On the characterisation of stereotactic radiotherapy fields

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A thesis submitted for the degree of
Philosophiae Doctor

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August 2010
DECLARATION OF AUTHENTICITY

Tout honnête homme doit avouer les livres qu’il publie.

*Rousseau, La Nouvelle Heloise*
Declaration of authenticity

I, Michael Leslie Taylor, attest that except where due acknowledgement has been made, the present work is that of the candidate alone. This work has not been submitted previously, in whole or in part, to qualify for any other academic award. The content of this thesis is the result of work that has been carried out since the official commencement date of the approved research program. Any editorial work, paid or unpaid, by a third party is acknowledged. All ethics procedures and guidelines have been followed.

Michael Leslie Taylor, August 2010
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To ask when you already know is politeness, to ask when you do not know is the rule.

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ACKNOWLEDGEMENTS

Den Göttern gleich ich nicht! zu tief ist es gefühlt;
Dem Wurme gleich ich, der den Staub durchwühlt,
Den, wie er sich im Staube nähernd lebt,
Des Wanders Tritt vernichtet und begräbt.
Ist es nicht Staub, was diese hohe Wand
Aus hundert Fächern mit verenget?
Der Trödel, der mit tausendfachem Tand
In dieser Mottenwelt mich dränget?
Hier soll ich finden, was mir fehlt?

Goethe, Faust
Acknowledgements

Lector benevole. This thesis describes a large body of work that has taken several years to complete. The intensity and fervour with which this work has been undertaken and the many moments of both illumination and exhaustion have shaped and defined my lifestyle, character and my interaction with others over the past few years. As such, it has been a very personal journey. I have certainly involved myself in many other studies and teaching along the way, but have, comme le forçat à la chaîne\textsuperscript{1}, nevertheless been most heavily engrossed in the present work. I apologise in advance for the prolix pages that follow, but I feel so genuinely thankful and indebted to the many that have helped and encouraged me throughout my candidature that I simply can’t allow myself to express my gratitude in a cursory fashion.

The three people I must thank first are Dr Rick Franich, Prof Tomas Kron and Prof Peter Johnston, as they have devoted the most time and advice to the direction of this research.

I am incredibly privileged to have had Dr Rick Franich and Prof Tomas Kron as my primary supervisors. I greatly admire Dr Franich, not only as a brilliant scientist and educator, but as a person. He is a knowledgeable and expert advisor, who has become a close friend and confidant. I similarly hold Prof Kron in great admiration. I hesitate to use such a clichéd word as ‘genius’, but after careful consideration I can’t think of a better word! It is his great humility that I respect the most. The primary reason I chose to decline scholarship offers from various other universities was so that I could continue to work with Prof Peter Johnston at RMIT University, who held the position of primary supervisor until he accepted a Directorship with a governmental scientific body. Prof Johnston exhibits many of the traits I wish I could somehow purchase. His piercing lucidity of thought extracts the key essence of any concept, regardless how multifariously complex. It is only a slight consolation that at least our physical height is comparable. I look forward to many years of working with Dr Franich, Prof Kron and Prof Johnston.

Dr Jamie Trapp also held the role of primary supervisor until accepting a post at the Queensland University of Technology (QUT). It is thanks to Dr Trapp that I have had so many forays into the world of gel dosimetry, many of which are described in the present thesis. It is unfortunate that the time I spent working directly with Dr Trapp was so limited, but thankfully we have managed to continue to collaborate throughout my candidacy. Also associated with QUT and (more recently) the Wesley Hospital, is Dr Tanya Kairn. Dr Kairn has been consistently helpful, far beyond the numerous formal collaborative studies we have undertaken. Dr Kairn is selfless in her enthusiasm to assist others and has been incredibly obliging and supportive many times over the past couple of years.

\textsuperscript{1} Baudelaire, Les Fleurs du Mal
This work has been based primarily at the Alfred Hospital (Victoria, Australia). I owe many thanks to Mr Trevor Ackerly who, as Chief Physicist, effectively inherited this project from the previous chief – to whom I am also thankful – Mr Malcolm Millar. Mr Ackerly has been consistently supportive of the project, providing significant assistance and advice and facilitating many hours of experimental work. I look forward to the opportunity to reciprocate the great assistance he has provided me. I would like to thank all of the physicists at the Alfred, in particular Dr Matthew Haynes who has expended many hours aiding with experimental measurements, treatment planning calculations and advice on any number of topics these past few years. I won’t dwell on this in case he realises how many favours I owe. I would like to thank Mr Craig Lancaster and Mr Ryan Smith who have also spent late nights assisting with measurements and providing advice.

