \frac{(BR)r[TV]^2}{|P_1 C||P_2 C||P_3 C|} = \frac{(BR)r[TV]^2}{|P_1 P_2 P_3 C^2|}. \hspace{1cm} (18)
$$

It is seen that $VTI_2$ can in fact be expressed in terms of $P_1$, $P_2$, $P_3$ and $R$, $C$. This $VTI_2$ index can be evaluated by computing the values of $(BR)$ and $r$, along with $(P_i C)$, as given by eqn. (17). Then, after evaluating $VTI_2$ for a number of patients, its distribution can enable us to categorize and differentially diagnose patients with various lung disorders and diseases.
4 Variations in \( R \) and \( C \) during a respiratory cycle (towards nonlinear)

Thus far, we have adopted the average cyclic values \( C_a \) and \( R_a \) for our \( DE_q \) model parameters. However, we expect that \( C \) will vary with lung volume (\( V \)), and that \( R \) will perhaps vary with the airflow rate or (\( \dot{V} \)) or even \( \omega \). Hence, for a true representation of the lung properties \( C \) and \( R \), let us determine their values for different times during the ventilatory cycle, and compare them with their average values \( C_a \) and \( R_a \), so as to make a case for a nonlinear ventilatory-function model.

Let us hence compute the instantaneous value of compliance \( (C) \) at time \( (t = t_m) \), when \( \dot{V} = 0 \). Let us differentiate eqn. (2a), giving:

\[
R \ddot{V} + \frac{\dot{V}}{C} = \sum_{i=1}^{3} P_i \omega_i \cos(\omega_i t + c_i) \tag{19}
\]

Now at about mid-inspiration, when \( t = t_m = 1.18 \) and \( \dot{V} = 0.48 \text{ l/s, } \ddot{V} = 0 \text{ l/s} \) and \( V = 0.291 \) (based on Fig. 2). By substituting for \( \ddot{V}, \dot{V} \) and \( V \) in eqn. (19), we obtain, \( C = 0.486 \text{ l/cmH}_2\text{O} \) (compared to its \( C_a \) value of 0.21). Now, in order to compute \( R \), we utilize the data information that at \( t_V = 2.02 \) s we substitute \( \ddot{V} = 0 \text{ l/s, } \dot{V} = -0.89 \text{ l/s} \) and \( V = 0.541 \) (from the Fig. 2 data) into eqn. (2a), to obtain:

\[
R \ddot{V} = \sum_{i=1}^{3} P_i \omega_i \cos(\omega_i t + c_i)
\]

\[
R = \frac{\sum_{i=1}^{3} P_i \omega_i \cos(\omega_i t + c_i)}{\ddot{V}} \tag{20}
\]

Substitute \( C \) (at \( t_m = 1.18 \) s) = 0.486 \text{ l/cmH}_2\text{O} in either eqns. (6) or (2b), and obtain \( R = 1.122 \text{ (cmH}_2\text{O)}\text{s}^{-1} \). This gives us some idea of the order of magnitude of \( R \) and \( C \), in comparison to their average values \( C_a \) and \( R_a \). We could naturally expect \( C \) at \( t = t_m \) (which is about mid-inspiration) to be higher than its value at the end of inspiration, when the lung is fully inflated. Also, we could expect the flow resistance to be minimum at the peak of inspiration, when \( \dot{V} = 0 \).

Because \( C \) and \( R \) are not constant, but a function of \( V \) and \( \dot{V} \), we can hence represent lung compliance \( (C) \) and resistance \( (R) \) as follows:

\[
C = C_0 e^{-k_v V} \text{ or } E = \frac{1}{C} = E_0 e^{k_v V} \tag{21a}
\]

\[
R = R_0 e^{k_e V} \tag{21b}
\]

wherein \( \dot{V} \) can also be varied by having the subjects breathe at different ventilation frequencies \( (\omega) \).
4.1 Nonlinear compliance

We note as per the conventional formulation of compliance, given by eqn. (2) in Fig. 1 as:

\[ P_{el} = \frac{V}{C} + P_{e0} = VE + P_{e0}. \]  
(22)

In the above formulation, we assume that \( C \) and \( E(=1/C) \) remains constant throughout the ventilation cycle. However, at the start of inspiration, \( C = C_0 \) at \( t = 0 \), and it decreases as the lung volume increases, based on the lung (static) volume vs pressure curve. So let us improve upon this (22) model, by making \( P_{el} \) a nonlinear function of volume, as follows:

\[ P_{el} = P_{e0} + VE_0 e^{kV}. \]  
(23a)

We can alternatively write eqn. (23) as:

\[ P_{el} = P_{e0} + V(E_0 + E_1 t + E_3 t^2). \]  
(23b)

Employing the above format of compliance, the governing \( DE_e (1) \) becomes

\[ RV \dot{V} + VE_0 e^{kV} = P_L(t) - P_{e0} = P_N(t) = \sum_{i=1}^{3} P_i \sin (\omega_it + c_i). \]  
(24)

Again at the end of expiration, \( P_{e0} = \) intrapulmonary pressure = \( (P_0 + P_1) \).

Hence eqn. (24) becomes:

\[ RV \dot{V} + VE_0 e^{kV} = \sum_{i=1}^{3} P_i \sin (\omega_it + c_i) \]  
(25a)

whose RHS is similar to that of eqn. (2a), and the values of \( P_1, P_2, \) and \( P_3 \) are given by eqn. (3) for the Fig. 2 data.

Solving eqn. (25a):

\[ RV \dot{V} + VE_0 e^{kV} = \sum_{i=1}^{3} P_i \sin (\omega_it + c_i), \]

or, \( \dot{V} + \frac{VE_0 e^{kV}}{R} = \sum_{i=1}^{3} \frac{P_i}{R} \sin (\omega_it + c_i), \)

or, based on eqn. (23b),

\[ \dot{V} + \frac{V}{R} [E_0 + E_1 t + E_2 t^2] = \sum_{i=1}^{3} \frac{P_i}{R} \sin (\omega_it + c_i). \]
This yields:

\[ V(t) = e^{-\frac{\varepsilon_0}{6k} + \frac{3}{6k} (\varepsilon_1 u + 2 \varepsilon_2 u^2)} \int_0^t e^{\frac{\varepsilon_0}{6k} + \frac{3}{6k} (\varepsilon_1 u + 2 \varepsilon_2 u^2)} \sum_{i=1}^3 \frac{P_i}{R} \sin(\omega_i u + c_i) \, du. \]  

(25b)

We could employ this expression for \( V(t) \) to fit the clinical \( V(t) \) data. However, let us try a simpler approach to evaluate these parameters \( k \) and \( E_0 \). For this purpose, we again bring to bear the situation that at the end of inspiration, for \( t = t_e = 2.02 \) s, we have \( \bar{V} = 0 \) and \( V = V_{\text{max}} = TV = 0.55 \) l. Hence, from Fig. 2 data, and eqns. (3) and (25a), we obtain:

\[ 0.55E_{0e}^{0.55k} = 2.55. \]  

(26)

Let us now employ the volume data point at which \( \bar{V} = 0 \). For this purpose, we differentiate eqn. (25a), to obtain:

\[ \bar{V} + \frac{E_0}{R} e^{kV} (1 + kV) = \sum_{i=1}^3 \frac{P_i C_a \omega_i}{R} \cos(\omega_i t + c_i) \]

\[ \bar{V} + \frac{(1 + kV)}{R} \left[ E_0 + E_1 + E_2 t^2 \right] = \sum_{i=1}^3 \frac{P_i C_a \omega_i}{R} \cos(\omega_i t + c_i). \]  

(27)

From the Fig. 2 data at about mid-inspiration, for which at \( t = t_m = 1.18 \) s, \( \bar{V} = 0 \), \( V = 0.29 \) and \( P = 2.53 \), from Fig. 2 data. Substituting these values into eqn. (27), we get:

\[ (1 + 0.29k)(E_0 + 1.18E_1 + 1.39E_2) = 2.53. \]  

(28)

Now, in eqns. (26) and (28), we have four unknowns to be identified: \( k, E_0, E_1, \) and \( E_2 \). Hence we need two more equations, corresponding to two additional time instants. From the values in the following table,

<table>
<thead>
<tr>
<th>( t )</th>
<th>( V )</th>
<th>( \bar{V} )</th>
<th>( \bar{V} )</th>
<th>( P )</th>
<th>Using eqn.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.18</td>
<td>0.29</td>
<td>0.48</td>
<td>0</td>
<td>2.53</td>
<td>26</td>
</tr>
<tr>
<td>2.02</td>
<td>0.55</td>
<td>0</td>
<td>-0.89</td>
<td>2.55</td>
<td>26</td>
</tr>
<tr>
<td>2.87</td>
<td>0.29</td>
<td>-0.47</td>
<td>0</td>
<td>0.29</td>
<td>28</td>
</tr>
<tr>
<td>4.19</td>
<td>-0.03</td>
<td>0</td>
<td>0.16</td>
<td>-0.15</td>
<td>26</td>
</tr>
<tr>
<td>4.76</td>
<td>-0.02</td>
<td>0.02</td>
<td>0</td>
<td>-0.06</td>
<td>28</td>
</tr>
</tbody>
</table>

we can determine the unknowns:

\[ k = -0.13, E_0 = 4.98, E_1 = -2.24 \text{ and } E_2 = 0.21. \]  

(29)

Hence, by employing the nonlinear formulation,

\[ P_{ei} = P_{ei0} + E_0 e^{-kV}, \]  

(30)
we obtain the following expression for nonlinear lung compliance (or elastance):

\[
\frac{dP_{el}}{dV} = E = \frac{1}{C} = E_0 ke^{kV} = 0.65e^{0.13V}.
\] (31)

Based on this expression, we obtain, for \( t = t_m \) and \( V = 0.29 \) l:

\[
E = \frac{1}{C} = 0.67 \text{ cmH}_2\text{O}/\text{l} \text{ and } C = 1.48 \text{ cm H}_2\text{O}.
\] (32)

Equation (31) can now provide us a more realistic characterization of lung compliance as follows:

\[
\begin{align*}
\text{At } t = 0 \text{ and } V = 0, \text{ we compute } E &= \frac{1}{C} = 0.65 \text{ and } C = 1.53 \text{ cmH}_2\text{O}/\text{l} \\
\text{At } t = t_m = 1.18 \text{ s and } V = 0.29 \text{ l}, E &= \frac{1}{C} = 0.67 \text{ and } C = 1.48 \text{ cmH}_2\text{O}/\text{l} \\
\text{At } t = t_v = 2.02 \text{ s and } V = 0.55 \text{ l and } E &= \frac{1}{C} = 0.70 \text{ and } C = 1.43 \text{ cmH}_2\text{O}/\text{l}
\end{align*}
\] (33)

which corresponds to the value of \( C_s \).

Our nonlinear formulation of lung compliance, as depicted by eqns. (31) and (33), indicates that compliance decreases from 1.53 cmH\(_2\)O/l at the start of inspiration to 1.48 cmH\(_2\)O/l at about mid-inspiration, and then to 1.43 cmH\(_2\)O/l at the end of inspiration. What this also tells us is that the ventilatory model (1) gives the correct reading of the compliance at \( V_{\text{max}} \), i.e. at the end of inspiration. At other times of inspiration and expiration, the \( C_s \) parameter underestimates the instantaneous value of lung compliance. Now, we could also obtain an analytical solution of eqn. (25) for \( V(t) \), and fit the expression for \( V(t) \) to the lung-volume data, to evaluate the parameters

(i) \( R, E_0 \) and \( k \) for an intubated patient
(ii) \( R, E_0, k \) and \( P_1, P_2 \) and \( P_3 \) for a non-intubated patient in the out-patient clinic.

However, this is outside the scope of this chapter.

5 Work of breathing (WOB)

This is an important diagnostic index, especially if it can be obtained without intubating the patient and even without using the ventilator. The premise for determining WOB is that the respiratory muscles expand the chest wall during inspiration, thereby lowering the pleural pressure (i.e., making it more negative) below the atmospheric pressure to create a pressure differential from the mouth to the alveoli during inspiration. Then, during expiration, the lung recoils passively.

Hence, the work done during a respiratory life cycle, is given by the area of the loop generated by plotting lung volume (\( V \)) versus net driving pressure (\( P_p \)).
Figure 4: Plot of pressure versus volume. The area under the curve provides the work done.

This plot is shown in Fig. 4. Its area can be obtained graphically, as well as analytically as shown below:

$$WOB = \int_0^T VdP_p(t) = \int_0^T V \frac{dP_p(t)}{dt} dt$$

$$= \int_0^T \left( \sum_{i=1}^3 P_i C_a \left[ \sin(\omega_i t + c_i) - \omega_i \tau_a \cos(\omega_i t + c_i) \right] \right)$$

$$\frac{1}{1 + \omega_i^2 \tau_a^2}$$

$$= \sum_{i=1}^3 P_i \omega_i \cos(\omega_i t + c_i) dt$$

$$= \sum_{i=1}^3 \frac{-P_i C_a \left[ \cos(\omega_i T + c_i) + \omega_i \tau_a \sin(\omega_i T + c_i) - \cos c_i - \omega_i \tau_a \sin c_i \right]}{\omega_i \left(1 + \omega_i^2 \tau_a^2\right)}.$$

The above expression for WOB can be evaluated, once the values of $C_1$ and $\tau$ (or $\omega\tau$) and $P_1$, $P_2$ and $P_3$ and have been computed (as shown in the previous section). So let us substitute into this equation, the following values associated with eqn. (3).

$$P_1 = 1.581 \text{ cmH}_2\text{O} \quad P_2 = -5.534 \text{ cmH}_2\text{O} \quad P_3 = 0.5523 \text{ cmH}_2\text{O}$$
$$\omega_1 = 1.214 \text{ rad/s} \quad \omega_2 = 0.001414 \text{ rad/s} \quad \omega_3 = 2.401 \text{ rad/s}$$
$$c_1 = -0.3132 \text{ rad} \quad c_2 = 3.297 \text{ rad} \quad c_3 = -2.381 \text{ rad}.$$
We compute the value of WOB to be 0.9446 (cmH₂O) in 5 s, or 0.19 cmH₂O 1 s⁻¹ or 0.14 mmHg 1 s⁻¹ or 0.02 W, which is equivalent to an oxygen consumption of about 0.51 ml/min or about 0.18% of the resting \( \dot{V}_{O_2} \) of 28.87 ml/min. This value can be verified by calculating the value of the area of the pressure-volume loop in Fig. 4 which is equal to 0.8 cmH₂O 1.

6 Second-order model for single-compartment lung model

Let us now consider the dynamic (instead of static) equilibrium of a spherical segment of the lung model in Fig. 1, obtained as (by dividing throughout by the elemental lung area):

\[
m_5 u^\circ + (P_p - P_a) + P_{elas} = 0, \tag{36a}
\]

wherein: \( P_a \) and \( P_p \) are the alveolar and pleural pressures, \( u \) is the alveolar-wall displacement, \( m_5 = \text{l lung mass (M) per unit surface area} = M/4\pi R^2 \), (1b) and

\[
P_{elas} = \frac{2\sigma h}{R} = \frac{V}{C} + P_{elb}, \tag{36b}
\]

where:

(i) \( C \) is in l (cmH₂O)⁻¹
(ii) \( m_5 \) (wall mass per unit surface area or surface density) = \( \rho h \), \( \rho \) is the density (mass per unit volume)
(iii) \( \sigma \) is the wall stress
(iv) \( h \) and \( R \) are the wall thickness and radius of the equivalent-lung model.

Now, the displaced alveolar volume, \( V = \frac{4}{3} \pi(R + u)^3 \),

from which we get \( \dot{V} \approx 4\pi R^2 \ddot{u} \), \( \tag{37} \)

Now, from eqn. (1), by putting

\[(i)\quad P_p - P_a = (P_0 - P_a) + (P_p - P_0) \quad \text{and} \quad P_L = P_o - P_p, \quad \tag{38}\]

so that \( P_p - P_a = P_0 - P_a - P_L = R\ddot{V} - P_L, \)

\[(ii)\quad m_5 \ddot{u} = \left( \frac{M}{4\pi R^2} \right) \left( \frac{\dot{V}^*}{4\pi R^2} \right) = \frac{M \ddot{V}}{16\pi^2 R^4} = M^* \ddot{V}; \quad M^* = \frac{M}{16\pi^2 R^4} \]

\[= \frac{m_5}{4\pi R^2}, \tag{39}\]
we obtain, from eqns. (1), (2) and (3):

\[ M^* \ddot{V} + (P_0 - P_a) + \frac{V}{C} = P_L - P_{el,0}; \quad M^* = \frac{M}{16\pi^2 R^4} = \frac{m_s}{4\pi R^2}. \]  \hspace{1cm} (40)

Now, putting \( P_0 - P_a = R \dot{V} \), we obtain:

\[ M^* \ddot{V} + R \dot{V} + \frac{V}{C} = P_L - P_{el0} = \sum_{i=1}^{3} P_i \sin (\omega_i t + c_i) - P_{el0} \]

\[ = P_N. \]  \hspace{1cm} (41)

Since at the end of expiration when \( \omega_i t = \omega_i T \) for \( i = 1 \) to 3 and \( P_L = P_{el0} \) so that \( P_{el0} = 0 \). In eqn. (6), we have:

wherein:

(i) \( M^* \) = \( m_s / 4\pi R^2 \) = \( \rho_s h \); \( \rho_s \) is the lung volume-density per unit surface area (in Kgm\(^{-2}\)) and \( M^* \) is in Kgm\(^{-4}\);

(ii) the clinical data in Fig. 2 is assumed to be represented by

\[ P_N(t) = \sum_{i=1}^{3} P_i \sin (\omega_i t + c_i) \quad \text{with} \]

\[ P_1 = 1.581 \text{ cmH}_2\text{O} \quad P_2 = -5.534 \text{ cmH}_2\text{O} \quad P_3 = 0.5523 \text{ cmH}_2\text{O} \]

\[ \omega_1 = 1.214 \text{ rad/s} \quad \omega_2 = 0.001414 \text{ rad/s} \quad \omega_3 = 2.401 \text{ rad/s} \]

\[ c_1 = -0.3132 \text{ rad} \quad c_2 = 3.297 \text{ rad} \quad c_3 = -2.381 \text{ rad}. \]

Then we can rewrite eqn. (6) as:

\[ \ddot{V} + \left( \frac{R}{M^*} \right) \dot{V} + \frac{V}{CM^*} = \sum_{i=1}^{3} \frac{P_i}{M^*} \sin (\omega_i t + c_i), \]  \hspace{1cm} (43a)

or as:

\[ \ddot{V} + 2n \dot{V} + p^2 V = \sum_{i=1}^{3} Q_i \sin (\omega_i t + c_i). \]  \hspace{1cm} (43b)

In the above equation:

(i) the damping coefficient, \( 2n = R/M^* \)

(ii) the natural frequency of the lung-ventilatory cycle, \( p^2 = 1/CM^* \)

(iii) \( Q_i = P_i/M^* \). \hspace{1cm} (43c)

So the governing eqn. (8) of the lung-ventilatory response to the inhalation pressure has three parameters: \( M^* \), \( R \) and \( C \) (if the lung pressure is also monitored by
The solution of this equation is given by:

$$V(t) = \sum_{i=1}^{3} \left[ \left( \frac{Q_i(-2\omega_c \cos(\omega_i t + \epsilon_i) + p \cos(\omega_i t + \epsilon_i))}{4n^2\omega_i^2 + p^4 - 2p^2\omega_i^2} \right) \right. \\
- \frac{1}{2}Q_i \left[ -(n^2 - p^2)^{\frac{1}{2}} \frac{\sin(\omega_i t + \epsilon_i) + p^2(n^2 - p^2)^{\frac{1}{2}} \sin(\omega_i t + \epsilon_i) - 2\omega_i n^2 \cos(\omega_i t + \epsilon_i) + p^2 n^2 - 2p^2 \omega_i^2 + \omega_i^4)}{(n^2 - p^2)^{\frac{1}{2}}(4n^2\omega_i^2 + p^4 - 2p^2\omega_i^2 + \omega_i^4)} \right] \left. \right] \\
+ \sum_{i=1}^{3} \left[ \left( \frac{2p^2\omega_i^2 \cos(\omega_i t + \epsilon_i) - 2\omega_i n^2 \cos(\omega_i t + \epsilon_i) + 2\omega_i n(n^2 - p^2)^{\frac{1}{2}} \cos(\omega_i t + \epsilon_i) + \omega_i^2(n^2 - p^2)^{\frac{1}{2}} \sin(\omega_i t + \epsilon_i) - \omega_i^3 \cos(\omega_i t + \epsilon_i)}{(n^2 - p^2)^{\frac{1}{2}}(4n^2\omega_i^2 + p^4 - 2p^2\omega_i^2 + \omega_i^4)} \right) \right. \\
- \frac{1}{2}Q_i \left( a - (-p - n)(p + n)^{\frac{1}{2}} \right)^{\frac{1}{2}} \right]$$

(44)

We will ignore the exponential terms and perform parameters identification by matching the above expression for $V(t)$ to the clinical data, shown in Fig. 2. The matching is illustrated in Fig. 5, wherein the first- and second-order differential equation solutions for $V(t)$ are depicted. The computed values of the model parameters are also shown in the table below the figure. Further, the first- and second-order model values of $R$ and $C$ are compared in the table.

Let us compare these values with those obtained by simulating the first-order model to the clinical data.

7 Two-compartmental linear model

Now, it is possible that only one of the two lungs (or lung lobes) may be diseased. So, let us develop a procedure to distinguish between the normal lung and the pathological lung? We hence employ the 2-compartment model (based on our first-order differential equation of lung ventilatory function) to solve the problem of a two-lung model (schematized in Fig. 6).

For this purpose we make the subject breath at different values of frequency ($\omega$), and monitor the total lung pressure $P^L(t)$ (i.e., $P_{1L}$ and $P_{2L}$) and total lung volume $V^L(t)$. Correspondingly, we have $P^R(t)$, $V^L(t)$ and $V^R(t)$ for the left and right lungs, respectively. The governing equations will be as follows
First order model | Second order model
\[ R \text{ [cmH}_2\text{O} \text{l}^{-1} \text{s}] \] 2.28 | 3.44
\[ C \text{ [l/cmH}_2\text{O}] \] 0.21 | 0.85
\[ M^* \text{ [cmH}_2\text{O} \text{l}^{-1} \text{s}^2] \] 3.02
\[ n \left( = \frac{R}{M^*} \right) [s^{-1}] \] 1.14
\[ p^2 \left( = \frac{1}{CM^*} \right) [s^{-2}] \] 0.39

Figure 5: Results of single compartmental model based on differentiate equation formulation, compared with the first-order differential equation model.

(refer to Fig. 3)

\[ p^T = p^l = p^R, \text{ i.e. } p^T_1 = p^l_1 = p^R_1 \quad \& \quad p^T_2 = p^l_2 = p^R_2 \quad (45) \]
\[ V^T = V^l + V^r \quad (46) \]

corresponding to \( \omega \); wherein

(i) \[ V^I(t) = f(\omega, R^I, C^I, P^T(t)) \quad (47) \]
(ii) \[ V^R(t) = f(\omega, R^R, C^R, P^T(t)). \quad (48) \]

In these equations (20),

(i) the variables \( \omega, P^T(t), V^T(t) \) are deemed to be known, i.e. monitored.
(ii) the parameters \( R^I, C^I, \) and \( R^R, C^R \) are to be evaluated.
Using the first-order differential equation model, (presented in sect. 2, as given by eqn. (6) or (14):

\[ V(t) = \sum_{i=1}^{3} (P_i C_i) \left[ -\sin(\omega t + c_i)\omega^2 + \omega^2 \tau_i^2 \cos(\omega t + c_i) \right] \left( 1 + \omega^2 \tau_i^2 \right)^{-1}. \]  

(49)

We put down the expression for \( V^T(t) = V^L(C_L, \tau_L) + V^R(C_R, \tau_R) \), match it with the volume data (using a parameter-identification technique (software), to obtain the values of \( (C_L, \tau_L) \) and \( (C_R, \tau_R) \) by means of which we can differentially diagnose left and right lung lobes’ ventilatory capacities and associated disorders (or diseases).