I was very fortunate to spend one year working closely with Dr Leah McDermott, now at Universitair Medisch Centrum (Netherlands). Dr McDermott is not only very knowledgeable and capable but highly driven. I would also like to thank Mr Leon Dunn, a doctoral candidate at RMIT. Mr Dunn is very competent and highly technically-minded. I have often relied upon his proficiency in programming in particular. His efforts have saved me significant time and his expertise with alternative Monte Carlo radiation transport modelling approaches has facilitated more rigorous scientific studies than would have otherwise been possible. Dr Alex Merchant, now at St Vincent’s Hospital, has also been of great assistance many times through my candidature. In particular, I thank Dr Merchant for informing me that the most important aspect of the thesis is the critical necessity of including quotes quite unrelated to the topic throughout the work (which, the reader will no doubt have observed, I have diligently undertaken to do). I like to think that this is because, as Aesop says, the mind ought to be diverted such that it may return to better thinking. I suspect, however, that with regard to the present thesis, Dr Merchant’s emphasis was on the first half of that notion.

I extend my thanks to all my colleagues within the physics discipline at RMIT. I have had experience working with a number of departments at other institutions and the group at RMIT is the most cordial and collegial by far. To be surrounded by so many brilliant minds that are also friendly and supportive has made it a pleasure to come to work each day. There are too many academics and students to mention individually that have been both a friend and guide to me, but I would like to make a point of thanking Mr Daniel Cachia whose helpfulness and efficiency has facilitated so many projects.

I would like to thank the Alfred Hospital and the Australian Research Council for financial support throughout my candidature (ARC Linkage Grant LP0562315).

I also thank my family and close friends for their support. My father James, mother Louise, brothers Grant and Alan, and little sister Beth have always encouraged me – despite my deviation from fine arts! I see them far less often than I would like. I enjoy challenges and
hard work and I hope my family and friends haven’t had to cope with too many complaints while sharing my journey. I also hope they aren’t too disappointed that the outcome is this simple document! Indeed I’m reminded of one of Phaedrus’ stories: *Mons parturibat, gemitus immanes ciens, eratque in terris maxima expectatio. At ille murem peperit*. Or perhaps, to quote Terence, *magno conatu nuges*…

Finally, I wish to extend my genuine thanks to the anonymous referees who expend significant time and effort to examine theses and manuscripts such as this one. It is unfortunate that the nature of academia is such that the remuneration received for such work is far from commensurate with the expertise and effort required. It is this latter point, however, that highlights the admirable character of the referees who – rather than undertake such work for financial gain – dedicate their time out of devotion to science and education. When reviewing scientific manuscripts or students’ works I find myself recalling Nietzsche’s words: *Man sollte einen Schriftsteller als einen Missetäter ansehen, der nur in den seltensten Fällen Freisprechung oder Begnadigung verdient: das wäre ein Mittel gegen das Überhandnehmen der Bücher*. So to my examiners I say thank you again – and hope that the philosophies to which we subscribe differ!

---

† “A mountain in the pangs of labour emitted a tremendous groan, and the lands were filled with great expectation; then behold – the mountain bore a mouse”.

‡ “[Performing] trifles with great effort”.

†† “One ought to regard a writer as a criminal who deserves acquittal or clemency only in the rarest of cases: that would be a good way to keep books from getting out of hand”.
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SCIENTIFIC ABSTRACT
Scientific abstract

Cancer is currently a leading cause of death in Australia, with recent data indicating a mortality rate of approximately 40,000 deaths per year. The projected cancer incidence in Australia for 2010 is almost 115,000 persons. Stereotactic radiotherapy is an increasingly common treatment modality for small lesions of the human body.

However, the small radiation fields inherent to this method have characteristics which make their resulting dose distributions difficult to both measure and calculate. Any inaccuracy in dose prediction or delivery may have detrimental consequences for patients as a result of under-dosage of the tumour or over-irradiation of healthy tissues in the immediate periphery of a targeted lesion. Furthermore, despite the small fields involved, scattered and leaked radiation result in a radiation dose to the patient far from the primary field which, whilst generally much smaller than the dose received by the target, can nonetheless result in health complications as a consequence of the treatment.

This thesis addresses the pressing need to characterise the fields used in stereotactic radiotherapy, to ensure accurate dose calculation and delivery, and thus the most positive outcome for patients. This refers to spectral, fluence and dosimetric properties in the primary beam and its immediate periphery (in-field), as well as in regions far from the primary field (out-of-field).

To facilitate in-field characterisation, methodologies for three-dimensional dose verification using radiosensitive gel dosimeters have been developed and employed. A novel means of characterising the radiological properties of gel dosimeters via use of an energy-dependent effective atomic number is defined and used to establish the tissue-equivalence of dosimetric gels. Furthermore, high-resolution Monte Carlo radiation transport methods are employed to identify the optimum calibration method for absolute dosimetry. Gel dosimetry for verification of stereotactic radiotherapy treatment of intracranial lesions is demonstrated for a 12-beam clinical treatment for a small meningioma in an anthropomorphic phantom, indicating good agreement with treatment planning predictions. In the context of stereotactic body radiotherapy, Monte Carlo methods are employed to investigate under-dosage to the periphery of lung tumours, providing a dataset for under-dosage estimation as a function of tumour size, location, beam energy and field size. Furthermore, for rigorous characterisation of stereotactic fields, a full Monte Carlo model of a linac-based stereotactic unit equipped with a mini-multileaf collimator as a tertiary collimation device was constructed. This
dosimetrically matched model was used to generate spectral, fluence and dosimetric data for a
systematic set of parameters and a number of trends are observed. The clinical consequences
of spatial and field size dependent spectral variations are assessed in the context of ionisation
chamber, radiographic film and thermoluminescent dosimetry.

For investigation of the out-of-field dosimetric characteristics of stereotactic fields, two key
studies were undertaken. The first was a systematic investigation of the variation of out-of-
field dose with a large set of parameters such as field size, depth in phantom, source-surface
distance, collimator rotation, and so on. The second study was an investigation of out-of-field
organ doses in an anthropomorphic phantom in the context of paediatric radiotherapy.

Estimates for radiation-induced cancer based on typical treatments are provided. A number of
straightforward methods for exploiting the spatial anisotropy of out-of-field dose are used to
develop recommendations for risk minimisation. Appropriate choices for linac type, patient
orientation and treatment type, for instance, may each reduce the out-of-field dose by at least
half.

While primarily concerned with stereotactic radiotherapy fields, the findings of this thesis
are also applicable to other areas in radiotherapy where small fields and field segments are used.
Intensity modulated radiotherapy is such an example. Most importantly, however, it is hoped
that the outcomes of this thesis will help to make the treatment of patients more accurate and
reproducible. By considering both theory and measurement, it is also hoped that building
blocks for future work that further enhances treatment approaches have been created.
EXECUTIVE SUMMARY
Executive summary

Cancer is one of the leading causes of deaths in Australia, with a mortality rate of approximately 40,000 deaths per year, contributing $3.8 billion AUD in direct health system costs. One advanced treatment modality for small tumours is stereotactic radiotherapy, which employs multiple beams of ionising radiation that spatially conform to a targeted lesion, using higher radiation doses in fewer fractions compared to other methods. This is increasingly popular because of patient convenience and an expectation of higher cure rates.

This work investigates and characterises stereotactic radiotherapy fields with the objective of improved treatments and hence better patient outcomes.

Calculation and measurement of in-field characteristics is complicated by issues such as electronic disequilibrium, spectral changes and detector volume averaging effects (when the detector is of comparable or larger size than the radiation field). In this work, 3D dosimetric methods based on radiosensitive gels are developed and implemented for dose measurement, and mathematical Monte Carlo radiation transport models are constructed and applied for accurate beam characterisation.

Out-of-field doses (i.e. beyond the targeted region) are of interest for the potential health complications they may give rise to. Comparatively little attention is given to out-of-field doses from stereotactic fields, which this study investigates both systematically and in the context of paediatric radiotherapy, providing risk estimates for radiation-induced cancer.

Key findings relate to the radiological properties and calibration of 3D gel dosimeters. Monte Carlo models reveal the spectral characteristics of stereotactic fields within and beyond the nominal treatment field, and these are investigated in terms of the effect on energy-dependent dosimeters. Investigations of out-of-field dose have revealed anisotropies in the radiation field far from the primary beam which may be exploited so as to minimise patient dose and corresponding risks.

The present work has yielded 11 publications in international peer-reviewed journals, a further 3 publications currently under review or preparation, 19 conference papers and 7 invited seminars.

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1 Intended for non-expert reader (<320 words).
CHAPTER ONE

Extremis malis, extrema remedia.