**7.1 Two compartmental model using first-order ventilatory model**

Using eqn. (6) without the exponential term, we put down the expression for the total lung volume equal to the sum of left and right lung volumes, as follows:

\[ V(t) = \sum_{i=1}^{3} P_i C_L \frac{\sin(\omega t + c_i) - \omega^2 \tau_L^2 \cos(\omega t + c_i)}{1 + \omega^2 \tau_L^2} \]

\[ + \sum_{i=1}^{3} P_i C_R \frac{\sin(\omega t + c_i) - \omega^2 \tau_R^2 \cos(\omega t + c_i)}{1 + \omega^2 \tau_R^2}, \]  

(50)
Two compartmental model

First order model

<table>
<thead>
<tr>
<th></th>
<th>Left lung</th>
<th>Right lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R \text{[cmH}_2\text{O}l^{-1}s]$</td>
<td>1.137</td>
<td>1.137</td>
</tr>
<tr>
<td>$C \text{[l/cmH}_2\text{O]}$</td>
<td>0.1066</td>
<td>0.0533</td>
</tr>
<tr>
<td>$VTL_1$</td>
<td>2.115</td>
<td>0.5289</td>
</tr>
<tr>
<td>$VTL_2$</td>
<td>0.2198</td>
<td>1.0320</td>
</tr>
</tbody>
</table>

Figure 7: Results of the two-compartment model, based on the first-order differential equation model. Based on our assumption of $TV^L/TV^R = 0.92$ we have $TV^L = 0.48 \times 0.48 = 0.2304 \text{l}$ and $TV^R = 0.52 \times 0.48 = 0.2496 \text{l}$.

wherein, for the clinical data, we have:

<table>
<thead>
<tr>
<th></th>
<th>$P_1$ = 1.581 cmH$_2$O</th>
<th>$P_2$ = 5.534 cmH$_2$O</th>
<th>$P_3$ = 5.523 cmH$_2$O</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\omega_1$</td>
<td>1.214 rad/s</td>
<td>0.001414 rad/s</td>
<td>2.401 rad/s</td>
</tr>
<tr>
<td>$c_1$</td>
<td>3.132 rad</td>
<td>3.297 rad</td>
<td>-2.381 rad</td>
</tr>
</tbody>
</table>

We further assume that the ratio of $TV$ of the left lung to that of the right lung is 0.92.

Now, in order to develop a measure of confidence in our analysis, we first generate the total lung-volume data by assuming different values of $C$ and $R$ for left
and right lung lobes. We then use eqn. (50) along with the above data on pressure and frequency, to generate the total lung-volume data. We adopt this generated lung volume data as the clinical-volume data.

We now make our volume-solution expression (eqn. (50)) match this generated clinical-volume data, by means of the parameter-identification procedures, to evaluate $C$ and $R$ for the left and right lung-lobes and hence $VTL_1$ and $VTL_2$ (eqns. (11) and (18)) for these lobes. Based on the values of $VTL_1$ and $VTL_2$, we can differentially diagnose the left and right lung lobes.
7.1.1 Stiff right lung (with compliance problems)
We now simulate a normal left lung and stiff right lung, represented by:

\[ R^L = R^R = 1.14 \text{cmH}_2\text{O}l^{-1} \text{s and } C^L = 0.11, C^R = 0.051/\text{cmH}_2\text{O}. \quad (51) \]

Substituting these parametric values into eqn. (50), we generate the total lung-volume data, as illustrated in Fig. 7.

Now our clinical data for this two-compartment model comprises of the pressure data of Fig. 2 and the generated volume data of Fig. 6. For this clinical data, we match the volume solution given by eqn. (50) with the generated volume data, illustrated in Fig. 7, and carry our parameter identification. The computed values of \( R \) and \( C \), listed in the table of Fig. 7, are in close agreement with the initially assumed parametric values of eqn. (51). This lends credibility to our model and to our use of parameter-identification method.

Now for differential diagnosis, we compute the lung-ventilatory indices, as shown in the table in Fig. 7.

7.1.2 Right lung with \( R \) problems
Now, we simulate a lung with an obstructive right lung, as represented by:

\[ R_L = 1.14 \text{ and } R^R = 2.28 \text{cmH}_2\text{O}l^{-1} \text{s and } C_L = C_R = 0.11/\text{cmH}_2\text{O}. \quad (52) \]

As in the case of the stiff right lung, we first generate the lung-volume data for the above values of compliance and resistances. We then match the total lung-volume solution given by eqn. (50) with the generated lung-volume data, and compute the compliance and flow resistance values of the right and left lung. These are tabulated in Fig. 8, and found to have good correspondence with the assumed values of eqn. (52).
<table>
<thead>
<tr>
<th>Term</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliance (C)</td>
<td>1, 4, 6, 9, 10, 23, 26</td>
</tr>
<tr>
<td>nonlinear compliance</td>
<td>12, 14, 4</td>
</tr>
<tr>
<td>Resistance (R)</td>
<td>4, 6, 10, 26</td>
</tr>
<tr>
<td>resistance-to-airflow</td>
<td>1, 6</td>
</tr>
<tr>
<td>lung-ventilatory index ($VTI$)</td>
<td>1, 7</td>
</tr>
<tr>
<td>second order differential equation</td>
<td>1</td>
</tr>
<tr>
<td>Second-Order model for Single-compartment Lung Model</td>
<td>16</td>
</tr>
<tr>
<td>Two-compartmental Linear Model</td>
<td>21</td>
</tr>
<tr>
<td>Using First Order Ventilatory Model</td>
<td>22</td>
</tr>
<tr>
<td>Stiff Right Lung (with compliance problems)</td>
<td>23</td>
</tr>
<tr>
<td>Right Lung with R problems</td>
<td>25</td>
</tr>
<tr>
<td>ventilation model</td>
<td>1, 2, 22</td>
</tr>
<tr>
<td>Work of Breathing (WOB)</td>
<td>15</td>
</tr>
</tbody>
</table>
### TABLE 1: Nomenclature

<table>
<thead>
<tr>
<th>SYMBOL</th>
<th>MEANING</th>
<th>UNITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Lung Compliance</td>
<td>$(cmH_2O)^{-1}$</td>
</tr>
<tr>
<td>$C_a$</td>
<td>Average Lung Compliance</td>
<td>$(cmH_2O)^{-1}$</td>
</tr>
<tr>
<td>$R$</td>
<td>Lung air-flow resistance</td>
<td>$cmH_2Os^{-1}$</td>
</tr>
<tr>
<td>$R_a$</td>
<td>Average Lung air-flow resistance</td>
<td>$cmH_2Os^{-1}$</td>
</tr>
</tbody>
</table>

### TABLE 2: ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTI</td>
<td>Lung-Ventilatory Index</td>
</tr>
<tr>
<td>WOB</td>
<td>Work of Breathing</td>
</tr>
</tbody>
</table>
Abstract—The primary function of the lung is to (i) oxygenate the blood and thereby provide oxygen to the cells for metabolization purposes, and (ii) to remove the CO\textsubscript{2} produced by the tissues from the pulmonary blood. Herein, we provide a noninvasive methodology to assess the capacity of the lung to oxygenate the pulmonary capillary blood and to reduce its CO\textsubscript{2} concentration. For this purpose, we analyze the compositions of the inspired and expired air per breath, and therefrom compute the metabolic O\textsubscript{2} consumption rate (\dot{V}O\textsubscript{2}) and CO\textsubscript{2} production rate (\dot{V}CO\textsubscript{2}). Next, we compute the cardiac output (CO) as

\[
CO = \dot{V}O_2(C_{V_{O2}}^{AB} - C_{V_{O2}}^{VB}).
\]

We have derived the expressions for diffusion coefficients (i) $D_{O2}$ in terms of $V_{O2}$ and the alveolar and venous partial pressures, $P_{O2}^{al}$ and $P_{O2}^{VB}$ and (ii) $D_{CO2}$ in terms of $V_{CO2}$, $P_{CO2}^{al}$ and $P_{CO2}^{VB}$. The coefficients $D_{O2}$ and $D_{CO2}$ represent the gas transfer capacity of the lung.

The paper provides a case study for the determination of $Q$, $D_{O2}$ and $D_{CO2}$. The derived information of $D_{O2}$ and $D_{CO2}$ as well as of $O_2$ and $CO_2$ metabolic rates can be of considerable clinical use including for SARS assessment.

Keywords—gas exchange, $O_2$ metabolic-rates, $CO_2$ metabolic-rates, diffusion coefficients $D_{O2}$, diffusion coefficients $D_{CO2}$, blood flow rate

I. INTRODUCTION

The lung functional performance is characterized by (i) its ventilatory capacity, to bring air (and hence $O_2$) into the alveoli, and (ii) its capacity to transfer $O_2$ and $CO_2$ into and from the pulmonary capillary bed. Hence, the $O_2$ and $CO_2$ diffusion coefficients $D_{O2}$ and $D_{CO2}$ as well as the $O_2$ consumption-rate and the $CO_2$ production rate represent the lung performance indices. In this paper, we are demonstrating their evaluations.

II. LUNG GAS-EXCHANGED MODEL

Fig. 1 schematically illustrates the gas-exchange between the lung alveolus and the pulmonary capillary-vasculature. Based on our earlier work [1, 2] the gas exchange between the alveolar air and pulmonary capillary blood is represented by the following $O_2$ and $CO_2$ conservation equations and Fig. 2.

\[
Q_{V}^{VE}C_{O2}^{VE} = Q_{V}^{AE}C_{O2}^{AE} + \dot{V}O_2 \quad \text{(from the alveolar air to capillary blood)}
\]

\[
Q_{V}^{VE}C_{CO2}^{VE} = Q_{V}^{AE}C_{CO2}^{AE} - \dot{V}CO_2
\]

wherein

(i) $Q_{V}^{AB}$ and $Q_{V}^{VB}$ are arterial and venous blood flow-rates;

(ii) $Q_{V}^{AB}$ (at venous end), $Q_{V}^{VB}$ (at arterial end)

(ii) $P_{O2}^{al}$ and $P_{O2}^{cap}$ are the alveolar and capillary $O_2$ partial pressures

(iii) $P_{CO2}^{al}$ and $P_{CO2}^{cap}$ are the alveolar and capillary $CO_2$ partial pressure.

(iv) $D_{O2}$ and $D_{CO2}$ are the $O_2$ and $CO_2$ diffusion coefficients

(v) $\Delta P_{av}^{O2}$ = average of $(P_{O2}^{al} - P_{O2}^{cap})$ over the capillary length;

$\Delta P_{av}^{CO2}$ = average of $(P_{CO2}^{al} - P_{CO2}^{cap})$ over the capillary length.
(vi) \( P^{\text{cap}}_{O_2} = P^{PRB}_{O_2} \) (\( O_2 \) concentration of the pre-oxygenated blood) = \( P^{AE}_{O_2} \)

(vii) \( P^{\text{cap}}_{CO_2} = P^{PRB}_{CO_2} \) (\( CO_2 \) concentration of the pre-oxygenated blood) = \( P^{VE}_{CO_2} \)

(viii) \( V^O_2 \) is the \( O_2 \) transfer rate from alveolar air to capillary blood (= \( O_2 \) consumption rate), \( V^CO_2 \) is the \( CO_2 \) transfer rate from capillary blood to alveolar air (= \( CO_2 \) production rate).

Now we can equate the arterial and venous blood flow rates, as \( Q^{AE} = Q^{AB} = Q^{VE} = Q = (SV)/(EP) \) = \( CO / 60 \)

SV, EP and CO being the stroke-volume, ejection-period and cardiac-output respectively.

\[
D_{O_2} = \frac{Q(C_{O_2}^{VE} - C_{O_2}^{AE})}{(\Delta P_{O_2}^{av})} = \frac{Q(C_{O_2}^{AB} - C_{O_2}^{VB})}{(\Delta P_{O_2}^{av})} = \frac{V^O_2}{\Delta P_{O_2}^{av}} \quad (3)
\]

\[
D_{CO_2} = \frac{Q(C_{CO_2}^{VE} - C_{CO_2}^{AB})}{(\Delta P_{CO_2}^{av})} = \frac{V^CO_2}{\Delta P_{CO_2}^{av}} \quad (4)
\]

III. CLINICAL DATA

The monitored data consists of inspired and expired air gas compositions (TABLE 1) and \( O_2 \) and \( CO_2 \) concentrations of arterial blood and venous blood (TABLE 2).

TABLE 1: Air Composition Analysis. Inspired and expired air composition and partial pressures are monitored. Assumed Breathing Rate (BR) = 12 breaths/min. Assumed \( P_{H,O} \) at 37°C = 47 mmHg.

<table>
<thead>
<tr>
<th>Respiratory gases</th>
<th>Atmospheric Air</th>
<th>Expired Air</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmHg</td>
<td>ml/%</td>
</tr>
<tr>
<td>( N_2 )</td>
<td>597</td>
<td>78.55%</td>
</tr>
<tr>
<td>( O_2 )</td>
<td>159</td>
<td>20.84%</td>
</tr>
<tr>
<td>( CO_2 )</td>
<td>0.3</td>
<td>0.04%</td>
</tr>
<tr>
<td>( H_2O )</td>
<td>3.7</td>
<td>2.5%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>760</td>
<td>100%</td>
</tr>
</tbody>
</table>

TABLE 2: Blood Gas Analysis. The monitored blood \( O_2 \) and \( CO_2 \) concentration.

\[
C_{O_2} \text{ of venous blood } (C_{O_2}^{vb}) = 0.13
\]

\[
C_{O_2} \text{ of arterial blood } (C_{O_2}^{ab}) = 0.18
\]

\[
C_{CO_2} \text{ of venous blood } (C_{CO_2}^{vb}) = 0.56
\]

\[
C_{CO_2} \text{ of arterial blood } (C_{CO_2}^{ab}) = 0.52
\]
IV. EXPRESSIONS FOR $D_{O_2}$ AND $D_{CO_2}$

If we want to evaluate the diffusion coefficients $D_{O_2}$ and $D_{CO_2}$, we need to also express $P_{O_2}^{al}$, $P_{O_2}^{cap}$ and $P_{CO_2}^{al}$, $P_{CO_2}^{cap}$ in terms of monitorable quantities [1 & 2].

(i) Alveolar $P_{O_2}^{al}$ can be expressed in terms of $V$ (the ventilation rate) and $V_{O_2}$ (the $O_2$ consumption rate).

$$P_{O_2}^{al} = 140 \left[ 1 - e^{-4.18 \frac{V^{\circ}}{V_{O_2}}} \right]$$  (5)

where the normalized ventilation rate $V^{\circ} = V / V_m = V / 60$ litres/min, is the consumption rate (in litres/min).

(ii) Alveolar $P_{CO_2}^{al}$ can be expressed in terms of $V$ and $V_{O_2}$.

$$P_{CO_2}^{al} = 107.18e^{-2.19 \frac{V^{\circ}}{V_{CO_2}}}$$  (6)

wherein $V_{CO_2}^{\circ}$ is the $CO_2$ production rate (in liters/min).

(iii) Blood $P_{O_2}$ can be obtained in terms of blood $C_{O_2}$, from the $O_2$ dissociation curve.

$$P_{O_2}^B = 30.5 \ln \left[ \frac{0.2}{0.2 - C_{O_2}^B} \right]$$  (7)

(iv) Blood $P_{CO_2}$ can be obtained in terms of $C_{CO_2}^B$, from the $CO_2$ dissociation curve.

$$P_{CO_2}^B = 37.94 \ln \left[ \frac{0.8}{0.8 - C_{CO_2}^B} \right]$$  (8)

Now, $\Delta P_{O_2}$ ($= P_{O_2}^{al} - P_{O_2}^{cap} = P_{O_2}^B - P_{O_2}^{V_B}$) and $\Delta P_{CO_2}$ ($= P_{CO_2}^{V_B} - P_{CO_2}^{al}$) vary along the capillary bed. Based on [3], we have:

$$\Delta P_{O_2}^{av} = 0.185 \Delta P_{O_2}^{max}$$  (9)

$$\Delta P_{CO_2}^{av} = 0.1 \Delta P_{CO_2}^{max}$$  (10)

Hence, from equations (3 & 9) and (4 &10),

$$D_{O_2} = \frac{V_{O_2}^{\circ}}{P_{G_{O_2}}^{al}} \frac{V_{O_2}^{\circ}}{0.185(\Delta P_{O_2}^{al} - \Delta P_{O_2}^{B})}$$  (11)

$$D_{CO_2} = \frac{V_{CO_2}^{\circ}}{P_{G_{CO_2}}^{al}} \frac{V_{CO_2}^{\circ}}{0.14(\Delta P_{CO_2}^{al} - \Delta P_{CO_2}^{B})}$$  (12)

V. EVALUATION OF $O_2$ AND $CO_2$ METABOLIC RATES AND CARDIAC OUTPUT

From monitored data of inspired-exhaled gas compositions, in TABLE 1:

$O_2$ consumption rate, $\dot{V}_{O_2} = BR(\text{Inspired} \text{ } O_2 - \text{Expired} \text{ } O_2) \text{ ml/min} = 12(104.2-80.6) = 283.2 \text{ ml/min}$  (13)

$CO_2$ consumption rate, $\dot{V}_{CO_2} = BR(\text{Expired} \text{ } CO_2 - \text{Inspired} \text{ } CO_2) \text{ ml/min} = 12(19.1-0.2) = 226.8 \text{ ml/min}$  (14)

From monitored $O_2$ and $CO_2$ concentrations of arterial and venous blood, in TABLE 2:

$\dot{V}_{O_2} = Q(C_{O_2}^A - C_{O_2}^V)$

where $Q=$blood flow rate=cardiac output

$\dot{V}_{O_2} = \frac{Q}{(0.18-0.13)} = \frac{283.2}{0.05} = 5664 \text{ ml/min}$

VI. EVALUATING OF THE LUNG DIFFUSION COEFFICIENTS $D_{O_2}$ AND $D_{CO_2}$

From equation (7) and TABLE 2 ($C_{O_2}^{V_B} = 0.13$), we get for (venous blood @ arterial end of the pulmonary capillary or $P_{O_2}^{V_B}$)

$$P_{O_2}^{V_B} = 30.5 \ln \left[ \frac{0.2}{0.2 - C_{O_2}^{V_B}} \right]$$

$$= 30.5 \ln \left[ \frac{0.2}{0.2 - 0.13} \right] = 32.02 \text{ mmHg}$$  (15)

From equation (8) and TABLE 2 ($C_{CO_2}^{V_B} = 0.56$), we get for $P_{CO_2}^{V_B}$ (venous blood @ arterial end of the pulmonary capillary or $P_{CO_2}^{V_B}$)

$$P_{CO_2}^{V_B} = 37.94 \ln \left[ \frac{0.2}{0.2 - C_{CO_2}^{V_B}} \right]$$

$$= 37.94 \ln \left[ \frac{0.2}{0.2 - 0.56} \right] = 32.02 \text{ mmHg}$$
\[
P_{CO_2}^{al} = 37.94 \ln \left( \frac{0.8}{0.8 - C^{TB}_{CO_2}} \right) \\
= 37.94 \ln \left( \frac{0.8}{0.8 - 0.56} \right) \\
= 45.68 \text{ mmHg} \quad (16)
\]

Also, from equation (5) and TABLE 1 \( V^* = 0.1 \), we get:

\[
P_{O_2}^{al} = 140 \left[ -4.18 \left( \frac{V^*}{V_{O_2}} \right) \right] \\
= 140 \left[ 1 - e^{-4.18(0.1/0.2832)} \right] = 108 \text{ mmHg} \quad (17)
\]

Hence, from equations (9, 15 & 17), we get:

\[
\Delta P_{av}^{O_2} = 0.185 \times (108 - 32.02) = 14.06 \text{ mmHg} \quad (18)
\]

Finally, from equations (11) and (18), we get:

\[
D_{O_2} = \frac{V_{O_2}^*}{\Delta P_{av}^{O_2}} = \frac{283.2 \text{ ml/min}}{140.06 \text{ mmHg}} \\
= 20.14 \text{ mmHg}^{-1} \text{ mmHg}^{-1} \quad (19)
\]

Then from equation (6), TABLE 1 \( V = 0.1 \), and equation (12) we get:

\[
P_{CO_2}^{al} = 107.18 e^{-2.19 \left[ \frac{V^*}{V_{CO_2}} \right]} \\
= 107.18 e^{-2.19(0.1/0.2268)} = 40.81 \text{ mmHg} \quad (20)
\]

Hence, from equations (10, 16 & 20), we get:

\[
\Delta P_{av}^{CO_2} = 0.1 \times (45.68 - 40.81) = 0.487 \text{ mmHg} \quad (21)
\]

Finally, from equations (12 & 21), we get:

\[
D_{CO_2} = \frac{V_{CO_2}^*}{\Delta P_{av}^{CO_2}} = \frac{226.8 \text{ ml/min}}{0.487 \text{ mmHg}} \\
= 465.71 \text{ ml/min} \text{ mmHg}^{-1} \quad (22)
\]

VII. CONCLUSION

We have demonstrated a noninvasive clinical procedure
• for obtaining (i) \( O_2 \) consumption rate and \( CO_2 \) production rate, (ii) cardiac output, \( Q \), (iii) and lung diffusion capacities for \( O_2 \) and \( CO_2 \).
• from inhaled and exhaled air composition analysis and blood-gas analysis.

This work could have application to SARS testing and evaluation.

REFERENCES

Quantitation of Renal Function Based on Two-Compartmental Modeling of Renal Pelvis

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Abstract—The primary functions of the kidney are: (i) to get rid of the body waste materials that are either ingested or produced by metabolism, and (ii) to control the volume and composition of the body fluids. Herein, we provide a noninvasive methodology to assess physiological function of the kidneys. For this purpose, we analyze the renograms with 2-compartmental modelling of the kidney-renal outflow system, and therefrom compute the amount of flow of renal radionuclide into and out of the renal pelvis compartment.

The derived information of uptake \( k/A \) and washout \( e^{-\frac{t}{2V_A} \sinh tA} \) rates can be of considerable use. The paper provides a number of case studies for the verification of the derived system governing equations against clinical renograms.

Keywords—Renal outflow obstruction, renal function, glomerular filtration rate, GFR

I. INTRODUCTION

The kidney functional performance is characterized by (i) its filtering capacity, getting rid the body waste materials that are either ingested or produced by metabolism, and (ii) control the volume and composition of the body fluids. Renogram studies have been used for the assessment of renal function for many years [1, 2]. Mathematical modelling has been performed for the kidneys, such as one-compartment model of clearance of tracer [3,4]. However, modeling of the tracer transport between renal parenchyma pool compartment and renal pelvis compartment; derivation of the governing equations for renogram curves has not been reported. Here, we note that the tracer uptake and washout rates can represent the performance indices. In this paper, we evaluate these rates and demonstrate their clinical relevance renogram data.

II. RENAL PELVIS TWO-COMPARTMENTAL MODEL

Fig. 1: illustrates the region of interest (ROI) and we have derived the compartmental model for renal pelvis and shown in Fig. 2.