Ἱπποκράτης
CHAPTER 1

Introduction
1.1 Propositum
The aim of this thesis is to characterise the small radiation fields employed in stereotactic radiotherapy. This refers to spectral, fluence and dosimetric properties in the primary beam and its immediate periphery (in-field), as well as in regions far from the primary field (out-of-field). Poor knowledge of in-field characteristics may lead to reduced treatment efficacy, whether by under-dosage of targeted tumours or over-irradiation of adjacent healthy tissues. Poor knowledge of out-of-field characteristics may result in adverse health consequences, such as radiation-induced carcinogenesis. Risk estimates of such negative outcomes are also provided in this work and, based on the investigations in this thesis, recommendations are made on improved means of dosimetry and treatment delivery.

1.2 Context
In the human body, cells grow and multiply in a regulated fashion to form tissues and organs which serve particular functions. Sometimes, however, abnormal behaviour is exhibited by cells that have incorporated a genetic mutation, whereby their normal inherent mechanism for cell population control fails, resulting in uncontrolled cellular proliferation. Such proliferation leads to formation of ‘tumours’ or ‘neoplasms’ – tissue masses that may be benign or malignant. The former case describes a growth that will not invade neighbouring tissues nor metastasise (spread to other parts of the body). Malignant forms are known as cancers – a name that encompasses a group of several hundred diseases, individually differentiated according to the type of cell and anatomic location from which it originated.

Cancer is currently a leading cause of death in Australia, with recent data indicating a mortality rate of approximately 40,000 deaths per year. The projected cancer incidence in Australia for 2010 is almost 115,000 persons (AIHW 2008). Due mostly to premature death, cancer is the leading cause of the burden of disease and injury in Australia (19 % of the total loss of ‘healthy life’) (Begg et al. 2007). Furthermore, cancer contributes approximately $3.8 billion (AUD) in direct health systems costs.

There are a number of modalities for the treatment of cancer (and benign lesions), including radiation therapy (radiotherapy). The objective of radiotherapy is to deliver a lethal dose of radiation to a tumour, whilst minimising damage to surrounding healthy tissues. To facilitate this, it is necessary to spatially restrict the high dose to a volume of tissue that incorporates only the tumour, and a small margin to ensure elimination of microscopic tumour extensions
and account for any error in setup. Controlling tumours with use of ionising radiation is a probabilistic process, in as far as delivering a given dose to a given tumour results in a probability that all cancerous cells are killed. The greater the dose delivered, the lower the probability of cancer cell survival, but the greater the likelihood of complications to surrounding regions of healthy tissue.

For the treatment of small lesions, stereotactic radiotherapy is often employed. It is appropriate to preface this discussion with a (lexical) definition of stereotactic radiotherapy, since it is not uncommon for the frequent and often unchecked usage of a term and unawareness of its etymology to result in obscuration of its meaning. In the field of medicine, the term stereotactic is synonymous with stereotaxic, which the Oxford English Dictionary defines as ‘involving or designed for the accurate three-dimensional positioning and movement of objects inside the brain’. A constituent of many scientific and technical terms, the prefix stereo- (or stere- before a noun) originates from the Greek στερεός (stereos), meaning solid and three-dimensional. The other constituent root word, -taxis, would again suggest Greek origin: τάξις (taxis), meaning arrangement or order – a common suffix in biology when referring to the oriented movement of organisms in response to stimuli. The word tactic also holds this meaning, although there has been suggestion elsewhere (Sheehan and Pouratian 2009) that tactic in this context is the rarer definition borne of the Latin tangère, relating to touch. Radiotherapy is defined as ‘the treatment of disease (in particular cancer) by means of ionising radiation’. The English term is most likely based on the French radiothérapie, a combination of Latin (radius, in this case meaning a ray or beam) and Greek (θεραπία, therapia, meaning healing) terms. Historic definitions aside, a contemporary definition of stereotactic radiotherapy is presented here as ‘the use of beams of ionising radiation from multiple directions intersecting at a target (usually intracranial) spatially defined using a fixed three-dimensional coordinate system’ (Taylor et al. 2010b). Stereotactic radiosurgery may be defined similarly, with the difference that it implies a single fraction treatment. The term radio-surgery is something of a misnomer, since it is a non-invasive operation.

Traditionally, stereotactic radiotherapy and radiosurgery have been applied to intracranial targets because of the obvious extension from invasive stereotactic procedures, the capacity to keep the head rigid and the relative homogeneity of the brain. Recently, targets at other anatomic locations have also been treated.

Stereotactic radiotherapy is an increasingly common treatment modality for small lesions of the human body. Notably, it is a strongly patient-preference driven treatment method, with
many patients – when the option is made available – preferentially requesting stereotactic radiotherapy as an alternative to surgical procedures, the invasive nature of which is undesirable. However, the small radiation fields inherent to this method have characteristics which make their resulting dose distributions difficult to both measure and calculate. Any inaccuracy in dose prediction or delivery may have detrimental consequences for patients as a result of under-dosage of the tumour or over-irradiation of healthy tissues in the immediate periphery of a targeted lesion. Furthermore, despite the small fields involved, scattered and leaked radiation result in a radiation dose to the patient far from the primary field which, whilst generally much smaller than the dose received by the target, can nonetheless result in health complications as a consequence of the treatment.

There is a pressing need to characterise the fields used in stereotactic radiotherapy, to ensure accurate dose calculation and delivery, and thus the most positive outcome for patients. The techniques and results discussed in this thesis are not restricted to stereotactic radiotherapy; small-field dosimetry is relevant to any number of new and emergent techniques, such as intensity-modulated radiotherapy, micro-beam radiotherapy, dose-painting and has extensions to proton/heavy-ion therapy.

1.3 The objective of this thesis

The objective of this thesis is to characterise the small fields used in stereotactic radiotherapy for the purpose of enabling accurate measurement and calculation of dose, both in-field and out-of-field. In-field characterisation refers to the determination of spectral and fluence information, and the dosimetric behaviour in the peripheral regions of the field. This is both important and complex for stereotactic fields, the small size of which means that penumbral regions occupy a significant portion of the field. In this work, promising methods of experimental dosimetry and dose calculation are implemented: gel dosimetry and Monte Carlo radiation transport methods. The studies described in this thesis not only involve application of these methods, but build on them fundamentally. In addition to the complexities of in-field doses are the issue of out-of-field doses – doses to distant critical structures of the patient that arise from scattered and leaked radiation. Epidemiological evidence shows that there is an increased relative risk of radiocarcinogenesis and other health complications that arises from exposure to relatively low radiation doses. These risks are particularly relevant for children and other patients with an otherwise long life expectancy. Such doses are not considered in the treatment optimisation process and limitations of
contemporary commercial planning systems do not allow accurate out-of-field dose calculation (nor are they designed for this). This restricts the detail of out-of-field dose available to clinicians. Studies presented in this thesis investigate out-of-field doses from linac-based stereotactic radiotherapy – which has received relatively little attention in published literature thus far – both in a systematic fashion (quantifying variation with treatment parameters) and in the context of paediatric radiotherapy.

The present work attempts to address all of these issues, contextualising each discussion and study in thorough reviews of contemporary published literature.

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**STEREOTACTIC (BODY) RADIOTHERAPY**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Associated complexities</th>
<th>Clinical consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small fields</td>
<td>– CHARGED particle disequilibrium :: difficult dose calculation</td>
<td>– INACCURATE output factors leads to erroneous monitor unit calculations</td>
</tr>
<tr>
<td></td>
<td>– DETECTOR volume averaging :: difficult dose measurement</td>
<td>– UNDER-DOSAGE of the tumour :: reduced treatment efficacy</td>
</tr>
<tr>
<td></td>
<td>– SPECTRAL data less well known</td>
<td>– OVER-DOSAGE of neighbouring tissue :: possible deterministic or stochastic health complications (including fatalities)</td>
</tr>
<tr>
<td></td>
<td>– Energy-dependent dosimeter response less well known.</td>
<td>– CANCER induction and other health complications</td>
</tr>
<tr>
<td>Heterogeneities</td>
<td>– CHARGED particle disequilibrium :: difficult dose calculation</td>
<td>– PARTICULAR risk for paediatric patients</td>
</tr>
<tr>
<td>Out-of-field dose</td>
<td>– TYPICALLY ignored clinically</td>
<td>– NOT incorporated into treatment planning :: hard to calculate clinically</td>
</tr>
</tbody>
</table>

**Figure 1.1** An overview of some of the complexities of stereotactic radiotherapy and the potential consequences that may arise as a result of them.
1.4 The scope and structure of the present study

1.4.1 Radiotherapy with small fields

This thesis encompasses the broad complexities of small-field radiotherapy, from pre-treatment dose calculation, to dose delivery verification and risk assessment. Particular attention is given to the potential detriment that may result from the irradiation of healthy tissues. The use of small fields is often considered to add a level of difficulty which, both anecdotal and published evidence suggests, renders clinicians less confident than when employing broader-beam treatments. An outline of the characteristics of stereotactic fields and their associated complexities is given in Figure 1.1. An overview of the content of the thesis is given in Figure 1.2. A concise introduction to these issues is given here, and more detail may be found in Chapter 2.