Fig. 1: Control volume around the renal pelvis area.[5]
III. DERIVATION and PHYSIOLOGICAL SIGNIFICANCE of MODELING SOLUTIONS

From Fig. 2, we derive the following:

\[ \frac{dG_1}{dt} = -FC_1 + I(t) \quad \text{for chamber 1} \]  
\[ \frac{dG_2}{dt} = FC_1 - C_2 U(t) \quad \text{for chamber 2} \]

where (i) \( G_1 = C_1 V \) represents the tracer amount in chamber 1, and (ii) \( G_2 = C_2 V \) represents the tracer amount in chamber 2.

In physiological studies of kidney function and urine outflow status (renography), the input function is a tracer bolus administered over a short period of time. Compared to the entire duration of the renal dynamics, this bolus injection of tracer can be approximated by an impulse function (Dirac’s delta function). In the following derivation, whenever \( I(t) \) appears it will be assumed to be equal to \( I_0 \delta(t) \).

We assume that the compartmental volumes \( V_1 \) and \( V_2 \) are constants (which they generally are), and the urinary flow rate \( U \) as unknown constant (urine flowing out of the kidney into the ureters is physiologically continuous and constant with time, unless there are changes in body fluid status). Here, we are only performing an intra-renal analysis for obstruction to the outflow, we have from (1) and (2):

\[ \frac{V_1 dC_1}{dt} = -FC_1 + I(t) \]  
\[ \frac{V_2 dC_2}{dt} = FC_1 - C_2 U \]

By differentiating and combining (3) and (4), we arrive at:

\[ V_2 C_2 = \left( \frac{F}{V_1} \right) I(t) - \beta C_2 - \gamma C_2 \]

or,

\[ V_2 C_2 + \beta C_2 + \gamma C_2 = \left( \frac{F}{V_1} \right) I_0 \delta(t) \]  
where:

\[ \frac{FV_2}{V_1} + U = \beta, \quad \frac{FU}{V_1} = \gamma \]

The equation (5) is a standard form of a linear second-order ordinary differential equation, with \( I(t) \) as the unit impulse function. This is the governing differential equation for the behavior of tracer within the renal pelvicalyceal compartment.

Solution by Laplace transform method yields the following equations, given the initial conditions of \( C(0) \) and \( C'(0) = 0 \).

\[ L\left[ V_1 \dot{C} + \beta \dot{C} + \gamma C \right] = L\left[ \left( \frac{F}{V_1} \right) I_0 \delta(t) \right] \]

\[ \therefore \left( V_2 s^2 + \beta s + \gamma \right) C_2(s) = \left( \frac{F}{V_1} \right) \frac{1}{s^2 + \beta s + \gamma} \]

\[ C_2(t) = C(t) = \left( \frac{F}{V_1} \right) \frac{1}{\sqrt{\frac{V_1}{\gamma - \beta^2 4V_2^2}}} \sin \left( \sqrt{\frac{\gamma - \beta^2}{4V_2^2}} t \right) \]  
(7)

Solving the above Laplace transform and taking care of the characteristics of the roots (which is now in standard form, by looking up standard tables), we obtain the results for the dynamic behavior of the tracer concentration in the renal pelvis for this physiological system. The term underneath the square root is the determinant of the behavior of the system with regards to whether there is underdamped, critical-damped or overdamped behaviour.

This term can be expressed as \( \beta^2 - 4V_2 \gamma \) and it yields a significant functional index for assessing the outflow status of the kidney. We will classify the observed physiological behaviours of renogram systems into underdamped, overdamped or critically damped systems based on the index, as follows:

**Case 1:**

If \( \beta^2 - 4V_2 \gamma < 0 \), the condition is underdamping, and (7) yields the solution:

\[ C(t) = \left( \frac{F}{V_1V_2} \right) \frac{1}{\sqrt{\frac{\gamma - \beta^2}{4V_2^2}}} \sin \left( \frac{\beta}{2V_2} \right) \left[ e^{-\frac{\beta}{2V_2}} \sin \left( \sqrt{\frac{\gamma - \beta^2}{4V_2^2}} t \right) \right] \]  
(8)

As can be seen from equation (8), the terms which describe urine outflow and determine the shape of the tracer-concentration curve of the renogram during the tracer washout phase are \( e^{-\frac{\beta}{2V_2}} \) and \( \sin \left( \sqrt{\frac{\gamma - \beta^2}{4V_2^2}} t \right) \). The important dynamic information captured in these two terms can be succinctly found in the physiological index that we have described. We will demonstrate the discriminatory nature of this index (which will be extracted as \( A \)) in section
IV when we analyse correlation with actual renogram studies.

Equation (8) is a linear second-order ordinary differential equation, very similar to that of the linear oscillator with damping. In a functioning renal system, the characteristic oscillating-underdamped conditions do not exist.

Case 2:
Whenever there is outflow obstruction, the key term
\[ \beta^2 - 4V_2y' = \left( \frac{FV_2}{V_1} + U \right)^2 - 4V_2 \left( \frac{FU}{V_1} \right) = \left( \frac{FV_2}{V_1} - U \right)^2 > 0 \]
and the condition is overdamping. Then,
\[ C(t) = \left( \frac{F}{V_1V_2} \right) \left( \frac{1}{\gamma} \right) e^{\frac{\beta^2}{4V_2^2}} \sinh \left( \frac{\gamma - \beta^2}{4V_2^2} \right) t \]  (9)

We can express output segment of the tracer curve of compartment 2 looks different from that of the tracer input
\[ \beta^2 - 4V_2y' = \left( \frac{FV_2}{V_1} + U \right)^2 - 4V_2 \left( \frac{FU}{V_1} \right) = \left( \frac{FV_2}{V_1} - U \right)^2 \]
so the key term actually reflects the rate of tracer input \((FC_1)\) minus the rate of tracer output \((UC_2)\).

Case 3:
In the normal case, most physiological systems are well-compensated, and hence the output are fairly similar, hence,
\[ \beta^2 - 4V_2y' = \left( \frac{FV_2}{V_1} + U \right)^2 - 4V_2 \left( \frac{FU}{V_1} \right) = \left( \frac{FV_2}{V_1} - U \right)^2 = 0 \]
In other words, the renal system is critically damped.

The governing equations for this will be
\[ C(t) = \left( \frac{F}{V_1V_2} \right) t e^{\frac{\beta^2}{2V_2^2}} \]  (10)

For model analysis, because of complications involved in monitoring \(U\) (urine flow rate), \(F\) (plasma flow rate into the renal pelvis) and \(V_1\) control volume, we propose that our model parameters will be lumped parameters \(k\) and \(A\). Next our parameters identification will be carried out for \(k, A, V_2\) and \(\beta\).

IV. CLINICAL DATA & EVALUATION

We will demonstrate and verify the application of our models using the renograms obtained from the Nuclear Medicine and PET Department. The radionuclide used are \(^{99m}\)Tc-DTPA and \(^{99m}\)Tc-MAG3. The degree of match with the governing equations is based on the area under the left and right kidney curves against the clinical curves between 60 and 120 seconds.

Model Application:
We will first digitize and normalized the renograms. Next, we will perform parameters identification and obtain the system parameters: \(k, A, \beta\) and \(V_2\). We will only accept the results of the best fit.

![Clinical renograms of volunteer coded Patient 7.](image)

**TABLE 1**: Comparison of clinical and calculated results. We can observe that the errors for each kidney is less than 1%.

<table>
<thead>
<tr>
<th>Identity</th>
<th>% Clinical Area Under the curves between 60 to 120 sec.</th>
<th>% Calculated Area Under the curves between 60 to 120 sec</th>
<th>% Error</th>
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<td>50</td>
<td>49.69</td>
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V. RESULTS

We have performed parametric identification for equations (9) and (10) using MatLab 7. The following are the best fitted results for patients 7 & 8.

TABLE 1 shows that the area under the curves from the simulation matches that of the clinical with an error less than 1%.

VI. CONCLUSION

We have demonstrated modeling of kidney-renal outflow tract compartments with derivation of the governing equations from second-order differential equations and assessed the clinical relevance with comparison with clinical renogram studies.

REFERENCES

Introduction

- Biofeedback entails providing a person with information about his own on-going physiological processes through parameters such as EEG or QEEG, ECG, EMG, etc.
Types of Biofeedback

- There are two types of biofeedback systems: Volitional Feedback Systems (VBFS) and Non-Volitional Feedback Systems (NVFS).

  - The VBFS require conscious effort to attain a desired physiological state. They hence cannot be used in the case of subjects who have mental dysfunction or mentally depressed.
  - The NVFS do not require subjects to be conscious.
Objectives

- The NVFS presented in this paper is designed for rehabilitation purpose. We will also present to you some results that we have gathered in our experiments with subjects with eyes opened with aids and eyes closed with and without aids.

International 10-20-2. EEGs are taken at 19 different channels to give us spatial & temporal information.
The Lexicor system that our experiments were conducted with.

Screen snapshot of the EEG display
Screen shot of the QEEG

Experimental Results

Objective: Similar to experiment 1. This time for open-eyes, we have the psychological board. Each setup up 10 minutes.

Location of experiment: INT:RM (07.22.10)

Name of subjects:

W (Close subject)

V (open subject)

Experiment Setup

<table>
<thead>
<tr>
<th>Channel</th>
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</tr>
</thead>
<tbody>
<tr>
<td>12</td>
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<tr>
<td>13</td>
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<td>16</td>
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(1) Eyes Open: Subjects correct on the psychological board
(2) Eyes Closed: Unaltered
(3) Eyes Closed; Warm Goggles with LCDs flashing at a constant frequency

Alpha waves in units of μV^2 (mean power)
Experimental results of subjects. Note that alpha energies are greatest when eyes closed with the goggles active. The goggles are designed to flash at 10 Hz. It has been found that the Red super-bright LEDs are most efficient.

![Graph showing Results of V and W](image)

**Application of the Concept**
Conclusions

- The above results have significant influence to the system we are designing for rehab purpose.
- The details will be elaborated later in our next coming presentation.

Thank You
Virtual Reality in Rehabilitation

ERAS 2002
22 Nov 2002
By
Loh Kah Meng and Prof Ghista

Introduction

- The use of Virtual Reality (VR) to enhance rehabilitation is a relatively new concept.
- The novel aspect of using VR as an evoked-psychological therapy for rehabilitation will cause a revolution in rehab technology.
Objectives

- In this paper we will discuss some of these concepts. There may be some ideas that could be obscure to some of the audience, so we elicit an open mind.

Concepts/Applications

- Firstly we would like to share with you the concept about stressed and relaxed mind. Next we would like to share with you how this concept can be incorporated into a rehabilitation system for spinal-cord injured patients.
Deformed Mind’s Transcendence into a high-conscious environment.

Evoked-Psychological Response to Initiate Rehabilitation Process

- When a person is under stress her/his mind is compressed and deformed as compared to a relaxed mind under a high consciousness level.
- This is especially so when the patients are undergoing long monotonous physical therapies without experiencing some definitive progress.
Then this self-induced frustration acts as a positive feedback, further bringing down the consciousness level.

Application of VR

- Our objective is to use VR to help conjure a curative and healthy environment, which can also bring her/him into a relaxed and higher consciousness level, which can be verified by examining the EEG alpha-wave energy-content. The amount of improvement is proportional to the increase in alpha wave density.
Spinal-Cord Injury Rehabilitation

- For Spinal Cord Injury (SCI) patients, the VR system will be designed to psychologically make the patient feel that the resected spinal cord reconnected, and thereby the associated physiologically disordered (such as bladder control, temperature regulation, etc) are also remedied.

- For sitting and lying-down, we can design a mattress, of skin-breathing synthetic material.
Spinal-Cord Injury Rehabilitation

- The mattress will be designed as a controllable pneumatic bed with turbulence generators.
- The waves will act as physiotherapists’ fingers, giving massage. The warm fluid with the massage can facilitate blood flow to the patient and reduce sustained-pressure bed-ridden related skin diseases.
SSREFS

- Additionally, a Sympathetic Signal-Reinforcing EEG Feedback System (SSREFS) will be designed to extract alpha signals and filter beta signals from the EEG. The extracted alpha signals can be fed into patient’s spinal cord, to stimulate cerebral-neuronal growth.

Conclusions

- For paraplegic patients, the VR would be employed to make the patient feel that she/he is ambulatory, and that autonomic system is reconnected and working, so that the patient can void independently and feel the outside temperature so the VR will help the patient develop a strong will power to be cured and adopt independent living mood.
Thank You
## Authors’ Index

<table>
<thead>
<tr>
<th>Author</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal A.</td>
<td>345, 361</td>
</tr>
<tr>
<td>Agarwal H.K.</td>
<td>125</td>
</tr>
<tr>
<td>Alini M.</td>
<td>33</td>
</tr>
<tr>
<td>Amis A.</td>
<td>185</td>
</tr>
<tr>
<td>Anand R.S.</td>
<td>369</td>
</tr>
<tr>
<td>Anantharaman V.</td>
<td>89, 440</td>
</tr>
<tr>
<td>Ang K.C.</td>
<td>385</td>
</tr>
<tr>
<td>Aziz A.</td>
<td>85</td>
</tr>
<tr>
<td>Aziz A.R.</td>
<td>328</td>
</tr>
<tr>
<td>Bockholt U.</td>
<td>25</td>
</tr>
<tr>
<td>Boey F.Y.C.</td>
<td>77</td>
</tr>
<tr>
<td>Cai Y.Y.</td>
<td>232</td>
</tr>
<tr>
<td>Cao J</td>
<td>373</td>
</tr>
<tr>
<td>Chai G.B.</td>
<td>278, 428</td>
</tr>
<tr>
<td>Chan K.L.</td>
<td>89, 217</td>
</tr>
<tr>
<td>Chan V.</td>
<td>42</td>
</tr>
<tr>
<td>Chan W.A.</td>
<td>77, 150</td>
</tr>
<tr>
<td>Chan Y.W.</td>
<td>217, 271</td>
</tr>
<tr>
<td>Chaudhari N.S.</td>
<td>228</td>
</tr>
<tr>
<td>Chen C.</td>
<td>209</td>
</tr>
<tr>
<td>Chen H.J.</td>
<td>93</td>
</tr>
<tr>
<td>Chen Q.</td>
<td>412</td>
</tr>
<tr>
<td>Cheng J.</td>
<td>420</td>
</tr>
<tr>
<td>Chew W.</td>
<td>213</td>
</tr>
<tr>
<td>Chia E.</td>
<td>469</td>
</tr>
<tr>
<td>Chia S.L.</td>
<td>33</td>
</tr>
<tr>
<td>Chian K.S.</td>
<td>51, 154</td>
</tr>
<tr>
<td>Chong A.</td>
<td>196</td>
</tr>
<tr>
<td>Chong C.</td>
<td>117</td>
</tr>
<tr>
<td>Chong C.K.</td>
<td>51</td>
</tr>
<tr>
<td>Chong V.</td>
<td>61</td>
</tr>
<tr>
<td>Chou S.M.</td>
<td>192, 196</td>
</tr>
<tr>
<td>Chu F.</td>
<td>244</td>
</tr>
<tr>
<td>Chua A.W.C.</td>
<td>213</td>
</tr>
<tr>
<td>Chua L.P.</td>
<td>154, 259, 263, 274, 278, 286, 289, 293</td>
</tr>
<tr>
<td>Chua T.</td>
<td>30, 49</td>
</tr>
<tr>
<td>Chuy Y.L.</td>
<td>30</td>
</tr>
<tr>
<td>Chutatape O.</td>
<td>424, 121</td>
</tr>
<tr>
<td>Dandapat S.</td>
<td>424</td>
</tr>
<tr>
<td>Dhar P.K.</td>
<td>221</td>
</tr>
<tr>
<td>Diao X.N.</td>
<td>240</td>
</tr>
<tr>
<td>Doraiswami R.</td>
<td>129</td>
</tr>
<tr>
<td>Drerup B.</td>
<td>202</td>
</tr>
<tr>
<td>Dutton A.Q.</td>
<td>27</td>
</tr>
<tr>
<td>Fan S.C.</td>
<td>412</td>
</tr>
<tr>
<td>Fang W.</td>
<td>89</td>
</tr>
<tr>
<td>Feng M.</td>
<td>77</td>
</tr>
<tr>
<td>Feng Z.Q.</td>
<td>42</td>
</tr>
<tr>
<td>Foo S.W.</td>
<td>54, 420</td>
</tr>
<tr>
<td>Fu C.Y.</td>
<td>141</td>
</tr>
<tr>
<td>Fung T.C.</td>
<td>51</td>
</tr>
<tr>
<td>Fuss F.K.</td>
<td>181, 312, 392, 397</td>
</tr>
<tr>
<td>Gao C.</td>
<td>224</td>
</tr>
<tr>
<td>Gao C.Q.</td>
<td>365</td>
</tr>
<tr>
<td>Garcia E.</td>
<td>145</td>
</tr>
<tr>
<td>Gogolewski K.</td>
<td>33</td>
</tr>
<tr>
<td>Goh J.</td>
<td>27</td>
</tr>
<tr>
<td>Goh J.C.H.</td>
<td>408</td>
</tr>
<tr>
<td>Goh K.W.</td>
<td>473</td>
</tr>
<tr>
<td>Gorna K.</td>
<td>33</td>
</tr>
<tr>
<td>Grant M.H.</td>
<td>38</td>
</tr>
<tr>
<td>Gu H.</td>
<td>213</td>
</tr>
<tr>
<td>Guo N.Q.</td>
<td>357</td>
</tr>
<tr>
<td>Gupta J.</td>
<td>125</td>
</tr>
<tr>
<td>Harris M.</td>
<td>81</td>
</tr>
<tr>
<td>Henderson C.</td>
<td>38</td>
</tr>
<tr>
<td>Heng P.A.</td>
<td>105</td>
</tr>
<tr>
<td>Hibbs A.</td>
<td>81</td>
</tr>
<tr>
<td>Ho K.L.I.</td>
<td>199</td>
</tr>
<tr>
<td>Hu Q</td>
<td>109</td>
</tr>
<tr>
<td>Hu Y.</td>
<td>170</td>
</tr>
<tr>
<td>Huang Z.</td>
<td>58</td>
</tr>
<tr>
<td>Hui J.P.P.</td>
<td>27</td>
</tr>
<tr>
<td>Indhumath C.</td>
<td>232</td>
</tr>
<tr>
<td>Irawan R.</td>
<td>137, 141, 457</td>
</tr>
<tr>
<td>Ji W.F.</td>
<td>293</td>
</tr>
<tr>
<td>Joshi M.</td>
<td>133</td>
</tr>
<tr>
<td>Kannathal N.</td>
<td>444</td>
</tr>
<tr>
<td>Kho K.W.</td>
<td>81</td>
</tr>
<tr>
<td>Khong K.S.</td>
<td>416</td>
</tr>
<tr>
<td>Khong P.W.</td>
<td>469</td>
</tr>
<tr>
<td>Khoo J.</td>
<td>21</td>
</tr>
<tr>
<td>Kim E.H.</td>
<td>461</td>
</tr>
<tr>
<td>Kim J.J.</td>
<td>461</td>
</tr>
<tr>
<td>Kim M.T.</td>
<td>251</td>
</tr>
<tr>
<td>Kim W.</td>
<td>202, 301, 305, 324</td>
</tr>
<tr>
<td>Kim Y.</td>
<td>19, 339, 345, 361, 461</td>
</tr>
<tr>
<td>Koh E.C.Y.</td>
<td>389</td>
</tr>
<tr>
<td>Koh L.M.</td>
<td>353, 373</td>
</tr>
<tr>
<td>Krishna K.R.</td>
<td>416</td>
</tr>
<tr>
<td>Krishna V.</td>
<td>192</td>
</tr>
<tr>
<td>Kugean C.</td>
<td>473</td>
</tr>
<tr>
<td>Kurniawati T.</td>
<td>158</td>
</tr>
<tr>
<td>Name</td>
<td>Page Numbers</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Kwok C. K.</td>
<td>93</td>
</tr>
<tr>
<td>Lam S.</td>
<td>58</td>
</tr>
<tr>
<td>Lao L.L.</td>
<td>69</td>
</tr>
<tr>
<td>Lee E.H.</td>
<td>24, 27</td>
</tr>
<tr>
<td>Lee K.K.</td>
<td>401</td>
</tr>
<tr>
<td>Lee K.T.</td>
<td>333, 336</td>
</tr>
<tr>
<td>Lee P.V.S.</td>
<td>408</td>
</tr>
<tr>
<td>Li J.Z.</td>
<td>213</td>
</tr>
<tr>
<td>Li P.</td>
<td>217</td>
</tr>
<tr>
<td>Liao K.</td>
<td>42</td>
</tr>
<tr>
<td>Lie D.T.T.</td>
<td>185</td>
</tr>
<tr>
<td>Liew C.S.</td>
<td>228</td>
</tr>
<tr>
<td>Lim B.H.</td>
<td>196</td>
</tr>
<tr>
<td>Lim C.H.</td>
<td>30</td>
</tr>
<tr>
<td>Lim C.M.</td>
<td>444</td>
</tr>
<tr>
<td>Lim G.H.</td>
<td>385</td>
</tr>
<tr>
<td>Lim S.L.</td>
<td>297</td>
</tr>
<tr>
<td>Lim T.M.</td>
<td>251</td>
</tr>
<tr>
<td>Ling K.V.</td>
<td>93</td>
</tr>
<tr>
<td>Liu J.</td>
<td>113, 170</td>
</tr>
<tr>
<td>Liu L.</td>
<td>278, 289, 428</td>
</tr>
<tr>
<td>Liu T.C.</td>
<td>30, 49</td>
</tr>
<tr>
<td>Liu W.</td>
<td>205</td>
</tr>
<tr>
<td>Liu X.</td>
<td>202, 324</td>
</tr>
<tr>
<td>Loh K.H.</td>
<td>170</td>
</tr>
<tr>
<td>Loh K.M.</td>
<td>377, 453</td>
</tr>
<tr>
<td>Loo C.M.</td>
<td>385</td>
</tr>
<tr>
<td>Lu B.F.</td>
<td>232</td>
</tr>
<tr>
<td>Lui H.</td>
<td>58</td>
</tr>
<tr>
<td>Ma X.</td>
<td>85</td>
</tr>
<tr>
<td>Mackie H.</td>
<td>328</td>
</tr>
<tr>
<td>Mao K.Z.</td>
<td>240</td>
</tr>
<tr>
<td>Matsen F.A.</td>
<td>461</td>
</tr>
<tr>
<td>McLean D.I.</td>
<td>58</td>
</tr>
<tr>
<td>McWilliams A.</td>
<td>58</td>
</tr>
<tr>
<td>Meena S.</td>
<td>274</td>
</tr>
<tr>
<td>Meher P.K.</td>
<td>125</td>
</tr>
<tr>
<td>Miao X.</td>
<td>158, 170</td>
</tr>
<tr>
<td>Minh P.D.</td>
<td>97</td>
</tr>
<tr>
<td>Mukherji S.</td>
<td>133</td>
</tr>
<tr>
<td>Ng B.H.</td>
<td>192</td>
</tr>
<tr>
<td>Ng B.K.</td>
<td>141</td>
</tr>
<tr>
<td>Ng E.Y.K.</td>
<td>65, 117, 267</td>
</tr>
<tr>
<td>Ng G.S.</td>
<td>65</td>
</tr>
<tr>
<td>Ng M.Y.</td>
<td>170</td>
</tr>
<tr>
<td>Ng S.Y.</td>
<td>196</td>
</tr>
<tr>
<td>Ng W. S.</td>
<td>93</td>
</tr>
<tr>
<td>Niegl G.</td>
<td>188, 312, 320</td>
</tr>
<tr>
<td>Nowinski W.L.</td>
<td>85, 97, 109, 113, 224, 247</td>
</tr>
<tr>
<td>Olivo M.</td>
<td>81</td>
</tr>
<tr>
<td>Ong J.H.</td>
<td>385</td>
</tr>
<tr>
<td>Ong V.</td>
<td>297</td>
</tr>
<tr>
<td>Ong W.F.</td>
<td>34</td>
</tr>
<tr>
<td>Ooi C.K.</td>
<td>408</td>
</tr>
<tr>
<td>Palaninippan R.</td>
<td>436</td>
</tr>
<tr>
<td>Pan J.</td>
<td>77</td>
</tr>
<tr>
<td>Prabaharan K.</td>
<td>473</td>
</tr>
<tr>
<td>Prakash K.N.B.</td>
<td>97</td>
</tr>
<tr>
<td>Qian G.</td>
<td>109</td>
</tr>
<tr>
<td>Qian X.</td>
<td>450</td>
</tr>
<tr>
<td>Quek C.</td>
<td>65</td>
</tr>
<tr>
<td>Rajendra A.U.</td>
<td>444</td>
</tr>
<tr>
<td>Ramanujan R.V.</td>
<td>69, 174</td>
</tr>
<tr>
<td>Ramgopal Y.</td>
<td>150</td>
</tr>
<tr>
<td>Rao R.</td>
<td>133</td>
</tr>
<tr>
<td>Ritchie A.C.</td>
<td>34, 381</td>
</tr>
<tr>
<td>Roy A.</td>
<td>247</td>
</tr>
<tr>
<td>Sabitiz R.J.</td>
<td>397, 401</td>
</tr>
<tr>
<td>Sathappan K.</td>
<td>154</td>
</tr>
<tr>
<td>Schmidt B.</td>
<td>205, 209, 237</td>
</tr>
<tr>
<td>Schneider F.K.</td>
<td>345, 361</td>
</tr>
<tr>
<td>Schroder H.</td>
<td>22</td>
</tr>
<tr>
<td>See W.N.W.</td>
<td>320</td>
</tr>
<tr>
<td>Shao W.</td>
<td>93</td>
</tr>
<tr>
<td>Sharkawy A.</td>
<td>20</td>
</tr>
<tr>
<td>Shen L.</td>
<td>73</td>
</tr>
<tr>
<td>Shi D. M.</td>
<td>93</td>
</tr>
<tr>
<td>Shim W.S.N.</td>
<td>30, 49</td>
</tr>
<tr>
<td>Sim E.K.W.</td>
<td>49</td>
</tr>
<tr>
<td>Sin Y.K.</td>
<td>30</td>
</tr>
<tr>
<td>Singh S.</td>
<td>101</td>
</tr>
<tr>
<td>Sivashanker S.</td>
<td>416</td>
</tr>
<tr>
<td>Song C.</td>
<td>213</td>
</tr>
<tr>
<td>Song G.L.</td>
<td>259</td>
</tr>
<tr>
<td>Soo K.C.</td>
<td>81</td>
</tr>
<tr>
<td>Spurway N.C.</td>
<td>328</td>
</tr>
<tr>
<td>Sridhar I.</td>
<td>416</td>
</tr>
<tr>
<td>Srikanthan T.</td>
<td>125</td>
</tr>
<tr>
<td>Srinivasan N.</td>
<td>271</td>
</tr>
<tr>
<td>Sung P.F.</td>
<td>166</td>
</tr>
<tr>
<td>Swain S.</td>
<td>424</td>
</tr>
<tr>
<td>Tai C.H.</td>
<td>255</td>
</tr>
<tr>
<td>Tan B.</td>
<td>328</td>
</tr>
<tr>
<td>Tan B.K.</td>
<td>213</td>
</tr>
<tr>
<td>Tan E. C.</td>
<td>73</td>
</tr>
<tr>
<td>Tan E.K.</td>
<td>436, 447, 473</td>
</tr>
<tr>
<td>Tan G.M.Y.</td>
<td>30, 49</td>
</tr>
<tr>
<td>Tan J.</td>
<td>30, 301, 305, 324</td>
</tr>
<tr>
<td>Tan L.P.</td>
<td>166</td>
</tr>
<tr>
<td>Tan M.A.</td>
<td>188, 312, 316, 308</td>
</tr>
<tr>
<td>Name</td>
<td>Pages</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Tan R.S.</td>
<td>278, 428</td>
</tr>
<tr>
<td>Tan T.Z.</td>
<td>65</td>
</tr>
<tr>
<td>Tan Y.S.</td>
<td>30, 274, 278, 282, 286, 289, 293</td>
</tr>
<tr>
<td>Tang C.L.</td>
<td>129</td>
</tr>
<tr>
<td>Tay F.E.H.</td>
<td>224, 247</td>
</tr>
<tr>
<td>Teh K.C.</td>
<td>328, 333, 297</td>
</tr>
<tr>
<td>Teh M.</td>
<td>30, 49</td>
</tr>
<tr>
<td>Teo E.C.</td>
<td>401, 405</td>
</tr>
<tr>
<td>Teu K.K.</td>
<td>301, 305, 324</td>
</tr>
<tr>
<td>Thakur A.</td>
<td>369</td>
</tr>
<tr>
<td>Thimm G.</td>
<td>381</td>
</tr>
<tr>
<td>Thng C.H.</td>
<td>54</td>
</tr>
<tr>
<td>Thong P.S.P.</td>
<td>81</td>
</tr>
<tr>
<td>Ting K.S.</td>
<td>38</td>
</tr>
<tr>
<td>Tjin S.C.</td>
<td>137, 141, 457</td>
</tr>
<tr>
<td>Tjoa M.P.</td>
<td>129</td>
</tr>
<tr>
<td>Toh C.</td>
<td>328</td>
</tr>
<tr>
<td>Toh S.L.</td>
<td>408</td>
</tr>
<tr>
<td>Tong J.H.</td>
<td>263</td>
</tr>
<tr>
<td>Tsou I.</td>
<td>196</td>
</tr>
<tr>
<td>Venkatraman S.</td>
<td>77, 162, 166</td>
</tr>
<tr>
<td>Verma H.K.</td>
<td>101</td>
</tr>
<tr>
<td>Vinod K.</td>
<td>101</td>
</tr>
<tr>
<td>Wang L.</td>
<td>244</td>
</tr>
<tr>
<td>Wang L.W.</td>
<td>162</td>
</tr>
<tr>
<td>Wang N.D.</td>
<td>38</td>
</tr>
<tr>
<td>Wang P.</td>
<td>440</td>
</tr>
<tr>
<td>Wang Q. B.</td>
<td>357</td>
</tr>
<tr>
<td>Wang X.T.</td>
<td>166</td>
</tr>
<tr>
<td>Wijaya S.</td>
<td>34</td>
</tr>
<tr>
<td>Wilson S.</td>
<td>26</td>
</tr>
<tr>
<td>Wong E.M.C.</td>
<td>349, 365</td>
</tr>
<tr>
<td>Wong J.</td>
<td>328</td>
</tr>
<tr>
<td>Wong M.T.</td>
<td>237, 271</td>
</tr>
<tr>
<td>Wong P.</td>
<td>30, 49, 166</td>
</tr>
<tr>
<td>Xia D.</td>
<td>105</td>
</tr>
</tbody>
</table>