The issue of charged particle equilibrium (CPE) is of great significance for the small fields employed in stereotactic radiotherapy. CPE describes the circumstance in which the energies, number and direction of charged particles are constant throughout the volume of interest (ICRU 1980). CPE is convenient because under such conditions the dose (a measurable quantity) is equivalent to kerma (a calculable quantity). For a 6 MV photon beam incident upon water, the range of resultant secondary electrons is approximately 16 mm, which is of the order of the lateral dimensions of a stereotactic field. For different spectra, the range may be much longer. As such, the nature of the resulting dose distribution is less readily calculated than a broad-beam dose distribution. This is especially the case for treatment planning systems, the dose algorithms of which frequently assume electronic equilibrium and hence may be of limited accuracy. This is further complicated if the targeted tumour is located in quite heterogeneous media, such as the lung or any other anatomy incorporating or juxtaposed with, for example, airways or bone.

The measurement of small fields is made difficult by effects of detector volume averaging, which act to broaden measured penumbra. Clinically, this may lead to systematic exposure of larger volumes of healthy tissue in the vicinity of the targeted tumour and miscalculation of dose volume histograms, tumour control and normal tissue complication probabilities. Such issues are highlighted by a recently reported accident (KPSR 2010), in which it was found that 76 stereotactic patients received doses up to 50% greater than the prescription, because the clinical physicist employed an unsuitable dosimeter to measure the small (<11 mm) fields and hence miscalculated output factors. Errors in dose measurement and calculation can lead not only to over-dosage of healthy tissues, but also to tumour under-dosage. Unfortunately,
the latency and stochastic nature of the potentially dire outcomes means that errors are often not identified immediately.

In addition to the aforementioned difficulties of small-field stereotactic radiotherapy and the associated – potentially hazardous – clinical consequences, there is the issue of *out-of-field* doses. In this thesis these are defined as doses to the patient at regions far from the primary field arising from leaked and scattered radiation. There is evidence that these low doses to untargeted structures have an associated probabilistic risk of inducing health complications such as secondary cancer.

Background information regarding radiotherapy with small fields is presented in much greater detail in the following chapter (Chapter 2). The quantity ‘dose’ is defined and radiobiological processes and their importance are explained in the context of radiotherapy. Stereotactic radiotherapy is described in detail and a comprehensive literature review is provided which concentrates on post-irradiation toxicity so as to highlight the potential harm that may arise from poor prediction/delivery of dose. The complexities of small-field dosimetry from a calculation perspective are explained in terms of the routine assumption of electronic equilibrium, which breaks down for small fields. The difficulties of measurement of small-fields are also introduced and addressed separately for different detector types.

Chapter 2 provides background information regarding the physics of small radiotherapy fields and their clinical use. Clear from the discussion in Chapter 2 is the necessity for the characterisation of small fields, in order to improve the prediction and delivery of small-field dose distributions and thereby reduce the likelihood of potential detriment to the patient. This leads logically into the subsequent two chapters which deal with methods of dosimetry and dose calculation.
Figure 1.2 An overview of the content of the thesis. The study is focused on characterisation of stereotactic radiation fields both in and out of the primary field. A number of dose measurement and calculation methods are employed.
1.4.2 Advanced dosimetric methods

The measurement of small-fields is a notoriously tricky undertaking. There are a number of dosimeters available, each with its own limitations as applied to small-field dosimetry. In Chapter 3, an overview of contemporary dosimeters is given. Gel dosimeters show great promise, meeting many of the requirements of the ‘ideal’ dosimeter for small fields (in particular three-dimensionality); however, there are a number of practical difficulties encountered with gels. Accordingly, gel dosimeters are treated in relatively great detail. A comprehensive literature review is given, along with detail regarding radiochemical processes and readout mechanisms. Not widely used in a clinical context, the present work investigates some of the fundamental characteristics of gel dosimeters.

The radiation interaction properties of gel dosimeters clearly differ from water and tissue because of the differences in their elemental composition. Many authors employ a single-valued ‘effective atomic number’ in an attempt to characterise media and indicate the degree of such differences, however, this method is dated and of questionable usefulness. Novel results presented in Chapter 3 include a more comprehensive treatment of the effective atomic number concept. Presented in this chapter are calculations of energy-dependent effective atomic numbers of gel dosimeters, for total and partial interaction processes of photons and electrons, surpassing the limited and dubious single effective atomic number approximations typically employed. The water equivalence of gel dosimeters under calibration conditions was investigated using Monte Carlo radiation transport calculations. With the criterion of water equivalence, these studies identified the most appropriate combinations of gel type and published calibration methodology.

1.4.3 Theoretical dose calculation

The calculation of dose delivered to a patient is of critical importance to ensure the best possible treatment outcome. There are a range of mechanisms for the interaction of ionising radiation in materials, and a range of mathematical constructs to describe them – each of which has its own limitations and approximations.

The algorithms employed by treatment planning systems typically sacrifice some level of accuracy during the treatment optimisation routine so as to generate efficient patient throughput. Chapter 4 introduces clinical dose calculation algorithms employed by commercial treatment planning systems, with a deliberate emphasis on the limitations of these
approaches. Considered to be the most accurate means of calculating dose and other relevant quantities, Monte Carlo radiation transport modelling is described in significant detail. The research projects included within this thesis primarily employ the Electron Gamma Shower transport code (Kawrakow 2000; Kawrakow and Rogers 2006), which is therefore discussed in greater detail. The process for commissioning a model of a linear accelerator is comprehensively described. Because each institution must commission their own model against measured data specific to their local machine, significant detail is given in Chapter 4 discussing the methodology, justification of different approximations that may be employed, and so on. The methods described in this chapter are employed directly in studies presented in Chapters 5 and 6 on the characterisation of stereotactic fields.

1.4.4 The in-field characterisation of stereotactic fields

The limitations of various dosimeter types and commercial dose calculation algorithms combined with the small size of stereotactic radiotherapy fields makes the characterisation of small fields difficult. In particular, detector volume averaging effects and assumptions of electronic equilibrium limit confidence in the accuracy of dose measurement and calculation respectively.

Chapter 5 describes in detail the use of Monte Carlo radiation transport calculations to investigate the characteristics of stereotactic fields from a linear accelerator. Spectral information is generally prohibitively difficult to measure in a clinical setting due to the high particle flux, so in this work spectral data is calculated using a dosimetrically-matched Monte Carlo model of a linac. To investigate the potential for gel dosimetry as a means of stereotactic field measurement, studies were carried out using polymer gels in an anthropomorphic head phantom exposed to clinical stereotactic radiotherapy treatments. The resulting dose distributions were read out with a laser optical computed tomography scanner and compared to film-stack measurements taken in the same head phantom, as well as the dose distribution calculated by the planning system. A study in the context of stereotactic body radiotherapy was also undertaken, investigating the extent of tumour under-dosage that may occur when small lung tumours are treated with stereotactic fields. Lung radiotherapy was chosen as a case study because of the strong recent interest in employing these techniques (Timmerman et al. 2009) and because the complexities of small-field dosimetry are compounded by the heterogeneity of tissues, which makes accurate dose calculation
difficult. The systematic set of results presented quantifies the extent of under-dosage to the tumour periphery.

1.4.5 The out-of-field characterisation of stereotactic fields

Despite the increasingly accurate means of dose delivery which conform the radiation beam to the geometry of the lesion, scattered and leaked radiation contribute a dose not just to the immediate periphery of the target, but to healthy tissues far from the primary field. There is epidemiological evidence to suggest that these doses, while low, nevertheless introduce an increased relative risk of radiation-induced carcinogenesis and other health problems such as cardiac or respiratory complications.

Such doses are generally small compared to that received by the intended target, and so little consideration is typically given to these out-of-field doses when developing a treatment plan. While this thesis does not contest the notion that the curative benefits from radiotherapy treatments outweigh the potential risks resulting from out-of-field doses, the results presented nonetheless underscore the importance of maintaining an awareness of such doses. The increasing success of radiotherapy is resulting in longer patient lifetimes, and as such there is greater time in which (typically latent) radiation-induced cancers may become manifest. This is particularly the case for paediatric patients, who have a long expected lifetime and are relatively radiosensitive compared to adults.