The papers presented in this Proceedings of the 1st International BioEngineering Conference 2004 in conjunction with 6th Annual NTU-SGH Biomedical Engineering Symposium 2004 “BioEngineering: Challenges and Innovations”, comprises of contributions made by the authors participating in the Conference. Therefore, the opinions expressed and contents provided herein reflect those of the authors and does not necessarily constitute endorsement by editors, organizers and sponsors of the Conference. All the papers have been peer-reviewed for the contents and their suitability for presentation at the Conference. The final papers sent by authors as Camera Ready Paper might have been modified and altered a bit to suit presentation and print style. The editors, organizers and sponsors are not liable to any claim whatsoever, arising out of the publication of these proceedings.

Editors: F. K. Fuss, S. L. Chia, S. S. Venkatraman, S. M. Krishnan, and B. Schmidt
# Conference Papers

## Invited Speakers

<table>
<thead>
<tr>
<th>Session</th>
<th>Title</th>
<th>Authors</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nanostructure Processing of Advanced Biomaterials (Ying J.)</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>Bioengineering, Technology Commercialization and Entrepreneurship (Kim Y.)</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>Esophageal Tissue Engineering (Ratner B.)</td>
<td></td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>A Case Study of Integrated Biomedical Engineering: A Novel Method for Creating an Automated Sutureless Anastomosis (Sharkawy A.)</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>Advances in Cancer Imaging (Khoo J.)</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>6</td>
<td>Tissue Engineering Heart Constructs using Bone Marrow Stem Cell (Wong P.)</td>
<td></td>
<td>--</td>
</tr>
<tr>
<td>7</td>
<td>Computational Technologies to Accelerate Biotech Innovation (Meier U.)</td>
<td></td>
<td>--</td>
</tr>
<tr>
<td>8</td>
<td>A new Approach to Protein Structure Prediction (Schroder H.)</td>
<td></td>
<td>22</td>
</tr>
<tr>
<td>9</td>
<td>Development of Microfluidic-Based Point-of-Care Diagnostic Systems (Yager P.)</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>10</td>
<td>Innovation in The Medical Device Industry: Development of Cypher - the first Drug-Eluting Stent (Mishra A.)</td>
<td></td>
<td>--</td>
</tr>
<tr>
<td>11</td>
<td>Heart Tissue Engineering (Ratner B.)</td>
<td></td>
<td>--</td>
</tr>
<tr>
<td>12</td>
<td>Biological Resurfacing of Articular Cartilage - from Bench to Bedside (Lee E.H.)</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>13</td>
<td>Virtual Reality, Augmented Reality and its Medical Application (Bockholt U.)</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>14</td>
<td>Vital Signs in the Real World (Wilson S.)</td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>15</td>
<td>Clinical Endoscopy System: Present and Future (Hidaka T.)</td>
<td></td>
<td>--</td>
</tr>
</tbody>
</table>

## Session: 01 Tissue Engineering  
Day 1 1515- 1715 hrs

<table>
<thead>
<tr>
<th>Session</th>
<th>Title</th>
<th>Authors</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Polyurethane Membranes for Chondrocyte Transplantation and Cartilage Engineering</td>
<td>(Chia S.L., Gorna K., Gogolewski K., Alini M.)</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>Theoretical and Experimental Determination of State of Two Dimensional Strain in a Bioreactor (Ong W.F., Wijaya S., Ritchie A.C.)</td>
<td></td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>Culture of Rodent Hepatocytes on Microgrooved Surfaces: Application for a Flat-Plate Bioartificial Liver Device (Ting K.S., Wang N.D., Grant M.H., Henderson C.)</td>
<td></td>
<td>38</td>
</tr>
<tr>
<td>6</td>
<td>Simultaneous Probing of Morphology, Cytoskeleton, and Adhesion Dynamics of HepG2 Cells (Feng Z. Q., Liao K., Chan V.)</td>
<td></td>
<td>42</td>
</tr>
<tr>
<td>7</td>
<td>ECM-Dependent Proliferation of Adult Bone Marrow Mesenchymal Stem Cells (Tan G.M.Y., Shim W.S.N., Chua T., Liu T.C., Teh M., Sim E.K.W., Wong P.)</td>
<td></td>
<td>49</td>
</tr>
<tr>
<td>8</td>
<td>Parameters for Scaffold Design of Esophageal Tissue from a Structural Constitutive Model (Yang W., Fung T.C., Chian K.S., Chong C.K.)</td>
<td></td>
<td>51</td>
</tr>
</tbody>
</table>

## Session 02: Cancer Detection & Therapy  
Day 1 1515-1700 hrs

<table>
<thead>
<tr>
<th>Session</th>
<th>Title</th>
<th>Authors</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Automated Segmentation of Breast Masses in Mammograms (Zhang H., Foo S.W., Thng C.H.)</td>
<td></td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>Diagnosis of Lung Cancer Using NIR Raman Spectroscopy (Huang Z., McWilliams A., Lam S., McLean D.I., Lui H., Zeng H.)</td>
<td></td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>Extraction of head and neck tumors using deformation models from MR images (Zhou J., Chong V.)</td>
<td></td>
<td>61</td>
</tr>
</tbody>
</table>
Session 03A: Medical Image Processing

Day 1 1515-1745 hrs


3. An Improved Active Contour Method for Heart Wall Boundary Detection in Echocardiographic Image Sequence (Fang W., Chan K.L., Anantharaman V.)

4. Augmented Reality Assisted Sinus Surgery (Shi D. M., Ng W. S., Ling K. V., Shao W., Chen H.J., Kwoh C. K.)


6. Removing Blocking Artifacts in Compressed Medical Images (Singh S., Vinod K., Verma H.K.)


8. Extraction of the Two Modified Talairach Cortical LandMarks (I and S) from MR T1-Weighted Images (Hu Q., Qian G., Nowinski W.L.)


10. Mapping Human Skin and Aural Temperature with ANNs and IR Imager (Ng E.Y.K., Chong C.)

Session 03B: Medical Image Processing

Day 3 1130-1215 hrs

1. Automatic 3-D optic Disk Image Reconstruction from Low-Resolution Fundus Image for Glaucoma Analysis (Xu J., Chutape O.)


3. Disposable Microfluidic Card and Fluorescence Detection System for Point-of-Care Diagnostic Applications (Irawan R., Tjin S.C., Fu C.Y., Ng B.K., Yuan X.-C., Zhang D.W.)

Session 04: Microfluidics/MEMS

Day 1 1700-1800 hrs

1. AFM Characterization and Selectivity of Immobilization of Antibodies in Bio-MEMS (Joshi M., Rao R., Mukherji S.)


3. Disposable Microfluidic Card and Fluorescence Detection System for Point-of-Care Diagnostic Applications (Irawan R., Tjin S.C., Fu C.Y., Ng B.K., Yuan X.-C., Zhang D.W.)

4. Microfluidic Protein Patterning using Embedded Cavities in Microchannels (Garcia E., Yager P.)
### Session 05: Biomaterials & Drug Delivery  Day 2 1015-1230 hrs

1. Smart Polymer Nanocarriers for Targeted Delivery (Yang Y.Y.)  
2. Release of Lipoplexes from a Biodegradable Polymer Film: Preliminary Study (Chan W.A., Ramgopal Y.)  
4. Porous Beta-TCP and Its Modification with PLGA Coating for Bone Regeneration (Miao X., Kurniawati T.)  
5. In vitro Study on the Release Kinetics of Bovine Serum Albumin (BSA) from Injectable PLGA/BB Depot (Wang L.W., Venkatraman S.)  
8. Clinical Applications of Magnetic Nanomaterials (Ramanujan R.V.)

### Session 06: Biomechanics  Day 2 1015-1230 hrs

1. Biomechanics Highlights in Sports, Physiology and Medicine (Ghista D.N.)  
2. Evolution and Biomechanics of the Cruciate Ligaments (Fuss F.K.)  
3. The Double-Bundle ACL Graft Reconstruction: A superior technique to restore knee kinematics (Lie D.T.T., Amis A.)  
4. Finger Pulley Injuries are Self-Propagating: A Mathematical Analysis of the A2-Pulley (Tan M.A., Fuss F.K., Niegl G.)  
5. A Comparative Study of Different Gripping Methods for Tendons (Ng B.H., Chou S.M., Krishna V.)  
8. Foot Characterization and Anatomical Landmarks Localization (Liu X., Kim W., Drerup B.)

### Session 07A: Computational Bioengineering  Day 2 1015-1230 hrs

1. A Case Study on Pattern-based Systems for Computational Biology (Liu W., Schmidt B.)  
2. A Grid Implementation of Database Searching (Chen C., Schmidt B.)  
3. The Use of Computer Modelling to elucidate the Efficacy of Slit Arteriortomy for End-to-side Arterial Anastomosis in Microsurgery (Chua A.W.C., Gu H., Tan B.K., Chew W., Li J.Z., Song C.)  
4. A Mixed SVM-Based Hierarchical Learning Approach for Abnormal ECG Beat Recognition (Li P., Chan K.L., Chan Y.W.)  
5. Capturing Cellular Life In-Silico (Dhar P.K.)  
7. Fuzzy c-Means and Neural Network Framework for Arrhythmia Classification (Chaudhari N.S., Siang L.C.)  
8. VRML Modeling for Bio-Molecular Structures (Indhumathi C., Lu B.F., Cai Y.Y.)  
9. BioSequence Comparison for Large Database on Reconfigurable Platforms (Wong M.T., Schmidt B.)
### Session 07B: Computational Bioengineering 2
**Day 2 1330-1415 hrs**

1. **Clustering Based Watershed Segmentation for Two-Dimensional Gel Electrophoresis**
   - Diao X.N., Mao K.Z.

2. **Estimating error-dimensionality relationship for gene expression based cancer classification**
   - Chu F., Wang L.

3. **Finite Element Analysis of Brain for Neurosurgical Procedure**
   - Roy A., Nowinski W.L., Tay F.E.H.

### Session 08A: Cardiovascular Engineering 1
**Day 2 1330-1530 hrs**

1. **A Decoupled Control Method for the Magnetic Bearings of a Blood Pump**
   - Lim T.M., Zhang D., Kim M.T.

   - Xia G.H., Zhao Y., Yeo J.H., Tai C.H.

3. **Computation of Gap Flow Field in a Bio-Centrifugal Blood Pump**
   - Chua L.P., Song G.L., Yu S.C.M.

4. **Computational Studies of Steady Flows In Designed Sleeve Models At Distal Anastomoses**
   - Chua L.P., Tong J.H.

5. **Contractility of the Left Ventricle in Terms of its Sacromere Power Generation**
   - Zhong L., Ghista D.N., Ng E.Y.K.

6. **Detection of Cardiac Arrhythmia using Phase Space Analysis**
   - Wong M.T., Srinivasan N., Chan Y.W.

7. **Flow Studies in Aorto-Right Coronary Bypass Graft System**
   - Meena S., Chua L.P., Ghista D.N., Tan Y.S.

8. **LV Twisting Analyzed for Pressure-Increase During Iso-Volumic Contraction**

### Session 08B: Cardiovascular Engineering 2
**Day 2 1545-1645 hrs**

1. **Multiple-Model Adaptive Control by Means of a Fuzzy Controller-based Control System**
   - Zheng H., Zhu K.Y., Tan Y.S.

2. **Numerical Investigation of Hemodynamics for the Coronary Artery Bypass Graft Model**

3. **Numerical Investigation of Stress Field in Distal End-to-side Anastomoses**
   - Liu L., Chua L.P., Ghista D.N., Tan Y.S.

4. **PIV Measurements on the Pulsatile Flow Characteristics in 45-degree Backward Proximal Anastomosis**

### Session 09A: Sports Engineering 1
**Day 2 1330-1530 hrs**

1. **Quantitative analysis of Singapore Golfers**
   - Lim S.L., Xie X., Ong V., Teh K.C.

2. **Three-Dimensional Kinematics Study of Left Hand During Golf Swing**
   - Teu K.K., Kim W., Fuss F.K., Tan J.

3. **Investigation of Weight Transfer during Golf Swing**
   - Teu K.K., Kim W., Fuss F.K., Tan J.

4. **Biomechanics of Push-up Exercise and Triceps Contractility**
   - Tan M.A., Zhong L., Fuss F.K., Ghista D.N.

5. **Comparison of Pinch- and Open Hand Grip during Sport Climbing**
   - Yap Y.H., Fuss F.K., Niegl G., Tan M.A.

6. **Friction at the Climbing Handhold under Different Conditions and its Implications for Sport Climbing**
   - Tan M.A., Fuss F.K., Niegl G.
7 Finger Load Distribution During Sport Climbing (See W.N.W., Fuss F.K., Niegl G., Yap Y.H.)
8 Analysis of Badminton Smash Using Dual Euler Angles Algorithm (Liu X., Teu K.K., Kim W., Tan J., Fuss F.K.)

Session 09B: Sports Engineering 2 Day 2 1545-1630 hrs
2 Comparative Study on the techniques of Singapore and Thailand Table Tennis players during SEA Games 2001 (Lee K.T., Xie W., Teh K.C.)
3 Experimental Study on Different Types of Service Spins for Singapore National Table Tennis players (Lee K.T., Xie W.)

Session 10A: Ultrasonic Imaging 1 Day 2 1415-1530 hrs
1 Medical Ultrasound Imaging: Current Status and Future Trends (Yoo Y.M., Kim Y.)
2 Reconfigurable and Programmable Architecture for Digital Receive Beamformer (Schneider F.K., Yoo Y.M., Agarwal A., Kim Y.)
3 Adaptive Speckle Reduction Based on Nakagami Distribution in Medical Ultrasound Imaging (Zhang L.C., Wong E.M.C.)
4 Specific Homomorphic Nonlinear Diffusion for Speckle Reduction in Ultrasound B-mode Images (Zhang F., Koh L.M.)
5 Design and Optimization of Broadband Ultrasonic Sparse Array Transducers for Medical Imaging Applications (Wang Q. B., Guo N. Q.)

Session 10B: Ultrasonic Imaging 2 Day 2 1545-1645 hrs
1 Field of View-based Imaging for Efficient Beamforming in Low-end Portable Ultrasound Systems (Agarwal A., Schneider F.K., Yoo Y.M., Kim Y.)
2 Low Sampling Frequency Digital Beamformer for Ultrasonic Imaging without Interpolation (Gao C.Q., Zhang L.C., Wong E.M.C.)
3 Comparative Evaluation of Wavelet Filters for Speckle Reduction in Ultrasound Medical Images (Thakur A., Anand R. S.)
4 Window Function Optimization by Genetic Algorithm for Ultrasound Imaging System (Cao J., Koh L.M.)

Session 11: Respiratory Biomechanics Day 2 1645-1730 hrs
1 Determination of O2 and CO2 Metabolic Rates and Lung O2 and CO2 Diffusion Coefficients (Loh K.M., Ghista D.N.)
2 Oxygen Saturation Profiles in a Hollow Fibre Oxygenator (Ritchie A.C., Thimm G.)
3 Graphical Technique for Assessing Pulmonary Disease (Loo C.M., Ang K.C., Ong J.H., Ghista D.N., Lim G.H.)

Session 12A: Orthopaedic Engineering 1 Day 2 1630-1745 hrs
1 Design Optimisation in BioMedical Engineering (Koh E.C.Y., Fuss F.K.)
2 Design Classification and Mechanics of Artificial Disks (Fuss F.K.)
3 Extraforaminal Lumbar Interbody Fusion: Simulation of the Fusion Process Based on Different Implant Materials (Fuss F.K., Sabitzer R.J.)
4 FE Investigation on Spinal Interbody Fusion (Lee K.K., Teo E.C., Fuss F.K., Sabitzer R.J.)
5 Optimization of Cervical Ring Cage by Taguchi Philosophy (Yang K., Teo E.C., Fuss F.K.)
Session 12B: Orthopaedic Engineering 2 Day 3 1130-1215 hrs
1 Integration of CAD to FEA for Prosthetic Socket Design (Goh J.C.H., Lee P.V.S., Toh S.L., Ooi C.K.) 408
2 Analyses of Fractured Bone (Femur) with Plate and Intra-Medullary Rod Fixations (Chen Q., Fan S.C., Ghista D. N.) 412
3 Biomechanics of Long Bone Geometry and Fracture Fixation (Krishna K.R., Sridhar I., Sivashanker S., Khong K.S., Ghista D.N.) 416

Session 13A: Biosignal Processing 1 Day 2 1645-1745 hrs
1 A Novel Approach to Automatic Left Ventricular Contour Tracking (Cheng J., Foo S.W.) 420
2 A Novel Wavelet Based ECG Compression with X-tree Coding (Swain S., Chutatape O., Dandapat S.) 424
3 Left Ventricular Surface Kinematics During Isovolumic Contraction (Yeo S.Y., Tan R.S., Liu L., Chai G.B., Ghista D.N.) 428
4 Evaluation of Slice Sensitivity Profiles for TPRF Algorithm (Yan M., Zhang C.) 432

Session 13B: Biosignal Processing 2 Day 3 1045-1130 hrs
1 Uni-channel PCA for noise reduction from ECG signals (Palaninippan R., Tan E.K.) 436
2 Wavelet-Based Denoising and Analysis of Phonocardiogram (Wang P., Anantharaman V.) 440
3 Dynamical Analysis of Heart Rate Variability Signals (Rajendra A.U., Kannathal N., Lim C.M.) 444

Session 14: Biosensors/ Diagnostic Tools Day 3 1045-1145 hrs
1 Multi-Parameter Clinical Diagnosis Using Neural Networks (Tan E.K.) 447
2 An Otoacoustic Emissions Detecting System using USB AD/DA Board (Qian X., Ye D.) 450
3 Oral Glucose Tolerance Test Modeling For Diabetes Characterization (Loh K.M., Ghista D.N.) 453
4 Feasibility of biosensing based on two-dimensional square photonic lattice (Zhang D.W., Irawan R., Tjin S.C., Yuan X.C.) 457

Session 15: Distributed Diagnosis & Home Healthcare Day 3 1045-1130 hrs
1 Distributed Diagnosis and Home Healthcare (D2H2) and Patient-Centered Electronic Medical Record (Kim E.H., Kim J.J., Matsen F.A., Kim Y.) 461
2 Application of Artificial Neural Network Technique in Healthcare Expenditure Analysis (Chia E., Khong P.W., Ghista D.N.) 469
3 Advanced System Architecture for Telecardiology (Goh K.W., Kugean C., Tan E.K., Prabaharan K.) 473
Determination of $O_2$ & $CO_2$ Metabolic-Rates and Lung $O_2$ & $CO_2$ Diffusion Coefficients, form on the Data of Inspired and Expired Air Compositions

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$^2$Department of Biomedical Engineering, Nanyang technological University, Singapore

Abstract—The primary function of the lung is to (i) oxygenate the blood and thereby provide oxygen to the cells for metabolism purposes, and (ii) to remove the collected $CO_2$ from the pulmonary blood. Herein, we provide a noninvasive methodology to assess physiological metabolic rates as well as blood-oxygenation capacity of the lung. For this purpose, we analyze the compositions of the inspired and expired air per breath, and therefrom compute the metabolic $O_2$ consumption and $CO_2$ production rates.

Next, we derive expressions for diffusion coefficients $D_{O_2}$ and $D_{CO_2}$, in terms of the evaluated cardiac-output $CO$, $O_2$ and $CO_2$ concentrations in arterial and venous blood as well as alveolar and blood $O_2$ and $CO_2$ partial-pressures. The coefficients $D_{O_2}$ and $D_{CO_2}$ represent the lung capability to oxygenate the blood. We can then also determine the cardiac output, from knowing the concentrations of oxygen and carbon dioxide in the arterial and venous bloods.

The derived information of $D_{O_2}$ and $D_{CO_2}$ as well as of $O_2$ and $CO_2$ metabolic rates can be of considerable use (including for SARS assessment). The paper provides a case study for the determination of $Q$, $D_{O_2}$ and $D_{CO_2}$.

Keywords—gas exchange, $O_2$ metabolic-rates, $CO_2$ metabolic-rates, diffusion coefficients $D_{O_2}$, diffusion coefficients $D_{CO_2}$, blood flow rate

I. SCOPE

The lung functional performance is characterized by (i) its ventilatory capacity, to bring air (and hence $O_2$) into the alveoli, and (ii) its capacity to transfer $O_2$ and $CO_2$ into and from the pulmonary capillary bed. Hence, the $O_2$ and $CO_2$ diffusion coefficients $D_{O_2}$ and $D_{CO_2}$ as well as the $O_2$ consumption-rate and the $CO_2$ production rate represent the lung performance indices. In this paper, we are demonstrating their evaluations.

II LUNG GAS-EXCHANGED MODEL

Figure 1 schematically illustrates the gas-exchange between the lung alveolus and the pulmonary capillary-vasculature. Based on our earlier work [2] the gas exchange between the alveolar air and pulmonary capillary blood is represented by the following $O_2$ and $CO_2$ conservation equations and Figure 2.

\[
\begin{align*}
Q^V E C_{O_2}^{VE} &= Q^A E C_{O_2}^{AE} + V_{O_2} \quad \text{(from the alveolar air to capillary blood)} \\
&= Q^A E C_{O_2}^{AE} + (\Delta P_{O_2}^{av}) D_{O_2} \\
Q^V E C_{CO_2}^{VE} &= Q^A E C_{CO_2}^{AE} - V_{CO_2} \\
&= Q^A E C_{CO_2}^{AE} - (\Delta P_{CO_2}^{av}) D_{CO_2}
\end{align*}
\]

wherein

(i) $Q^{AB}$ and $Q^{VB}$ are arterial and venous blood flow-rates;

(ii) $P_{O_2}^{al}$ and $P_{O_2}^{cap}$ are the alveolar and capillary $O_2$ partial pressures

(iii) $P_{CO_2}^{al}$ and $P_{CO_2}^{cap}$ are the alveolar and capillary $CO_2$ partial pressure

(iv) $D_{O_2}$ and $D_{CO_2}$ are the $O_2$ and $CO_2$ diffusion coefficients

(v) $\Delta P_{O_2}^{av}$ = average of $(P_{O_2}^{al} - P_{O_2}^{cap})$ over the capillary length;

$\Delta P_{CO_2}^{av}$ = average of $(P_{CO_2}^{al} - P_{CO_2}^{cap})$ over the capillary length

(vi) $P_{O_2}^{cap} = P_{O_2}^{PRB}$ ($O_2$ concentration of the pre-oxygenated blood) = $P_{O_2}^{AE}$

(vii) $P_{CO_2}^{cap} = P_{CO_2}^{PRB}$ ($CO_2$ concentration of the pre-oxygenated blood) = $P_{CO_2}^{VE}$
(viii) \( V_{O_2}^o \) is the \( O_2 \) transfer rate from alveolar air to capillary blood (= \( O_2 \) consumption rate), \( V_{CO_2}^o \) is the \( CO_2 \) transfer-rate from capillary blood to alveolar air.

Now we can equate the arterial and venous blood flow rates, as
\[ Q^{AE} = Q^{AB} = Q^{VE} = Q = (SV)/(EP) \]
SV, EP and CO being the stroke-volume, ejection-period and cardiac-output respectively.

III. CLINICAL DATA

The monitored data consists of inspired and expired air gas compositions (Table 1) and \( O_2 \) and \( CO_2 \) concentrations of arterial blood and venous blood (Table 2).

Table 1: Air Composition Analysis. Inspired and expired air composition and partial pressures are monitored. Assumed Breathing Rate (BR) = 12 breaths/min. Assumed \( P_{H_2O}^o \) at 37°C = 47 mmHg.

<table>
<thead>
<tr>
<th>Respiratory gases</th>
<th>Atmospheric Air</th>
<th>Expired Air</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmHg</td>
<td>ml/%</td>
</tr>
<tr>
<td>( N_2 )</td>
<td>597</td>
<td>78.55%</td>
</tr>
<tr>
<td>( O_2 )</td>
<td>159</td>
<td>20.84%</td>
</tr>
<tr>
<td>( CO_2 )</td>
<td>0.3</td>
<td>0.04%</td>
</tr>
<tr>
<td>( H_2O )</td>
<td>3.7</td>
<td>0.49%</td>
</tr>
<tr>
<td>Total</td>
<td>760</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 2: Blood Gas Analysis. The monitored blood \( O_2 \) and \( CO_2 \) concentration.

\[
\begin{align*}
C_{O_2} \text{ of venous blood (} C_{O_2}^{VB} \text{)} &= 0.13 \\
C_{O_2} \text{ of arterial blood (} C_{O_2}^{AB} \text{)} &= 0.18 \\
C_{CO_2} \text{ of venous blood (} C_{CO_2}^{VB} \text{)} &= 0.5 \\
C_{CO_2} \text{ of arterial blood (} C_{CO_2}^{AB} \text{)} &= 0.46
\end{align*}
\]

IV. EXPRESSIONS FOR \( D_{O_2} \) AND \( D_{CO_2} \)

If we want to evaluate the diffusion coefficients \( D_{O_2} \) and \( D_{CO_2} \), we need to also express \( P_{O_2}^{al} \), \( P_{O_2}^{cap} \) and \( P_{CO_2}^{al} \), \( P_{CO_2}^{cap} \) in terms of monitorable quantities [1 & 2].

(i) Alveolar \( P_{O_2}^{al} \) can be expressed in terms of \( V \) (the ventilation rate) and \( V_{O_2} \) (the \( O_2 \) consumption rate).
\[ P_{O_2}^{al} = 140 \left[ -4.18 \left( V/O_2 \right) \right] \left( 1 - e^{-4.18 \left( V/O_2 \right)} \right) \] \quad (3)

wherein the normalised ventilation rate, \( V^* = V/V_m = V/60 \) litres/min, is the consumption rate (in liters/min).

(ii) Alveolar \( P_{CO_2}^{al} \) can be expressed in terms of \( V^* \) and \( V_{O_2} \).

\[ P_{CO_2}^{al} = 114.68 e^{-2.46 \left( V^*/V_{CO_2} \right)} \] \quad (4)

wherein \( V_{CO_2}^* \) is the \( CO_2 \) production rate (in liters/min).

(iii) Blood \( P_{O_2} \) can be obtained in terms of \( O_2 \), from the \( O_2 \) dissociation curve.

\[ P_{O_2}^B = 29.72 \ln \left[ \frac{0.2}{0.2 - C_{O_2}^B} \right] \] \quad (5)

(iv) Blood \( P_{CO_2} \) can be obtained in terms of \( C_{CO_2}^B \), from the \( CO_2 \) dissociation curve.

\[ P_{CO_2}^B = 29.72 \ln \left[ \frac{0.8}{0.8 - C_{CO_2}^B} \right] \] \quad (6)

Now, \( (= P_O^{al} - P_O^{cap} = P_{O_2}^{al} - P_{O_2}^{VB}) \) both \( P_{O_2} \) and \( P_{CO_2} \)
\( (= P_{CO_2}^{VB} - P_{CO_2}^{al}) \) vary along the capillary bed. Based on [3], we have:

\[ \Delta P_{O_2}^{AV} = 0.185 \Delta P_{O_2}^{MAX} \] \quad (7)

\[ \Delta P_{CO_2}^{AV} = 0.1 \Delta P_{CO_2}^{MAX} \] \quad (8)

From the above expressions, we obtain:

\[ D_{O_2} = \frac{V_{O_2}^*}{\Delta P_{O_2}^{AV}} = \frac{V_{O_2}^*}{0.185 \left( P_{O_2}^{al} - P_{O_2}^{VB} \right)} \] \quad (9)

\[ D_{CO_2} = \frac{\Delta P_{CO_2}^{VB}}{\Delta P_{CO_2}^{AV}} = \frac{\Delta P_{CO_2}^{VB}}{0.1 \left( P_{CO_2}^{al} - P_{CO_2}^{VB} \right)} \] \quad (10)

V. DETERMINATION OF \( O_2 \) AND \( CO_2 \) METABOLIC RATES AND CARDIAC OUTPUT

From monitored data of inspired-exhaled gas compositions, in Table 1:

\[ O_2 \text{ consumption rate, } V_{O_2} = BR(\text{Inspired } O_2 - \text{Expired } O_2 \text{ )ml/min} = 12(104.2-83.37) = 250 \text{ ml/min} \] \quad (11)

\[ CO_2 \text{ consumption rate, } V_{CO_2} = BR(\text{Expired } CO_2 - \text{Inspired } CO_2 ) \text{ ml/min} = 12(16.87-02)=200 \text{ ml/min} \] \quad (12)

From monitored \( O_2 \) and \( CO_2 \) concentrations of arterial and venous blood, in Table 2:

\[ V_{O_2} = Q( CO_2 \text{ of arterial blood - } CO_2 \text{ of venous blood}) \]

where \( Q=\text{blood flow rate=cardiac output} \)

\[ Q = \frac{V_{O_2}}{0.18 - 0.13} = \frac{250}{0.05} = 5000 \text{ ml/min} \]

VI. EVALUATING OF THE LUNG DIFFUSION COEFFICIENTS \( D_{O_2} \) AND \( D_{CO_2} \)

From equation (3) and Table 2 ( \( C_{AB}^{O_2} =0.18 \)), we get for (arterial blood @ venous end of the pulmonary capillary or \( P_{O_2}^{al} \))

\[ P_{O_2}^{al} = 29.72 \ln \left[ \frac{0.2}{0.2 - C_{O_2}^{AB}} \right] \]

\[ = 29.72 \ln \left[ \frac{0.2}{0.2 - 0.18} \right] \]

\[ = 68.43 \text{ mmHg} \] \quad (13)

From equation (5) and Table 2 ( \( C_{VB}^{CO_2} =0.13 \)), we get for
\( P_{CO_2}^{al} \) (venous blood @ arterial end of the pulmonary capillary or \( P_{CO_2}^{al} \))
\[ p_{O_2}^{IV} = 29.72 \ln \left[ \frac{0.2}{0.2 - C_{O_2}^{IVB}} \right] \]

\[ = 29.72 \ln \left[ \frac{0.2}{0.2 - 0.13} \right] = 31.20 \text{ mmHg} \]  

(14)

Also, from equation (3) and Table 1 (\( V^* = 0.1 \)), we get:

\[ p_{O_2}^{ol} = 140 \left[ 1 - e^{-4.18 \left( \frac{V^*}{V_{O_2}} \right)} \right] \]

\[ = 140 \left[ 1 - e^{-4.18(0.1/0.25)} \right] = 113 \text{ mmHg} \]  

(15)

Hence, from equations (14 & 15), we get:

\[ \Delta p_{O_2}^\circ = 0.185 \times (113 - 31.2) = 14.95 \text{ mmHg} \]  

(16)

Finally, from equations (11) and (16), we get:

\[ D_{O_2} = \frac{V_{O_2}^\circ}{\Delta p_{O_2}^\circ} = \frac{250 \text{ ml/min}}{14.95 \text{ mmHg}} \]

\[ = 16.72 \text{ ml/min}^{-1} \text{ mmHg}^{-1} \]  

(17)

From equation (6) and Table 2 (\( C_{CO_2}^{IVB} = 0.5 \)), we get:

\[ p_{CO_2}^{IVB} = p_{CO_2}^{AE} = 29.72 \ln \left[ \frac{0.8}{0.8 - C_{CO_2}^{IVB}} \right] \]

\[ = 29.72 \ln \left[ \frac{0.8}{0.8 - 0.5} \right] = 29.15 \text{ mmHg} \]  

(18)

Then from equation (4), Table 1 (\( V = 0.1 \)), and equation (12) we get:

\[ p_{CO_2}^{ol} = 114.68 e^{-2.46 \left( \frac{V^*}{V_{CO_2}} \right)} \]

\[ = 114.68 e^{-2.46(0.1/0.2)} = 33.52 \text{ mmHg} \]  

(19)

Hence, from equations (8, 18 & 19), we get:

\[ \Delta p_{CO_2}^\circ = 0.1 \times (33.52 - 29.15) = 0.44 \text{ mmHg} \]  

(20)

Finally, from equations (10 & 20), we get:

\[ D_{CO_2} = \frac{V_{CO_2}^\circ}{\Delta p_{CO_2}^\circ} = \frac{200 \text{ ml/min}}{0.44 \text{ mmHg}} \]

\[ = 454.55 \text{ ml/min}^{-1} \text{ mmHg}^{-1} \]  

(21)

**VII. CONCLUSION**

We have demonstrated a noninvasive clinical procedure:

- for obtaining (i) \( O_2 \) consumption rate and \( CO_2 \) production rate, (ii) cardiac outflow-rate or output, \( Q \), (iii) and lung diffusion capacities for \( O_2 \) and \( CO_2 \).
- from inhaled and exhaled air composition analysis, and blood-gas analysis.

This work could have application to SARS testing and evaluation.

**REFERENCES**

[1] Loh Kah Meng, Dhanjoo N. Ghista and Heiko Rudolph, *Determination of \( O_2 \) and \( CO_2 \) Metabolic-Rates and Lung Diffusion Coefficients, based on the Data of Inspired and Expired Air Compositions*, Annals, Academy of Medicine.


Abstract— This paper provides a systems-engineering analysis of the glucose-insulin responses to an ingested bolus of glucose for OGTT (Oral Glucose Tolerance Test). The clinical data of patients is fitted by either under-damped or over-damped or critically-damped solutions of the model’s governing equations for glucose and insulin responses to glucose bolus ingestion. Based on the best fit of the three types of solutions, we designate the patients (and their response) to be normal (and under-damped), diabetic (and over-damped) and either border-line or at-risk of becoming diabetic (and critically-damped). In this way, the model simulation of the clinical data enables more reliable diagnosis relative to the clinical assessment.

Keywords—diabetic, systems-engineering model, under-damp, over-damp, critically-damped, R-square, fitting, clinical diagnosis

I.  INTRODUCTION

Oral Glucose Tolerance Testing Protocol

The test subjects need to fast for 12 hours before the test and during the 2-hour test. A blood sample of the subject is taken before the beginning of the test. Then after the subject drinks a 75 g of glucose solution dissolved in 250–300 mL of water, the subject’s blood glucose and insulin concentrations are measured at specified intervals 30 minutes, 60 minutes, 90 minutes and 120 minutes [1, 2, 4].

Qualitative interpretation of the results, for preliminary categorization of the patients [1, 2, 4]:

(a) Blood glucose normal values:
   - fasting: 70 to 115 mg/dl
   - 30 min.: less than 200 mg/dl
   - 1 hour : less than 200 mg/dl
   - 2 hour : less than 140 mg/dl

(b) Normal insulin level (reference range): 1-30 mU/L

When a person has a fasting glucose equal to or greater than 110 mg/dl and less than 126 mg/dl, it is considered as impaired fasting glucose. This is considered a risk factor for future diabetes and will likely trigger another test in the future, but, by itself, does not make the diagnosis of diabetes.

A person is said to have impaired glucose tolerance when the 2-hour glucose results from the oral glucose tolerance test are greater than or equal to 140 but less than 200 mg/dl. This is also considered a risk factor for future diabetes. A person has diabetes when oral glucose tolerance tests show that the blood glucose level at 2 hours is equal to or more than 200 mg/dl. This must be confirmed by a second test (any of the three) on another day.

II. SYSTEM SOLUTIONS FOR DIABETIC, NON-DIABETIC AND AT-RISK PATIENTS

The governing differential equation for glucose response to glucose bolus intake is:

\[ y' = q(t) - \gamma x - \delta y \]  \hspace{1cm} (1)

The governing differential equation for insulin response to glucose bolus intake is:

\[ x' = p(t) - \alpha x + \beta y \]  \hspace{1cm} (2)

\[ y(t) : \text{Glucose response of the patient to the oral bolus of glucose.} \]
\[ x(t) : \text{Insulin response of the patient due to } y(t). \]

Solution For Underdamped Case (non-diabetic):

\[ y(t) = \left( G/\omega \right) e^{\alpha t} \sin \omega t \]  \hspace{1cm} (3)

\[ x(t) = \left( \frac{-\sin(wt)\alpha e^{(-At)}}{-\sin(wt)\alpha e^{(-At)} - e^{(-\alpha t)}w + \cos(wt)e^{(-At)} w} \right) \left[ \frac{x\beta G}{w} \right] \left( A^2 - 2A\alpha + \alpha^2 + w^2 \right) \]  \hspace{1cm} (4)
Solution For Overdamped Case (diabetic):

\[ y(t) = \frac{G}{\omega} e^{-At} \sinh(\omega t) \]  \hspace{1cm} (5)

\[ x(t) = \frac{1}{2} \left[ \cosh(wt + At - \alpha t)A - \sinh(wt + At - \alpha t)A \right] \]
\[ + \cosh(wt - At - \alpha t)A - \sinh(wt - At - \alpha t)A \]
\[ + \sinh(wt - At - \alpha t)w \cosh(wt + At - \alpha t)w \]
\[ - \sinh(wt + At - \alpha t)w \cosh(wt - At - \alpha t)w \]
\[ - \cosh(wt + At - \alpha t)A - \sinh(wt + At - \alpha t)A \]
\[ + \cosh(wt - At - \alpha t)A + 2w \]
\[ + \sinh(wt + At - \alpha t)w \sinh(wt - At - \alpha t)w \]
\[ \left( -w^2 + A^2 - 2A\alpha + \alpha^2 \right) \]  \hspace{1cm} (6)

Solution For Critically Damped Case (at the dangerous boundary):

\[ y(t) = G e^{-At} \]  \hspace{1cm} (7)

\[ x(t) = -\beta G t A e^{-At} - t\alpha e^{-At} + e^{-At} - e^{-(At)} \left( A - \alpha \right)^2 \] \hspace{1cm} (8)

III. CLINICAL APPLICATION AND DISCUSSION

Under-damped Category and Normal Designated Patient

These \( y(t) \) and \( x(t) \) response solutions are fitted to the monitored glucose and insulin data, and the fitness coefficients are determined. Based on the high degree of fit, patient S14 fits best the under-damped category, and hence is designated to be normal. His Glucose and Insulin responses, shown in Figure 1, illustrates the fast recovery of blood glucose and insulin concentrations.

The below table displays the values of the model parameters and the R-Square coefficients of fitness and the model solution to the clinical data.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
<th>Fitting</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2.007</td>
<td>Glucose SSE</td>
</tr>
<tr>
<td>G</td>
<td>2.795</td>
<td>Fit</td>
</tr>
<tr>
<td>( \omega )</td>
<td>1.882</td>
<td></td>
</tr>
<tr>
<td>( \alpha )</td>
<td>2.8243</td>
<td>Insulin SSE</td>
</tr>
<tr>
<td>( \beta )</td>
<td>0.1059</td>
<td>Fit</td>
</tr>
<tr>
<td>( \gamma )</td>
<td>1.1895</td>
<td></td>
</tr>
<tr>
<td>( \delta )</td>
<td>2.6355</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1: Patient S14 is designated to be under-damped and normal. However, this patient is quite hyper-insulinemic; in other words, this patient has elicited considerable insulin response in order to maintain an under-damped glucose response.

Over-damped Category of Patients Designated as Diabetic

For patients D05, our over-damped model solution fits the clinical data best of the 3 solution categories. Hence, this patient is designated to be diabetic. His Glucose and Insulin responses are shown in Figure 2, and the model parameters are given in the Table.

![Diabetic Glucose and Insulin Response](image_url)

The below table displays the values of the model parameters and the R-Square coefficients of fitness and the model solution to the clinical data.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
<th>Fitting</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1.385</td>
<td>Glucose SSE</td>
</tr>
<tr>
<td>G</td>
<td>5.32</td>
<td>Fit</td>
</tr>
<tr>
<td>( \alpha )</td>
<td>0.0001507</td>
<td>Insulin SSE</td>
</tr>
<tr>
<td>( \beta )</td>
<td>0.01742</td>
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</tr>
<tr>
<td>( \gamma )</td>
<td>0.4972</td>
<td></td>
</tr>
<tr>
<td>( \delta )</td>
<td>3.8560</td>
<td></td>
</tr>
</tbody>
</table>
Figure 2: This patient D05 has the higher R-Square value when fitted by the over-damped solution, and is hence classified as diabetic.

Critically-damped Category of Patients

There are some patients clinically diagnosed to be normal for which the critically-damped solution gives a better fit of the data (and a higher value of R-Square) than the under-damped solution. One such patient is S04, whose under-damped and critically-damped model response-curves are shown in Figures 3 and 4. Similarly, patients S06 and S19 are not normal as clinically diagnosed, but at the risk of becoming diabetic. Their response curves are illustrated in Figures 5 and 6.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
<th>Fitting</th>
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<tbody>
<tr>
<td>A</td>
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<tr>
<td>G</td>
<td>3.0480</td>
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<tr>
<td>α</td>
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<td>γ</td>
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<td>δ</td>
<td>0.7170</td>
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<tr>
<td>δ</td>
<td>0.9320</td>
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</table>

Figure 3: This S04 patient’s data is fitted by the under-damped solution. Next, we will compare the results fitted by the critically-damped solution as shown in the following figure.

Figure 4: This S04 patient’s data is better fitted (i.e. at higher R-Square value) by the critically-damped solution than by the under-damped solution. Because of the critically-damped model solution giving us a better fit (iterations of a higher value of R-Square), we differ from the clinical diagnosis and alert this patient that he is at risk at becoming diabetic.
Figure 5: This S06 patient’s data is better fitted (i.e. at higher R-Square value) by the critically-damped solution than by the under-damped solution. Hence, we will differ from the clinical diagnosis and designate this patient to be at risk of becoming diabetic.

<table>
<thead>
<tr>
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<td>$\delta$</td>
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Figure 6: This S19 patient’s response curves are best fitted (with a higher value of R-Square) by the critically-damped solution than by the under-damped solution.

V. CONCLUSION

We have shown that we can obtain more accurate assessment of diabetic patients by means of our under-damped, over-damped and critically-damped simulation model solutions. Some patients (diagnosed to be normal) were designated by us to be in the borderline category. However, some patients who were clinically declared to be diabetic turned out to be only border-line. As we continue this work, we will develop a clinically-implementable software for model parameter identification and designation of the subjects as normal or at-risk of becoming diabetic or border-line diabetic or distinctly diabetic.

REFERENCES


## Technical Programme

### Scientific Programme – DAY 1

**Wednesday, September 08 2004**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>0800 – 0920</td>
<td>Registration</td>
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<tr>
<td>0920 – 0940</td>
<td>Opening Ceremony</td>
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<tr>
<td>0940 – 1010</td>
<td>Nanostructure Processing of Advanced Biomaterials</td>
</tr>
<tr>
<td></td>
<td>Invited Speaker: Dr. Jackie Ying</td>
</tr>
<tr>
<td>1010 – 1040</td>
<td>Bioengineering, Technology Commercialization and Entrepreneurship</td>
</tr>
<tr>
<td></td>
<td>Invited Speaker: Dr. Yongmin Kim</td>
</tr>
<tr>
<td>1040 – 1100</td>
<td>Tea break</td>
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<tr>
<td>1100 – 1130</td>
<td>Esophageal Tissue Engineering</td>
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<tr>
<td></td>
<td>Invited Speaker: Dr. Buddy Ratner</td>
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<tr>
<td>1130 – 1200</td>
<td>A Case Study of Integrated Biomedical Engineering: A Novel Method for</td>
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<tr>
<td></td>
<td>Creating an Automated Sutureless Anastomosis</td>
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<td>Invited Speaker: Dr. Adam Sharkawy</td>
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<tr>
<td>1200 – 1230</td>
<td>Advances in Cancer Imaging</td>
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<tr>
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<td>Invited Speaker: Dr. James Khoo</td>
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<tr>
<td>1230 – 1330</td>
<td>Lunch</td>
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<tr>
<td>1330 – 1400</td>
<td>Tissue Engineering Heart Constructs using Bone Marrow Stem Cells</td>
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<tr>
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<td>Invited Speaker: Dr. Philip Wong</td>
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<tr>
<td>1400 – 1430</td>
<td>Computational Technologies to Accelerate Biotech Innovation</td>
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<td>Invited Speaker: Dr. Ulrich Meier</td>
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<tr>
<td>1430 – 1500</td>
<td>A new Approach to Protein Structure Prediction</td>
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<td>Invited Speaker: Dr. Heiko Schroder</td>
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<td>1500 – 1515</td>
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<tr>
<td>Session 01 Tissue Engineering (Room 1)</td>
<td>Session 02 Cancer Detection &amp; Therapy (Room 2)</td>
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<tr>
<td>1515 – 1730</td>
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</table>

**Session 01 Tissue Engineering**
- Enhancement of Meniscus Repair using Mesenchymal Stem Cells
- Cardiac Differentiation of Adult Bone Marrow Mesenchymal Stem Cells
- Polyurethane Membranes for Chondrocyte Transplantation and Cartilage Engineering
- Theoretical and Experimental Determination of State of Two Dimensional Strain in a Bioreactor
- Culture of Rodent Hepatocytes on Microgrooved Surfaces: Application for a Flat-Plate Bioartificial Liver Device
- Simultaneous Probing of Morphology, Cytoskeleton, and Adhesion Dynamics of HepG2 Cells
- ECM-Dependent Proliferation of Adult Bone Marrow Mesenchymal Stem Cells
- Parameters for Scaffold Design of Esophageal Tissue from a Structural Constitutive Model
- Surface modification of biodegradable poly(L-lactide-co-caprolactone) (PLLC) membrane with proteins to enhance the growth of esophageal smooth muscle cells

**Session 02 Cancer Detection & Therapy**
- Automated Segmentation of Breast Masses in Mammograms
- Diagnosis of Lung Cancer Using NIR Raman Spectroscopy
- Extraction of head and neck tumors using deformation models from MR images
- Breast Cancer Diagnosis using Thermography and complementary learning fuzzy neural network
- Magnetic Particles for Hyperthermia Treatment of Cancer
- Gene Selection for Cancer Classification from Microarray Data using PLS-RLSC
- Micelle-like Nanoparticles of Linear and Branched PLA/PEG Block Copolymer as Anti-Cancer Drug Carrier
- Identify human colorectal cancerous via Laser Induced Autofluorescence spectra confocal image
- Parameters for Scaffold Design of Esophageal Tissue from a Structural Constitutive Model

**Session 03A Medical Image Processing**
- ALA-Induced-PPIX Fluorescence Imaging of Normal and Neoplastic Tongue Tissue using Confocal Endomicroscopy
- A Simulation System for Remote Interventional Radiology Procedures
- An Improved Active Contour Method for Heart Wall Boundary Detection in Echocardiographic Image Sequence
- Augmented Reality Assisted Sinus Surgery
- Brain Atlas-assisted Segmentation of the Hippocampus from MR Neuroimages
- Removing Blocking Artifacts in Compressed Medical Images
- Simulated Annealing based Simplified Snakes for Weak Edged Medical Image Segmentation
- Extraction of the Two Modified Talairach Cortical LandMarks (I and S) from MR T1-Weighted Images
- Knowledge-based Interpolation of the Talairach-Tournoux Brain Atlas
- Mapping Human Skin and Aural Temperature with ANNs and IR Imagery

**Session 04 Microfluidics/MEMS**
- AFM Characterization and Selectivity of Immobilization of Antibodies in Bio-MEMS
- Cross-Talk, a Potential Source of Noise in a Fluorescence Multi-channel Microfluidic System
- Microfluidic Protein Patterning using Embedded Cavities in Microchannels
- A LA-Induced-PPIX Fluorescence Imaging of Normal and Neoplastic Tongue Tissue using Confocal Endomicroscopy
- A Simulation System for Remote Interventional Radiology Procedures
- An Improved Active Contour Method for Heart Wall Boundary Detection in Echocardiographic Image Sequence
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END OF DAY 1
## Scientific Programme – DAY 2

**Thursday, September 09 2004**

<table>
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<tr>
<th>Time</th>
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<tr>
<td>0830 – 0900</td>
<td>Development of Microfluidic-Based Point-of-Care Diagnostic Systems</td>
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<td>Invited Speaker: Dr. Paul Yager</td>
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<tr>
<td>0900 – 0930</td>
<td>Innovation in The Medical Device Industry: Development of Cypher - the first Drug-Eluting Stent</td>
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<td>Invited Speaker: Mr. Alok Mishra</td>
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<td>0930 – 1000</td>
<td>Heart Tissue Engineering</td>
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<td>Invited Speaker: Dr. Buddy Ratner</td>
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<tr>
<td>1000 – 1015</td>
<td>Tea break</td>
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<tr>
<td>Session 05 Biomaterials &amp; Drug Delivery (Room 1)</td>
<td>Session 06 Biomechanics (Room 2)</td>
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<tr>
<td>• Smart Polymer Nanocarriers for Targeted Delivery Yang Y.Y</td>
<td>• Biomechanics Highlights in Sports, Physiology and Medicine Ghista D.N.</td>
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<td>• Release of Lipoplexes from a Biodegradable Polymeric Film: Preliminary Study Chan W.A., Ramgopal Y.</td>
<td>• Evolution and Biomechanics of the Cruciate Ligaments Fuss F.K.</td>
</tr>
<tr>
<td>• Cross linking of Bovine Serum Albumin with Genipin: Investigation of Mechanical Properties Sathappan K., Chian K.S., Chua L.P.</td>
<td>• The Double-Bundle ACL Graft Reconstruction: A superior technique to restore knee kinematics Lie D.T.T., Amis A.</td>
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<tr>
<td>• In vitro Study on the Release Kinetics of Bovine Serum Albumin (BSA) from Injectable PLGA/BB Depot Wang L.W., Venkatraman S.</td>
<td>• A Comparative Study of Different Gripping Methods for Tendons Ng B.H., Chou S.M., Krishna V.</td>
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<td>• LUNCH 1230 - 1330</td>
<td>• A Comparative Study of Different Gripping Methods for Tendons Ng B.H., Chou S.M., Krishna V.</td>
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<tr>
<td>Session 08A Cardiovascular Engineering 1 (Room 1)</td>
<td>Session 09A Sport Engineering 1 (Room 2)</td>
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<td>1330 – 1530 Chair: A.C. Ritchie</td>
<td>1330 – 1530 Chairs: W. Kim, F.K. Fuss</td>
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<tr>
<td>• Computational Studies of Steady Flows In Designed Sleeve Models At Distal Anastomoses Chua L.P., Tong J.H.</td>
<td>• Biomechanics of Push-up Exercise and Triceps Contractility Tan M. A., Zhong L., Fuss F. K., Ghista D. N.</td>
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<td>• Contractility of the Left Ventricle in Terms of its Sacromere Power Generation Zhong L., Ghista D.N., Ng E.Y.K</td>
<td>• Comparison of Pinch- and Open Hand Grip during Sport Climbing Yap Y. H., Fuss F. K., Niegl G., Tan M. A.</td>
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<td>• Detection of Cardiac Arrhythmia using Phase Space Analysis Wong M. T., Srinivasan N., Chan Y.W.</td>
<td>• Friction at the Climbing Handhold under Different Conditions and its Implications for Sport Climbing Tan M. A., Fuss F. K., Niegl G.</td>
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<td>Tea Break 1530 -1545</td>
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| Session 08B Cardiovascular Engineering 2 (Room 1) 1545 – 1645  
Session Chair:  A.C. Ritchie | Session 09B Sport Engineering 2 (Room 2) 1545 – 1630  
Chairs:  B. Tan, K.C. Teh | Session 10B Ultrasonic Imaging 2 (Room 3) 1545 – 1645  
Chair:  M. Kezhi |
|---|---|---|
| • Multiple-Model Adaptive Control by Means of a Fuzzy Controller-based Control System  
Zheng H., Zhu K. Y., Tan Y. S.  
• Numerical Investigation of Hemodynamics for the Coronary Artery Bypass Graft Model  
• Numerical Investigation of Stress Field in Distal End-to-side Anastomoses  
Liu L., Chua L.P., Ghista D.N., Tan Y.S.  
• PIV Measurements on the Pulsatile Flow Characteristics in 45-degree Backward Proximal Anastomosis  
• Determinants of Maximal Hiking Performance in Laser Sailors  
• Comparative Study on the techniques of Singapore and Thailand Table Tennis players during SEA Games 2001  
Lee K.T., Xie W., Teh K.C.  
• Experimental Study on Different Types of Service Spins for Singapore National Table Tennis players  
Lee K.T., Xie W.  
• Field of View-based Imaging for Efficient Beamforming in Low-end Portable Ultrasound Systems  
Agarwal A., Schneider F.K., Yoo Y.M., Kim Y.  
• Low Sampling Frequency Digital Beamformer for Ultrasonic Imaging without Interpolation  
Gao C.Q., Zhang L.C., Wong E.M.C.  
• Comparative Evaluation of Wavelet Filters for Speckle Reduction in Ultrasound Medical Images  
Thakur A., Anand R.S.  
• Window Function Optimization by Genetic Algorithm for Ultrasonic Imaging System  
Cao J., Koh L.M. |  
| | |  
| • Determination of O2 and CO2 Metabolic Rates and Lung O2 and CO2 Diffusion Coefficients  
Loh K.M., Ghista D.N.  
• Oxygen Saturation Profiles in a Hollow Fibre Oxygenator  
Ritchie A.C., Thimm G.  
• Graphical Technique for Assessing Pulmonary Disease  
Loo C. M., Ang K. C., Ong J. H., Ghista D. N., Lim G. H.  
• Design Optimisation in BioMedical Engineering  
Koh E.C.Y., Fuss F. K.  
• Design Classification and Mechanics of Artificial Discs  
Fuss F.K.  
• Extraforaminal Lumbar Interbody Fusion: Simulation of the Fusion Process Based on Different Implant Materials  
Fuss F. K., Sabitzer R. J.  
• FE Investigation on Spinal Interbody Fusion  
Lee K. K., Teo E. C., Fuss F. K., Sabitzer R. J.  
• Optimization of Cervical Ring Cage by Taguchi Philosophy  
Yang K., Teo E. C., Fuss F. K.  
• A Novel Approach to Automatic Left Ventricular Contour Tracking  
Cheng J.R., Foo S.W.  
• A Novel Wavelet Based ECG Compression with X-tree Coding  
Swain S., Chutatape O., Dandapat S.  
• Left Ventricular Surface Kinematics During Isovolumic Contraction  
Yeo S.Y., Tan R.S., Liu L., Chai G.B., Ghista D.N.  
• Evaluation of Slice Sensitivity Profiles for TPRF Algorithm  
Yan M., Zhang C.S.  
|
### Scientific Programme – DAY 3

**Friday, September 10 2004**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker/Topic</th>
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<tr>
<td>0830-0900</td>
<td>Biological Resurfacing of Articular Cartilage – from Bench to Bedside</td>
<td>Invited Speaker: Dr. Lee Eng Hin</td>
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<tr>
<td>0900-0930</td>
<td>Virtual Reality, Augmented Reality and its Medical Application</td>
<td>Invited Speaker: Dr. Uli Bockholt</td>
</tr>
<tr>
<td>0930-1000</td>
<td>Vital Signs in the Real World</td>
<td>Invited Speaker: Mr. Stephen Wilson</td>
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<tr>
<td>1000-1030</td>
<td>Clinical Endoscopy System: Present and Future</td>
<td>Invited Speaker: Dr. Tsuneo Hidaka</td>
</tr>
<tr>
<td>1030-1045</td>
<td>Tea break</td>
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<tr>
<td>Session 14 Biosensors/Diagnostic Tools (Room 1)</td>
<td>Session 13B Biosignal Processing 2 (Room2)</td>
<td>Session 15 Distributed Diagnosis &amp; Home Healthcare (Room 3)</td>
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<tr>
<td>1045-1200 Chair: K. L. Chan</td>
<td>1045-1130 Chair: C. Zhang</td>
<td>1045-1130 Chair: S. C. Tjin</td>
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<tr>
<td>• Multi-Parameter Clinical Diagnosis using Neural Networks Tan E.K.</td>
<td>• Uni-channel PCA for noise reduction from ECG signals Palaniappan R., Tan E.K.</td>
<td>• Distributed Diagnosis and Home Healthcare (D2H2) and Patient-Centered Electronic Medical Record Kim E.H., Kim J. J., Matsen F.A., Kim Y.M.</td>
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<tr>
<td>• An Otoacoustic Emissions Detecting System using USB AD/DA Board Qian X., Ye D.</td>
<td>• Wavelet-Based Denoising and Analysis of Phonocardiogram Wang P., Anantharaman V.</td>
<td>• Advanced System Architecture for Telecardiology Goh K. W., Kugean C., Tan E. K., Prabaharan K.</td>
</tr>
<tr>
<td>• Feasibility of biosensing based on two-dimensional square photonic lattice Zhang D. W., Irawan R., Tjin S. C., Yuan X. C.</td>
<td>• Application of Artificial Neural Network Technique in Healthcare Expenditure Analysis Chia E., Khong P.W., Ghista D.N.</td>
<td>• Integration of CAD to FEA for Prosthetic Socket Design Goh J. C. H., Lee P. V. S., Toh S. L., Ooi C. K.</td>
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<tr>
<td>• Application of Artificial Neural Network Technique in Healthcare Expenditure Analysis Chia E., Khong P.W., Ghista D.N.</td>
<td>• Analyses of Fractured Bone (Femur) with Plate and Intra-Medullary Rod Fixations Chen Q., Fan S.C., Ghista D.N.</td>
<td>• Automatic 3-D optic Disk Image Reconstruction from Low-Resolution Fundus Image for Glaucoma Analysis Xu J., Chutatape O.</td>
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<td>• Modified Deformable region model for Lumen Extraction from Colonoscopic Image and Comparison with FCM Tjoa M. P., Zheng M. M., Doraiswami R., Tang C.L.</td>
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</table>
Appendix J

System and Method for Detecting Pulmonary Diseases
17 February 2005

Mr. Fong Siew Cheong
NANYANG POLYTECHNIC
180 Ang Mo Kio Ave 8
Singapore 569830

Dear Mr. Fong,

Applicant: NANYANG POLYTECHNIC
Entitled: SYSTEM AND METHOD FOR DETECTING OF PULMONARY DISEASES
Our Ref: 1138.P056SG/GDL/faa

Further to our letter dated 21 December 2004, we are pleased to inform you that we have received a notification for the “Allocation of Filing Date” from the Intellectual Property Office of Singapore for the above-referenced application.

Enclosed please find a copy of the Registry’s notification, providing as follows:

Filing Date : 20 December 2004

Please do not hesitate to contact us should you have any queries or concerns.

Yours sincerely,

LAWRENCE Y D HO & ASSOCIATES PTE LTD

Farah Aziz
International Department
Email: farah.aziz@patents.com.sg

Encl. (via Mail)
8 November 2004

Mr Fong Siew Cheong
Nanyang Polytechnic
180 Ang Mo Kio Ave 8
Singapore 569830

Dear Mr Fong,

Re.: PCT Application Corresponding to


Applicant: NANYANG POLYTECHNIC

Entitled: SYSTEM AND METHOD FOR DETECTING OF PULMONARY DISEASES

Our Ref: 1138.P056SG/GDL/jc

We are pleased to inform you that we have received the “Notification of the International Application Number and of the International Filing Date” from the Intellectual Property Office of Singapore for the above referenced application.

Enclosed is a copy of the filing receipt as follows:

International Application No. PCT/SG2005/000300
Filing date: 1 September 2005

Please do not hesitate to contact us should you have any questions or concerns.

Yours sincerely,

LAWRENCE Y D HO & ASSOCIATES PTE LTD

Jennifer Cheng
International Department
Email: jennifer.cheng@patents.com.sg

End

Please note our direct fax is (65) 6732-3188 (International Dept)

SINGAPORE OFFICE: 30 BIDEFORD ROAD, #07-01 THONGSIA BUILDING, SINGAPORE 229922.

MALAYSIA OFFICE: SUITE 8,02, 8TH FLOOR, PLAZA FIRST NATIONWIDE, 161 JLN TUN H. S. LEE 50000 KUALA LUMPUR, MALAYSIA. EMAIL: lawrence.ho@patents.com.my WEBSITE: www.patents.com.my
**From the RECEIVING OFFICE**

**To:**
Lawrence Y D Ho & Associates Pte Ltd  
30 Bideford Road #07-01  
Thongsia Building  
Singapore 229822

**PCT**

**NOTIFICATION OF THE INTERNATIONAL APPLICATION NUMBER AND OF THE INTERNATIONAL FILING DATE**

(PCT Rule 20.5(c))

<table>
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<th>Date of mailing (day/month/year)</th>
<th>06 SEP 2005 (06/09/2005)</th>
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**Applicant's or agent's file reference**

1138P056PCTJ

**International application No.**

PCT/SG2005/000300

**International filing date (day/month/year)**

01 SEP 2005 (01/09/2005)

**Priority date (day/month/year)**

20 DEC 2004 (20/12/2004)

**Applicant**

NANYANG POLYTECHNIC

**Title of the invention**

SYSTEM AND METHOD FOR DETECTING OF PULMONARY DISEASES

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.

2. The applicant is further notified that the record copy of the international application:

   ☑ was transmitted to the International Bureau on 06 SEP 2005 (06/09/2005)

   ☐ has not yet been transmitted to the International Bureau for the reason indicated below and a copy of this notification has been sent to the International Bureau*:

     ☐ because the necessary national security clearance has not yet been obtained.

     ☐ because (reason to be specified):

* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).

**Name and mailing address of the receiving Office**

Intellectual Property Office of Singapore  
S1 Bras Basah Road, #04-01  
Post Box 1437, Singapore 119954  
Facsimile No. 63989200

**Authorized officer**

SURIAT BTE RAAT  
63302750  
Telephone No.

Form PCT/RO/105 (July 1992; reprint January 2004)
2 September 2005

Mr. Fong Siew Cheong
NANYANG POLYTECHNIC
180 Ang Mo Kio Ave 8
Singapore 569830

Dear Mr. Fong,

Re: New PCT Application based on
Applicant: NANYANG POLYTECHNIC
Entitled: SYSTEM AND METHOD FOR DETECTING OF PULMONARY DISEASES
Our Ref: 1138.P056SG/GDL/jc

We are pleased to inform you that we have filed the above-referenced PCT application with the Intellectual Property Office of Singapore on 1 September 2005. We should be receiving the official filing receipt in a few weeks at which time the application number should become available.

Enclosed by mail please find a copy of our cover letter to the Registrar and the documents as filed, for your records.

Please do not hesitate to contact us should you have any questions or concerns.

Thank you very much for entrusting this matter to us.

Yours sincerely

LAWRENCE YD HO & ASSOCIATES PTE LTD

[Signature]

Jennifer Cheng
International Department
Email: jennifer.cheng@patents.com.sg

Encl: Invoice - via Mail
SYSTEM AND METHOD FOR DETECTING OF PULMONARY DISEASES

Field of the Invention

[0001] The present invention generally relates to systems and method for detecting of pulmonary diseases, and more particularly to non-invasive systems and methods for detecting of pulmonary diseases by analyzing inhalation and exhalation.

Background of the Invention

[0002] Lung is a vital organ allowing exchanges of O₂ and CO₂ between the alveolar sockets and bloods. When the lung is impaired, e.g., viral or bacterial infections, its physical appearance and/or functions will be altered, resulting in pulmonary diseases. The current detection of pulmonary diseases is mainly done by X-ray. However, the X-ray is not only invasive, but also only able to detect the physical alterations of lungs. Thus, the X-ray is not applicable for detecting pulmonary diseases at early stages. In addition, there are a broad range of so-called pulmonary function tests. For example, spirometry measures how well the lungs exhale. Lung volume measurement permits detection of restrictive lung diseases. Testing the diffusion capacity permits an estimate of how efficiently the lungs are able to transfer oxygen from the air into the bloodstream. However, all the available function tests are mere measures of systemic metabolism rather than of pulmonary functions.

[0003] It is well known that the components of exhalation could be utilized for diagnosis of certain diseases. For example, U.S. Pat. 4,823,803 discloses a device for testing human exhalation for halitosis by using sensors that are sensitive to malodorant gases of predetermined chemical compositions for producing signals variable with the detected concentrations of the malodorant gases. However, this patent is directed to the detection of malodorant gases rather than the lung functions.

[0004] There are situations in which an early detection of viral infection is critical for treatment of the victim and more importantly for the control of the epidemic. For example, the recent epidemic of SARS (Severe Acute Respiratory Syndrome) has raised concerns about effective detection of such relevant diseases, especially at a much earlier
stage of infection in human bodies. Upon early detection, scarce and precious medical resources can be focused on the infected persons. In the early stages of the infections, the X-ray screening may not be useful because the pathogenic damages on the lungs may not be evident enough to be detected by the machine. The current available function tests may not be able to detect the early signs of infections because the functions tests measure the systemic metabolism only. While PCR is powerful in detecting the early infection, it is prone to mutations. Massive mutations will handicap this technique severely.

Therefore, there is an imperative need to develop non-invasive systems and methods for detecting pulmonary diseases, especially ones inflicted by viral or bacterial infections. Furthermore, the detection is independent of the mutations of infectious agents. This invention satisfies this need by disclosing systems and methods of detecting pulmonary diseases by analyzing of the inhalation and exhalation of a test person. Other advantages of this invention will be apparent with reference to the detailed description.

Summary of the Invention

The present invention provides a to be completed upon agreement of claims.

The objectives and advantages of the invention will become apparent from the following detailed description of preferred embodiments thereof in connection with the accompanying drawings.

Brief Description of the Drawings

Preferred embodiments according to the present invention will now be described with reference to the Figures, in which like reference numerals denote like elements.

FIG 1 is a block diagram of the pulmonary disease detection system (PDSS) in accordance with one embodiment of the present invention.

FIG 2 shows a breath analyzer configured in accordance with one embodiment of the present invention.
FIG 3 shows a flowchart of detecting pulmonary diseases on the basis of altered oxygen consumption and carbon dioxide generation.

FIG 4 shows another functional flowchart of detecting pulmonary diseases in accordance with another embodiment of the present invention.

FIG 5a shows a diagram illustrating the directional relationships among the different pressures that may be detected or induced from the air flow rates detected by the breath analyzer as shown in FIG 2.

FIG 5b shows that different pressures are functions of time.

Detailed Description of the Invention

The present invention may be understood more readily by reference to the following detailed description of certain embodiments of the invention.

Throughout this application, where publications are referenced, the disclosures of these publications are hereby incorporated by reference, in their entireties, into this application in order to more fully describe the state of art to which this invention pertains.

The present invention provides systems and methods for detecting pulmonary diseases. While there are provided more details about the systems and methods hereinafter, it is to be appreciated that the present systems and methods are based on the understanding that anyone developing any pulmonary diseases would demonstrate certain detectable breathing deficiencies. The deficiencies may be manifested by the changes of the oxygen consumption and carbon dioxide generation, or the differences of lung compliance and airflow-resistance.

There is provided a block diagram of the pulmonary disease detection system (PDDS) as shown in FIG 1 in accordance with one embodiment of the present invention. The PDDS 100 comprises a breath analyzer 102, a computer processor 103, and a medical database 104. The breath analyzer 102 will take in the breath from a test person 101 and output the information of components of the breath from the person to the computer processor 103. The computer processor 103 contains algorithms for manipulating the information of the breath and comparing the manipulated results with the medical database 104, so that the computer processor provides the results of diagnosis 105.
The breath analyzer 102 may be any apparatus that can obtain breathing information from a test person that is sufficient for the application of the algorithms embedded in the computer processor 103. For example, for the application of an algorithm based on oxygen consumption and carbon dioxide generation, the breath analyzer 102 basically comprises of gas sensors such as sensors for oxygen, carbon dioxide and water vapor. The compositions of both inhale and exhale gases are analyzed. Then the respective compositions are further processed by the computer processor 103.

FIG 2 shows a breath analyzer 102 configured in accordance with one embodiment of the present invention. The breath analyzer 102 comprises a mask 1, a data acquisition unit 7, and an air tank 11. The mask 1 is configured to cover the nose and mouth of a test person so that maximum fresh air is delivered to the test person and minimum exhaled air is lost before proper measurement is completed. As shown in FIG 2, the mask 1 includes an air outlet membrane 2 as a seal for preventing air within the mask from leaking; an exhaust flip valve 3 that will open to allow all the expired air to flow out 4 of the mask when the test person breathes out; an air inlet membrane 21 as a seal for preventing air within the mask from leaking; an inhale flip valve 22 that will open to allow the fresh air from the air tank 11 to flow in 23 when the test person breathes in; an oxygen electrode 25 for detecting the oxygen in the air composition; a carbon dioxide gas electrode 24 for detecting the carbon dioxide in the air composition; a nitrogen gas electrode 17 for detecting the nitrogen in the air composition; a water vapor electrode 18 for detecting the water vapor in the air composition; an inspired air flow rate electrode 19 for determining the flow rate of exhale air; an expired air flow rate electrode 20 for determining the flow rate of exhale air; and signal conductors 5 that transmit the information from the electrodes to the data acquisition unit 7. The signal conductors may be ultra-low impedance conductor or fiber optic.

The air tank 11 contains pressurized air so as to ensure a measurable and controllable air supply to the test person. An air delivery pipe 16 connects the air tank with the mask so as to deliver a stream of controlled air from the air tank to the mask. The air tank 11 also includes four electrodes 12, 13, 14, 15 for detecting the oxygen, carbon dioxide, nitrogen, and water vapor respectively. The signal conductors 10 transmit the data from the four electrodes to the data acquisition unit 7. The signal conductors may be ultra-low impedance conductor or fiber optic.
The data acquisition unit 7 includes connectors 6, 9 for connecting to the signal conductors 5, 10 so that it will receive all the information from the air tank and the mask. Then the data acquisition unit 7 transmits the received signals to the computer processor 103 which acts as the central processing unit (CPU). The transmitted information may be digitalized packets.

After the CPU receives the data of the air compositions from the data acquisition unit 7, it will process the air composition data. In one aspect of the present invention, the detection of pulmonary diseases is based on the understanding that anyone developing any pulmonary diseases would demonstrate certain detectable breathing deficiencies. The inventors of the present invention further discovered that the breathing deficiencies are manifested by altered oxygen consumption and carbon dioxide generation. FIG 3 shows a flowchart of detecting pulmonary diseases on the basis of altered oxygen consumption and carbon dioxide generation.

Referring now to FIG 3, when the PDDS 100 starts 301, it obtains through the data acquisition unit 7 the information including oxygen composition, carbon dioxide composition, nitrogen composition, water vapor composition, and air flow rate 302. It is to be noted that the air flow rate data will be discussed hereinafter when the air flow rate will be used to calculate the volume compliance and air-flow resistance in another algorithm of the present invention. Then the CPU will calculate the overall relatives of all gases compositions 303. Then the processed data is searched against the stored database to determine whether the test person has pulmonary diseases 304. Then diagnostic results will be outputted 305 and the operation comes to an end 306. It is noted from FIG 3 that the stored database is continuously updated so that the database will become more useful when more data is collected.

Now there is provided a more detailed description of detecting pulmonary diseases on the basis of altered oxygen consumption and carbon dioxide generation. The basic assumption is that the composition of expired air from a patient such as a person with SARS infection is different from that of a normal person. It is further assumed that with an expired air, (a) its O2 content (or % vol.) will be greater (because of less O2 consumed from alveoli) and closer to that of inspired air; (b) its CO2 content will be lesser, and more akin to that of inspired air; and (c) the transfer coefficients for O2 & CO2 will be lesser as compared to a medically normal person. Therefore, the mass balance analysis involves (i)
compositions of air breathed in and out; and (ii) consumption or generation of \( O_2 \), \( CO_2 \) and \( H_2O \).

For calculation of inhale and exhale compositions, there are a few general assumptions: (1) Breathing Rate (BR) = 12 breaths/min; (2) \( P_{H_2O} \) at 37°C = 47mmHg; (3) \( O_2 \) metabolic consumption rate at (at BTP) = 284 ml/min; and (4) \( CO_2 \) production rate (at BTP) = 227 ml/min. Thus, the expected compositions of the expired air can be calculated from the atmospheric air or vice versa. For example, as shown in Table 1, the expected expired air compositions can be calculated from the numbers of the atmospheric air column:

\[
N_2 = 393.1 \text{ ml} \\
O_2 = 104.2 - (284/12) = 80.53 \text{ ml} \\
CO_2 = 0.2 + (227/12) = 19.12 \text{ ml} \\
\text{Total} = 492.75 \text{ ml (1)}
\]

Ratio of water vapor/dry gas in the expired air = 49.5mmHg/(760-47)
\[
= 49.5/713 = 6.94\% \quad (2)
\]

Volume of water vapor in the Expired air = (1)x(2)=492.75 0.0694=34.21ml
(3)

Total Expired air = [1]+[3]=492.75+34.21=526.96 ml \quad (4)

Thus the percentage of the gases components in the expired air can be calculated as follows:

\[
N_2 = 393.1/526.96 = 74.6\%; \\
O_2 = 80.52/526.96 = 15.28\%; \\
CO_2 = 19.12/526.96 = 3.63\%; \text{ and} \\
H_2O = 34.21/526.96 = 6.49\%.
\]

All the numbers of the atmospheric air and expired air are presented in Table 1.

Table 1. An exemplary air compositions

<table>
<thead>
<tr>
<th>Respiratory gases</th>
<th>Atmospheric Air</th>
<th>Humidified Air</th>
<th>Alveolar Air</th>
<th>Expired Air</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmHg</td>
<td>ml/%</td>
<td>mmHg</td>
<td>mmHg</td>
</tr>
<tr>
<td>( N_2 )</td>
<td>597</td>
<td>393.1</td>
<td>563.3</td>
<td>569</td>
</tr>
<tr>
<td></td>
<td>78.62%</td>
<td></td>
<td>78.5%</td>
<td>74.9%</td>
</tr>
<tr>
<td>( O_2 )</td>
<td>159</td>
<td>104.2</td>
<td>149.3</td>
<td>104</td>
</tr>
<tr>
<td></td>
<td>20.84%</td>
<td></td>
<td>20.9%</td>
<td>13.6%</td>
</tr>
</tbody>
</table>
So far it has been shown that if the rates of oxygen consumption and carbon dioxide generation are known, the ideal composition of an expired air can be calculated from the original composition of the atmospheric air. This is important for initializing the stored databases because in the early stages, the PDDS may have to generate part of the database by calculating the components of the expired airs from the atmospheric airs based on certain assumptions. With the gradual accumulation of the database, more and more actual data will supplement or substitute the calculated ones. As discussed earlier, the breath analyzer 102 of the present invention can acquire the data of individual gas components of the expired air from the test person and the CPU can manipulate the data to give the percentages of each gas component as to the expired air. The processed data of each gas components will be compared with the stored medical database. If the test person suffers from any illness that affects pulmonary functions, it is expected that the processed data of the expired air from a test person will be deviated from that of the stored database for a normal person. If this is so, the CPU will output the diagnostic results showing that the test person is probably having pulmonary diseases. Then the test person can seek further examinations to determine which kind of pulmonary diseases he/she is developing.

As shown in Table 1, it is apparent that the rates of oxygen consumption and carbon dioxide generation may be derived from the actual measurements of individual gas components of the atmospheric air and expired air. It is noted that all of the data of individual gas components can be obtained by the breath analyzer as shown in FIG 2. The calculated rates can be compared with the stored database to determine whether the test person is suffering any pulmonary diseases.

As mentioned earlier, the choice of a breath analyzer 102 for the present PDDS is limited by its function only. For example, when the lung compliance and airflow-resistance are used for detecting pulmonary diseases, the breath analyzer 102 may be a commercially available spirometer. Now referring to FIG 4, there is provided another functional flowchart of detecting pulmonary diseases in accordance with another
embodiment of the present invention. When the PDDS starts 400, it obtains data from the breath analyzer 401 (the same as the one shown in FIG 2) to determine the volume breath characteristics of the test person 402, and further extract the parameters of P0, P1, P2, Ra, Ca and W 403. If the extracted parameters are not the best filtered results 404, the program will go back to step 403 to try to get the best parameters. If the extracted parameters are the best filtered results 404, then the VTI1, VTI2 and VTI3 will be determined 405. Then the program will conduct diagnosis 407 by utilizing the medical databases 406, 408, and output the results 409, resulting the end of the program 410.

FIG 5a shows a diagram illustrating the directional relationships among the different pressures that may be detected or induced from the air flow rates detected by the breath analyzer as shown in FIG 2. FIG 5b shows that different pressures are functions of time. From there are derived a few fundamental equations that are the foundation for the algorithm shown in FIG 4:

\[ \begin{align*}
(i) \quad (P_a - P_p) - P_{el} &= 0 \\
(ii) \quad P_{el} &= \frac{(2 \omega h)}{R} \int r = \frac{2 T}{r} = \frac{V}{C} + P_{el, 0} \\
(iii) \quad (P_o - P_o) &= R{dV/dt} \\
(iv) \quad P_L &= P_o - P_p \\
(v) \quad R{dV/dt} + V/C &= P_L - P_{el, 0}
\end{align*} \]

Now there is provided a more detailed description of determination of the volume breath characteristics of the test person 402. In one embodiment of the present invention, the lung ventilation function is analyzed by means of a very simple model represented by a first-order differential equation (Deq) in lung-volume (V) dynamics in response to the driving pressure (\(P_L = \text{atmospheric pressure} - \text{pleural pressure}\)), as shown in FIG 5.

First, the model governing equation derived from the basic equations is as follows:

\[ RV + \frac{V}{C} = P_L(t) - P_{el, 0} = P_o + P_1 \cos \omega t + P_2 \sin \omega t - P_{el, 0} \]  \( (1) \)

wherein (i) \(P_o, P_1\) and \(P_2\) are obtained from the given \(P_L = (P_o - P_p)\) data; (ii) the parameters of this Governing Deq are lung compliance (C) and airflow-resistance (R), wherein in the equation both R and C are instantaneous valves; (iii) \(V = V(t) - V_o \) (the
lung volume at the end-expiration); and (iv) $P_{el,o}$ is the lung elastic recoil pressure at the end of expiration and $P_{el,o} = P_{el} - V/C$. 

At end-expiration when $\omega t = \omega T$, $P_L = P_{el,o}$. Hence, $P_{el,o} = P_a + P_I$, and the governing equation (1) becomes:

$$R\cdot \dot{V} + V/C = -P_1 + P_1 \cos \omega t + P_2 \sin \omega t = P_n \quad (2-a)$$

where the right-hand side represents the net pleural pressure. $(P_n = P_{atm} - P_p - P_{el,o})$ curve. This $P_n$ is in fact the driving pressure $(P_o - P_p)$ normalized with respect to its value at end-expiration. Equation(2-a) can be rewritten as follows:

$$\dot{V} + V/R \cdot C = -P_1 / R + (P_1 / R) \cos \omega t + (P_2 / R) \sin \omega t; \quad RC = \tau \quad (2-b)$$

wherein the P(t) clinical data displayed in FIG 5b is assumed to be represented by:

$$P_o = 9.84 \text{ cm H}_2 \text{O, } P_I = -1.84 \text{ cm H}_2 \text{O, and } P_2 = 3.16 \text{ cm H}_2 \text{O} \quad (3)$$

If, in equation (1), $R_a$ and $C_a$ are designated as the average values ($R$ and $C$) for the ventilatory cycle, then the solution of equation (1) is given by:

$$V(t) = -P_1 C_a + P_I C_a \left[ \frac{(\cos \omega t + \omega R_a C_a \sin \omega t)}{(1 + \omega^2 R_a^2 C_a^2)} \right] + P_2 C_a \left[ \frac{(\sin \omega t - \omega R_a C_a \cos \omega t)}{(1 + \omega^2 R_a^2 C_a^2)} \right] + H e^{-t/R_a} \quad (4)$$

wherein the term $(R_a C_a)$ is denoted by $\tau_a$, and $\omega = 1.55 \text{ rad/s}$ (based on the data in FIG 5b. If $V = 0$ at $t = 0$, then, putting $V(at t = 0) = 0$ gives us:

$$H = \frac{C_a \omega \tau_a}{(1 + \omega^2 \tau_a^2)} \{ P_2 + P_1 \omega \tau_a \} \quad (5)$$

Then from equations (4) and (5), the overall expression for $V(t)$ becomes:

$$V(t) = -P_1 C_a + \left\{ P_I C_a \left( \cos \omega t + \omega \tau_a \sin \omega t \right) / (1 + \omega^2 \tau_a^2) \right\} + \left\{ P_2 C_a \left( \sin \omega t - \omega \tau_a \cos \omega t \right) / (1 + \omega^2 \tau_a^2) \right\} + \left\{ e^{-t/R_a} \omega C_a \tau_a \left( P_2 + P_1 \omega \tau_a \right) / (1 + \omega^2 \tau_a^2) \right\} \quad (6)$$

If $dV/dt = 0$ at $t = 0$, implying no air-flow at the start of inspiration, then equation (6) can be differentiated into:
\[
\dot{V} = \frac{P_1 C_a}{(1 + \omega^2 \tau_a^2)} \left( -\omega \sin \omega t + \omega^2 \tau_a \cos \omega t \right) \\
+ \frac{P_2 C_a}{(1 + \omega^2 \tau_a^2)} \left( \omega \cos \omega t + \omega^2 \tau_a \sin \omega t \right) \\
+ \left\{ \frac{-C_a e^{-t/\tau_a}}{(1 + \omega^2 \tau_a^2)} \right\} \left( \omega P_2 + P_1 \omega^2 \tau_a \right)
\]  

(7)

From equation (7), we get: \( \dot{V} = 0 \) at \( t = 0 \), thereby also satisfying this initial condition. By matching the above \( V(t) \) expression (6) with the given \( V(t) \) data (in FIG 5b), and carrying out parameter-identification, the in vivo values of \( R_a \) and \( C_a \) can be determined. As a check, it can be verified that the substitution of (6) and (7) satisfies equation (2).

However, we can also analytically evaluate \( R_a \) and \( C_a \) by satisfying some conditions. For this purpose, we first note that \( V \) is maximum (=Tidal Volume, TV) at about \( t (= t_v) = 1.6s \), i.e. at \( \omega t_v = 2.48 \) rad. Now, for \( \omega t_v = 2.48 \) rad, we get: \( \sin(\omega t_v) = 0.62, \cos(\omega t_v) = -0.79 \) and \( \tan(\omega t_v) = -0.78 \). Also, for \( \omega t_v = 2.48 \) rad (and based on the knowledge of the range of \( \tau_a \)), the exponential term \( e^{-t/\tau_a} \) (in equation 6) becomes of the order of \( e^{-3} \) and less; hence, we decide to neglect it. So then, by and putting \( \dot{V} = 0 \) in equation (7), we obtain:

\[
\tan(\omega t_v) = \frac{P_2 + \omega \tau_a P_1}{P_1 - P_2 \omega \tau_a} = -0.78
\]  

(8)

Upon substituting the values of \( P_1 \) and \( P_2 \) from equation (3), and putting \( \omega = 1.55 \) rad s\(^{-1} \), we obtain the value of \( \tau_a = 0.26s \). We can also put \( \dot{V} = 0 \) at \( t=0.58 \) or \( \omega t=93 \) and obtain a similar value for \( \tau_a \). Then, we also note that at \( t_v = 1.6s \) (for which \( dV/dt = 0 \)), \( V = 0.6l \). Hence upon substituting for \( \cos(\omega t_v) = -0.79 \) and \( \sin(\omega t_v) = 0.62 \) in equation (7), and again neglecting the exponential term we get the following algebraic equation:

\[
-P_1 C_a - \left( 0.54 P_1 C_a / D \right) + \left( 0.94 P_2 C_a / D \right) = 0.6;
\]  

(9)

wherein \( D = 1 + \omega^2 \tau_a^2 \), \( \omega = 1.55 \) rad/s, and \( \tau_a = 0.26s \); this equation can hence be rewritten as:

\[
C_a \left( -1.54 P_1 + 0.94 P_2 \right) = 0.7
\]  

(10)

We can substitute, therein, the values of \( P_1 \) & \( P_2 \) from equation (3), and obtain the value of \( C_a = 0.12 \) L (cm H\(_2\)O\(^{-1} \). Since we have computed \( \tau_a = 0.26 \) s,
therefore \( R_a = 2.20 \text{ (cm H}_2\text{O) s L}^{-1} \). These are the average values of resistance to airflow and lung compliance during the ventilatory cycle shown in FIG 5b.

Since Lung disease will influence the values of \( R \) and \( C \), these parameters can be employed to diagnose lung diseases. For instance in the case of emphysema, the destruction of lung tissue between the alveoli produces a more compliant lung, and hence results in a larger value of \( C \). In asthma, there is increased airway resistance \( (R) \) due to contraction of the smooth muscle around the airways. In fibrosis of the lung, the membranes between the alveoli thicken and hence lung compliance \( (C) \) decreases. Thus by determining the normal and diseased ranges of the parameters \( R \) and \( C \), we can employ this simple Lung-ventilation model for differential diagnosis. Let us, however formulate just one non-dimensional number to serve as a ventilatory performance index \( VTI_1 \) (to characterize ventilatory function), as:

\[
VTI_1 = \left\lfloor \frac{(Ra \cdot Ca) \cdot (\text{Ventilatory rate in s}^{-1}) \cdot 60}{\tau^2 \cdot (BR)^2 \cdot 60^2} \right\rfloor \tag{11}
\]

where \( BR \) is the breathing rate. Now, let us obtain its order-of-magnitude by adopting representative values of \( R \) and \( C \) in normal and disease states. Let us take the above computed values of \( Ra = 2.2 \text{(cm H}_2\text{O) s L}^{-1} \) and \( Ca = 0.12 \text{L (cm H}_2\text{O)}^{-1} \) and \( BR = 12 \text{m}^{-1} \) or \( 0.2 \text{s}^{-1} \), computed for the data of Fig(1) and equation(3). Then, in a supposed normal situation, the value of \( VTI_1 \) is of the order of 9.75. In the case of obstructive lung disease, (with increased \( Ra \)), let us take \( Ra = 3 \text{cm H}_2\text{O s L}^{-1} \), \( Ca = 0.12 \text{L (cm H}_2\text{O)}^{-1} \) and \( BR = 0.3 \text{s}^{-1} \); then we get \( VTI_1 = 42 \). For the case of emphysema (with enhanced \( Ca \)), let us take \( Ra = 2.0 \text{cm H}_2\text{O s L}^{-1} \), \( Ca = 0.2 \text{L (cm H}_2\text{O)}^{-1} \) and \( BR = 0.2 \text{s}^{-1} \); then we obtain \( VTI_1 = 23.04 \). In the case of lung fibrosis (with decreased \( Ca \)), we take \( Ra = 2.0 \text{cm H}_2\text{O s L}^{-1} \), \( Ca = 0.08 \text{L (cm H}_2\text{O)}^{-1} \) and \( BR = 0.2 \text{s}^{-1} \); then we obtain \( VTI_1 = 3.7 \). We can, hence summarize that \( VTI_1 \) would be in the range of 2-5 in the case of fibrotic lung disease, 5-15 in normal persons, 15-25 for the case of emphysema, 25-50 in the case of obstructive lung disease. This would of course be needed to be verified by analyzing a big patient population.

Now, all of this analysis requires pleural pressure data, for which the patient has to be intubated. If now we evaluate the patient in an outpatient clinic, in which we can
only monitor lung volume and not the pleural pressure, then we have to develop a non-invasively obtainable Ventilatory index.

In order to formulate a non-invasively determinableVentilatory index from equation (1), we need to redesignate the model parameters, and indicate their identification procedure. So we make use of the following features from the volume-time data to facilitate evaluation of the following three parameters: \((P_1 C), (P_2 C)\) and \(\tau\):

At \(t = t_v = 1.6s\ & \omega t_v = 2.48\), \(V\) is \(\text{max}\ & dV/dt = 0\); hence we rewrite equation (9) as:

\[
\tan(\omega t_v) = -0.78 = \frac{(P_2 + \omega t P_1)}{(P_1 - P_2 \omega t)}
\]  

\((12)\)

At \(t = t_m\), \(V = 0\); hence by differentiating equation. (7), without the exponential term, we obtain:

\[
V = \frac{P_1 C (-\omega^2 \cos \omega t_m - \omega^3 \tau \sin \omega t_m)}{1 + \omega^2 \tau^2} + \frac{P_2 C (-\omega^2 \sin \omega t_m - \omega^3 \tau \sin \omega t_m)}{1 + \omega^2 \tau^2}
\]

i.e.

\[
\tan \omega t_m = \frac{-P_1 + \omega \tau P_2}{P_1 \omega \tau + P_2}
\]

\((13)\)

At \(t = 1s\ & \omega t = \pi/2\), \(V = V_1\) (whose value is obtainable from FIG 5b); this condition yields (without the exponential term):

\[
V_1 = -(P_1 C) - \frac{\omega \tau (P_1 C)}{1 + \omega^2 \tau^2} + \{\frac{(P_2 C)}{1 + \omega^2 \tau^2}\}
\]

\((14)\)

At \(t = 2s\ & \omega t = \pi/2\), \(V = V_2\) (whose value is obtainable from FIG 5b); this condition yields (without the exponential term):

\[
V_2 = -(P_1 C) - \{\frac{(P_1 C)}{1 + \omega^2 \tau^2}\} + \{\omega \tau (P_2 C) / (1 + \omega^2 \tau^2)\}
\]

\((15)\)

At \(t = 0.3s\ & \omega t = 270\), \(V = V_3\) gives:

\[
V_3 = -(P_1 C) - \{\omega \tau (P_1 C) / (1 + \omega^2 \tau^2)\} - \{\frac{(P_2 C)}{1 + \omega^2 \tau^2}\}
\]

\((16)\)

From equations (12) & (13) and any one of the equation(s) (14-16), we can only obtain the values of \(\omega \tau\) (or of \(\tau\), since \(\omega = 1.55\)) and of \(P_1 C\) & \(P_2 C\) but not of \(P_1\) & \(P_2\) by themselves. On the other hand, by also fitting equation (6), (without the exponential term) to the \(V(t)\) data, we obtain:
We can nevertheless formulate another non-invasively-determinable non-dimensional ventilatory index \( VT_2 \) in terms of these parameters, \( \omega \tau, P_1 C \) and \( P_2 C \) as follows:

\[
VT_2 = \frac{60 (\omega \tau) (TV)^2}{2\pi (P_1 C)(P_2 C)}
\]

\[
= 30 \frac{\omega (R/C)}{P_1 P_2} (TV)^2 / \pi
\]

It is seen that \( VT_2 \) can in fact be expressed in terms of \( P_1, P_2 \) and \( R, C \). This \( VT_2 \) index can be evaluated by computing the values of \( \tau \), along with \( (P_1 C) \) & \( (P_2 C) \) as given by equation (17). Then, after evaluating \( VT_2 \) for a number of persons, and patients its distribution can enable us to categorize and differentially diagnose patients with various lung disorders and diseases. Between the two indices \( VT_1 \) and \( VT_2 \), we can employ the one that enables more distinct separation of subjects with different ventilatory disorders.

Thus far, we have adopted the average cyclic values \( C_a \) and \( R_a \) for our DEq model parameters. However, we expect that \( C \) will vary with lung volume \( V \), and that \( R \) will perhaps vary with the airflow-rate or \( \dot{V} \) or even \( \omega \). Hence, for a true representation of the lung properties \( C \) & \( R \), let us determine their values for different times during the ventilatory cycle, and compare them with their average values \( C_a \) & \( R_a \), so as to make a case for a non-linear ventilatory-function model.

Let us hence compute the instantaneous value of compliance \( C \) at mid-inspiration at \( t = t_m \), and compare it with that of its average cyclic value of \( C_a \). For this purpose let us differentiate equation (2-a), giving:

\[
R \dddot{V} + \dot{V} / C = - P_1 \omega \sin \omega t + P_2 \omega \cos \omega t
\]

Now at about mid-inspiration, when \( t \leq 0.87 \) s and \( \omega t = \omega t_m \approx 1.32 \) rad or 78°, \( \dddot{V} = 0 \) and \( \dot{V} = 0.5 \) L/s (based on fig1). By substituting for \( \dddot{V} \) and \( \dot{V} \) in equation (19), we obtain, \( C \approx 0.14 \) L/cm H2O (compared to its \( C_a \) value of 0.118). Now, in order to also
compute $R$ at $\omega t_m = 1.32$ we substitute $V = 0.5 \text{ L/s and } V = 0.3\text{L}$ (from the fig1 data) into equation (2-a), to obtain:

\[
0.5 R + 0.3 / C = - P_1 + P_1 \cos 78^\circ + P_2 \sin 78^\circ = 3.8 \quad (20)
\]

Now, since $C(at \omega t_m = 1.32) \approx 0.14\text{ L/cm H}_2\text{O}$, we obtain $R=4.6(\text{cmH}_2\text{O}) \text{s} \text{L}^{-1}$, compared to $R_a = 2.20$. This gives us some idea of the order of magnitude of $R & C$, in comparison to their average values $C_a & R_a$. We could also expect $C$ at mid-inspiration to be higher than its value at end-inspiration, when the lung is fully inflated. Also, we could expect the flow-resistance to be maximum at mid-inspiration, when $\dot{V}$ is maximal.

We can hence represent lung compliance ($C$) and resistance ($R$) as follows:

\[
C = n_1 (V)^{n_2} - C_o \quad \text{or} \quad C = C_o \, (V)^{n(V)} \quad , \quad (21-a)
\]

\[
R=s\dot{V}_2 \quad \text{or} \quad R=R_o \dot{V} \quad (21-b)
\]

wherein $\dot{V}$ can also be varied by having the subjects breathe at different tidal volumes ($TV_s$) and ventilation frequency ($\omega$)

We note as per the conventional formulation of compliance, given by equation(ii) in FIG 5b as:

\[
P_{el} = V/C + P_{el,0} \quad ; \quad (22)
\]

In the above formulation, we assume that $C$ and $E(= 1/C)$ remains constant throughout the ventilation cycle. However at the start of inspiration, $C = C_o$ at $t=0$, and it decreases as the lung volume increases, based on the lung (static) volume vs pressure curve. So let us improve upon this equation(22) model, by making $P_{el}$ to be a non-linear function of volume, as follows:

\[
P_{el} = P_{el,0} + E_0 e^{kv} \quad (23)
\]

Employing the above format of compliance, the governing $DE_q$ (1) becomes
\[ R \dot{V} + E_0 e^{kV} = P_L(t) - P_{el,0} = P_0 + P_1 \cos \omega t + P_2 \sin \omega t - P_{el,0} \quad (24) \]

Again at end-expiration, \( P_{el,0} = \) intra-pulmonary pressure =\((P_0 + P_1)\). Hence equation (24) becomes:

\[ R \ddot{V} + E_0 e^{kV} = -P_1 + P_1 \cos \omega t + P_2 \sin \omega t \quad (25) \]

whose RHS is similar to that of equation (2-a), and the values of \( P_1 \) & \( P_2 \) are given by equation (3) for the FIG 5b data.

In order to evaluate these parameters \( k \) & \( E_0 \), we again bring to bear the situation that at end-inspiration, for \( t = t_v = 1.6 \) s (for which \( \omega t = \omega t_v = 2.48 \) rad, \( \sin \omega t_v = 0.62 \) & \( \cos \omega t_v = -0.79 \)), we have

\[ \dot{V} = 0 \quad \text{and} \quad V = V_{max} = TV = 0.6 \text{ L}. \]

Hence, from fig (1) data, and equations (3 & 25), we obtain:

\[ E_0 e^{0.6k} = 8.75 \quad (26) \]

Let us now employ the volume data point at which \( \ddot{V} \) =0. For this purpose, we differentiate equation (25), to obtain:

\[ R \dddot{V} + E_0 k e^{kV} = -P_1 \omega \sin (\omega t) + P_2 \omega \cos (\omega t) \quad (27) \]

From the Fig (1) data at about mid-inspiration, for which \( t = t_m = 0.87 \) s & \( \omega t_m = 1.32 = 78^\circ \) with \( \cos (\omega t_m) = 0.2 \) & \( \sin (\omega t_m) = 0.98 \), we have \( \dddot{V} \equiv 0, \dot{V} =-0.5 \text{ Ls}^{-1}, V = 0.3 \text{ L}, \) from fig(1) data. Substituting these values into equation (27), we get:

\[ E_0 e^{0.3k} = 3.8 \quad (28) \]

Now from equation(s) (27) & (28), we get:

\[ e^{-0.3k} = 1.38 \quad (29) \]

for which, \( k = 1.07 \) and (from equation 26 or 28) \( E_0 = 2.75 \) (30)

Hence, by employing the non-linear formulation,
we obtain the following expression for lung compliance (or elastance):

\[ P_{el} = P_{el,0} + E_o \cdot e^{kV} \]  

(31)

Based on this expression, we obtain, for \( t = t_m \& V = 0.3L \):

\[ E = \frac{1}{C} = 2.94 \text{ cm H}_2\text{O /L}; \quad \text{and} \quad C = 0.25 \text{ L/cm H}_2\text{O}. \]  

(32)

Equation (32) can now provide us a more realistic characterization of lung compliance as follows:

At \( t = 0 \) and \( V = 0 \), we compute \( E = \frac{1}{C} = 2.94 \) and \( C = 0.34 \text{ cm H}_2\text{O /L}. \)

At \( t = t_m = 0.87s \& V = 0.3L \), \( E = \frac{1}{C} = 4.06 \), and \( C = 0.25 \).

At \( t = t_v = 1.6s \& V = 0.6L \), and \( E = \frac{1}{C} = 5.6 \) and \( C = 0.18 \),

which corresponds to the value of \( C_a \).

Our non-linear formulation of lung compliance, as depicted by equation (31 & 33), indicates that compliance decreases from \( 0.34 \text{ cm H}_2\text{O /L} \) at start-inspiration to \( 0.25 \text{ cm H}_2\text{O /L} \) at about mid-inspiration, and then to \( 0.18 \text{ cm H}_2\text{O /L} \) at the end of inspiration. What this also tells us is that the ventilatory model equation (1) gives the correct reading of the compliance at \( V_{max} \), i.e. at end-inspiration. At other times of inspiration and expiration, the \( C_a \) parameter underestimates the instantaneous value of lung compliance. Now how about obtaining an analytical solution of equation (25) for \( V(t) \), and fitting the expression for \( V(t) \) to the lung volume data, to evaluate the parameters (i) \( R, E_o \) & \( k \) for an intubated patient and (ii) \( R, E_o, k \) & \( P_1 \& P_2 \) for a non-intubated patient in the outpatient clinic.

Finally, while it is important to determine the normal and pathological diagnostic ranges of \( C_a \& R_a \), or better still of the parameters \( (E_0 \& k) \) of the \( C \text{ vs} V \) and \( R \text{ vs} V \) relationships, it would be more useful to construct and employ a non-dimensional ventilatory index. We have already formulated \( VT I_1 \& VT I_2 \) in equations (11) & (18), respectively. We will now formulate yet another index:
VTI₃ = \[60 \left( \frac{R_a}{C_a} \right) (BR) (TV)^2 \] / P₁P₂ \tag{34}

wherein (i) BR (the breathing rate in \#/sec) = 0.5 \omega / \pi (ii) and \(|P₁P₂|\) is the absolute value of the product P₁P₂ (because of P₁ being negative). For the fig (1) clinical data, of BR= 0.25, with TV=0.6L & \(|P₁P₂|^{(3)} = 18.1\), and for the computed value of \(R_a/C_a=18.33cm H_2O s L^{-1}\), we obtain \(VTI₃ = 5.47\). Between \(VTI₁\) and \(VTI₃\), we can decide which index enables us to better differentially diagnose subjects with ventilatory disorders.

Now, let us go one step further and recognize that, for non-intubated patients, we cannot monitor \(P₁\) and \(P₂\), and hence cannot evaluate \(R_a & C_a\) as demonstrated in § A. However for evaluating ventilatory index in out-patient clinics, we can in fact adopt \((P₁ C)\) and \((P₂ C)\) to be the model-system parameters, and evaluate them as delineated in § B. We can hence adopt the non-invasively-obtainable ventilatory-performance index \(VTI₂\) (given by equation 18):

\[VTI₂ = 30 \omega\tau (TV)^2 / \pi (P₁ C) (P₂ C); \quad \omega = 2\pi(BR)(in \#s^{-1})\]

\[= 60 (BR)(R / C) (TV)^2 / (P₁ P₂) = \quad VTI₃\] \tag{35}

which is noted to be the same expression as for index \(VTI₃\), except that it can be evaluated without intubating the patient. Hence, it would be even more useful to determine the distribution of \(VTI₂\) for patients with a wide range of lung pathologies and ventilatory disorders. Then, we can delineate the normal and pathological ranges of this index, and employ this information to diagnose patients into different disease categories.

Now referring to FIG 6 and FIG 7, there is provided a more detailed description of the ways by which the PDDS searches the database.

The index will fire up numerous search engine in finding the best match diseases. There is a possibility that there is more than one type of diseases being suspected. Statistical means are used to determine which is the best match diseases and thereby putting all these best fit diseases to the expert database system to further refine the possibilities.

This expert database will feedback data which is erroneous through a database interface to the intelligent DBMS for further confirmation by firing up other
possibilities of diseases type. This interface can be realise through a query module interface. The query module will consult the expert DB2 for expert information before in deciding the redundancy of the data.

[00117] The DISS (disease identification software system) is used to identify the best match disease after consulting the expert DB. The algorithm can be found in annex. The query module is responsible for all communication between the DISS, expert DB, GUI and also the intelligent DBMS. In particular, it can decide whether an DISS request can be displayed with the expert DB helps or whether it is necessary to require input from the user.

[00118] While the present invention has been described with reference to particular embodiments, it will be understood that the embodiments are illustrative and that the invention scope is not so limited. Alternative embodiments of the present invention will become apparent to those having ordinary skill in the art to which the present invention pertains. Such alternate embodiments are considered to be encompassed within the spirit and scope of the present invention. Accordingly, the scope of the present invention is described by the appended claims and is supported by the foregoing description.
CLAIMS

What is claimed is:

1. A pulmonary disease detection system for detecting breathing deficiencies of a test person, comprising:
   a breath analyser for analysing the inhale and exhale airs of the test person;
   a computer processor for receiving from the breath analyser the information and processing the received analysis data to give values to different parameters of the inhale and exhale airs of the test person; and
   a medical database for storing different parameters of breaths of the public and normal ranges for healthy persons;
   thereby the computer processor compares the values of different parameters of the inhale and exhale airs of the test person with the ones stored in the medical database so as to yield a test result of whether the test person is suffering breath deficiencies.

2. The pulmonary disease detection system of claim 1, wherein the breathing deficiencies may be caused by bacterial infection, viral infection, physical injuries and cancer.

3. The pulmonary disease detection system of claim 1, wherein the breath analyser comprises:
   a mask for covering the nose and mouth of the test person so as to maximizing the delivery of fresh air and minimizing the loss of the exhaled air;
   an air tank for supplying measurable and controllable air to the mask; and
   an acquisition unit electrically connected with the mask and the air tank so as to receive all the information from the air tank and the mask.

4. The pulmonary disease detection system of claim 3, wherein the mask comprises a group of electrodes including an oxygen electrode, a carbon dioxide gas electrode, a nitrogen electrode, a water vapor electrode, an inspired air flow rate electrode and an
expired air flow rate electrode; wherein each electrode detects each designated component of the inhale and exhale airs.

5. The pulmonary disease detection system of claim 4, wherein the computer processor is embedded with an algorithm for processing the information from the breath analyser; wherein the algorithm calculates the breathing rate, oxygen consumption rate and carbon dioxide generation rate from the composition information of the inhale and exhale airs of the test person; thereby comparing the rates of the test person with the ones stored in the medical database so as to conclude whether the test person is suffering any breath deficiencies.

6. The pulmonary disease detection system of claim 4, wherein the computer processor is embedded with an algorithm for processing the information from the breath analyser; wherein the algorithm calculates the composition values of the exhale air from the composition values of the inhale air and the assumed normal rates including breathing rate, oxygen consumption rate and carbon dioxide generation rate; thereby comparing the composition values of the exhale air with the ones stored in the medical database so as to conclude whether the test person is suffering any breath deficiencies.

7. The pulmonary disease detection system of claim 4, wherein the computer processor is embedded with an algorithm for processing the information from the breath analyser; wherein the algorithm calculates the volume compliance and air-flow resistance of the test person from the composition values and pressure values derived from the inhale air rate and exhale air rate; thereby comparing the volume compliance and air-flow resistance values with the ones stored in the medical database so as to conclude whether the test person is suffering any breath deficiencies.

8. The pulmonary disease detection system of claim 7, wherein the derived pressure values include pleural pressure and alveolar pressure.

9. The pulmonary disease detection system of claim 8, wherein the volume compliance and air-flow resistance are calculated by the equation:
\[
VTI_1 = f(R_a C_a)(Ventilatory rate in s^{-1}) \times 60 \int^2 \tau (BR)^2 60^2
\]

wherein \( VTI_1 \) is denoted as ventilatory performance index; \( C \) as lung-volume compliance; and \( R \) as air-flow resistance; and wherein \( R_a \) and \( C_a \) are designated as the average values (\( R \) and \( C \)) for the ventilatory cycle, and \( BR \) is the breathing rate.

10. The pulmonary disease detection system of claim 8, wherein the volume compliance and air-flow resistance are calculated by the equation:

\[
VT I_2 = 60 (\omega \tau) (T V)^2 /2\pi (P_1 C)(P_2 C) = 30 \omega (R/C) (T V)^2 /\pi P_1 P_2
\]

wherein \( VTI_2 \) is denoted as ventilatory performance index; \( C \) as lung-volume compliance; and \( R \) as air-flow resistance; and wherein \( TV \) is tidal volume; \( P_1 \) & \( P_2 \) as pleural pressures and \( \omega \tau \) as determined by equations (14-16).

11. The pulmonary disease detection system of claim 8, wherein the volume compliance and air-flow resistance are calculated by the equation:

\[
VT I_3 = [60 (R_a / C_a ) (BR) (TV)^2] / P_1 P_2
\]

wherein \( VTI_3 \) is denoted as ventilatory performance index; \( C \) as lung-volume compliance; and \( R \) as air-flow resistance; and wherein \( TV \) is tidal volume; \( P_1 \) & \( P_2 \) as pleural pressures.

12. A method of detecting a pulmonary disease of a test person by investigating the breath deficiencies of the test person:

acquiring the information of inhale and exhale airs of the test person;

processing the acquired information to give values of designated aspects of the inhale and exhale airs of the test person; and

comparing the calculated values with the ones stored in a medical database so as to conclude whether the test person is suffering any pulmonary diseases.

13. The method of claim 12, wherein the breathing deficiencies may be caused by bacterial infection, viral infection, physical injuries and cancer.

14. The method of claim 12, wherein the information of inhale and exhale airs of the test person is acquired by a breath analyser; and wherein the breath analyser comprises:
a mask for covering the nose and mouth of the test person so as to maximizing the delivery of fresh air and minimizing the loss of the exhaled air;
an air tank for supplying measurable and controllable air to the mask; and
an acquisition unit electrically connected with the mask and the air tank so as to receive all the information from the air tank and the mask.

15. The method of claim 14, wherein the mask comprises a group of electrodes including an oxygen electrode, a carbon dioxide gas electrode, a nitrogen electrode, a water vapor electrode, an inspired air flow rate electrode and an expired air flow rate electrode; wherein each electrode detects each designated component of the inhale and exhale airs.

16. The method of claim 15, wherein the processing is executed within a computer processor that is embedded with an algorithm for processing the information from the breath analyser; wherein the algorithm calculates the breathing rate, oxygen consumption rate and carbon dioxide generation rate from the composition information of the inhale and exhale airs of the test person; thereby comparing the rates of the test person with the ones stored in the medical database so as to conclude whether the test person is suffering any breath deficiencies.

17. The method of claim 15, wherein the processing is executed within a computer processor that is embedded with an algorithm for processing the information from the breath analyser; wherein the algorithm calculates the composition values of the exhale air from the composition values of the inhale air and the assumed normal rates including breathing rate, oxygen consumption rate and carbon dioxide generation rate; thereby comparing the composition values of the exhale air with the ones stored in the medical database so as to conclude whether the test person is suffering any breath deficiencies.

18. The method of claim 15, wherein the processing is executed within a computer processor that is embedded with an algorithm for processing the information from the breath analyser; wherein the algorithm calculates the volume compliance and air-flow resistance of the test person from the composition values and pressure values derived from the inhale air rate and exhale air rate; thereby comparing the volume compliance and air-
flow resistance values with the ones stored in the medical database so as to conclude whether the test person is suffering any breath deficiencies.

19. The method of claim 18, wherein the derived pressure values include pleural pressure and alveolar pressure.

20. The method of claim 19, wherein the volume compliance and air-flow resistance are calculated by the equation:

\[
VTI_1 = \int (R_a C_a)(\text{Ventilatory rate in s}^{-1})\ 60\ t^2 = \omega^2 (BR)^2\ 60^2
\]

wherein \(VTI_1\) is denoted as ventilatory performance index; \(C\) as lung-volume compliance; and \(R\) as air-flow resistance; and wherein \(R_a\) and \(C_a\) are designated as the average values \((R\ and \ C)\) for the ventilatory cycle, and \(BR\) is the breathing rate.

21. The method of claim 19, wherein the volume compliance and air-flow resistance are calculated by the equation:

\[
VTI_2 = 60 (\omega \tau) (T V)^2 /2\pi (P_1 C )(P_2 C) = 30 (R/C) (T V)^2 /\pi P_1 P_2
\]

wherein \(VTI_2\) is denoted as ventilatory performance index; \(C\) as lung-volume compliance; and \(R\) as air-flow resistance; and wherein \(TV\) is tidal volume; \(P_1\ & P_2\) as pleural pressures and \(\omega \tau\) as determined by equations (14-16).

22. The method of claim 19, wherein the volume compliance and air-flow resistance are calculated by the equation:

\[
VTI_3 = [60 (R_a C_a) (BR) (TV)^2] / P_1 P_2
\]

wherein \(VTI_3\) is denoted as ventilatory performance index; \(C\) as lung-volume compliance; and \(R\) as air-flow resistance; and wherein \(TV\) is tidal volume; \(P_1\ & P_2\) as pleural pressures and \(\omega \tau\) as determined by equations (14-16).
SYSTEM AND METHOD FOR DETECTING OF PULMONARY DISEASES

ABSTRACT

The present invention provides a to be completed upon agreement of claims.
Data is fed into analysis computing system.

Processed data is examined against databases.

Database will also be updated with the next processed data.

FIG 1
FIG 4

Start

Data from the spirometer

Volume Growth Characteristics of the patients

Parameters identification of P0, P1, P2, Ra, Ca & w

Is the best fitted results with the parameters obtained?

Yes

Determination of VT1, VT2 & VT3

Access of reference database

Reference Medical Database

Initial Database Set up and Continual Improvement

No

Diagnostics

Updating of database

Results

End

Expert Advice

FIG 4
FIG 6