Chapter 6 provides a large review of the literature pertaining to the measurement and calculation of out-of-field doses. Significant detail is also provided in the description of radiocarcinogenesis and corresponding dose response behaviour. There is sometimes an impression amongst clinicians that the out-of-field doses from stereotactic fields (as opposed to larger fields) are likely to be small and hence less relevant. The novel studies undertaken in this work shine light on this misconception, and include a systematic study characterising the out-of-field doses from a linac-based stereotactic unit as well as a study of out-of-field doses from small fields as used in paediatric radiotherapy.
1.5 Scientific publications arising from this work

1.5.1 Refereed publications

2011  **ML Taylor, L Dunn, T Kron and RD Franich**, *Determination of peripheral under-dosage at the lung-tumour interface using Monte Carlo radiation transport calculations*  
Medical Dosimetry, in press

2011  **ML Taylor** and T Kron  
*INVITED REVIEW: Assessment of the radiation dose delivered away from the treatment field to patients in radiotherapy*  
Journal of Medical Physics, 36 (2011) 59-71

2011  **ML Taylor, T Kron and RD Franich**, *A contemporary review of stereotactic radiotherapy: Inherent dosimetric complexities and the potential for detriment*  
Acta Oncologica, 50 (2011) 483-508

2011  **ML Taylor, T Kron and RD Franich**, *Assessment of out-of-field doses in paediatric radiotherapy*  
Journal of Medical Physics, 36 (2011) 59-71

2011  **ML Taylor, T Kron and RD Franich**, *Robust determination of effective atomic numbers for electron interactions with TLD-100 and TLD-100H thermoluminescent detectors*  
Nuclear Instruments and Methods B, 269 (2011) 770-773

2010  **T Kairn, T Aland, AL Fielding, RD Franich, PN Johnston, M Kakakhel, J Kenny, RT Knight, CM Langton, D Schlect, ML Taylor** and JV Trapp  
*Adapting a generic BEAMnrc model of the BrainLAB m3 micro-multileaf collimator to simulate a local collimation device*  

2010  **ML Taylor, LN McDermott, PN Johnston, M Haynes, T Ackerly, T Kron and RD Franich**, *Stereotactic fields shaped with a micro-multileaf collimator: Systematic characterisation of peripheral dose*  

2009  **ML Taylor, RD Franich, JV Trapp and PN Johnston**, *Electron interaction with gel dosimeters: effective atomic numbers for collisional, radiative and total interaction processes*  
Radiation Research, 171 (2009) 123-126

2009  **ML Taylor, RD Franich, JV Trapp and PN Johnston**, *A comparative study of the effect of calibration conditions on the water equivalence of a range of gel dosimeters*  
Transactions on Nuclear Science, 56 (2009) 429-436

2008  **ML Taylor, RD Franich, JV Trapp and PN Johnston**, *The effective atomic number of dosimetric gels*  
Australasian Physical and Engineering Sciences in Medicine, 31 (2008) 131-138

2007  **ML Taylor, RD Franich, PN Johnston, RM Millar and JV Trapp**, *Systematic variations in polymer gel dosimeter calibration due to container influence and deviation from water equivalence*  
Physics in Medicine and Biology, 52 (2007) 3991-4005
1.5.2 Scientific papers submitted and in preparation

2011  **ML Taylor, T Kairn, L Dunn, T Kron and RD Franich**  
*The effect of field size dependent spectral changes on stopping power ratios in the context of linac-based stereotactic radiotherapy*  
Medical Physics, submitted Dec 2010

2011  **ML Taylor, T Kairn, L Dunn, L McDermott, T Kron and RD Franich**  
*Evaluation of small-field stereotactic dose distributions using three-dimensional gel and film dosimetry*  
Medical Physics, in prep

2011  **ML Taylor, T Kairn, L Dunn, L McDermott, T Kron and RD Franich**  
*Spectral characteristics of stereotactic fields: Implications for dosimetry*  
Physica Medica, in prep

1.5.3 Conference presentations

2011  **ML Taylor, L Dunn, T Kron and RD Franich**  
*The influence of spectral changes in non-reference conditions on stopping power ratios in small-field dosimetry*  
European Society for Therapeutic Radiology and Oncology (ESTRO) 8 – 12 May 2011, London, United Kingdom

2010  **ML Taylor, T Kron, RD Franich**  
*Reducing the risk of radiocarcinogenesis in paediatric patients treated with external beam radiotherapy*  
Engineering and Physical Sciences in Medicine (EPSM) 5 – 9 Dec 2010, Melbourne, Australia

2010  **ML Taylor**  
*Evaluation of effective atomic numbers of LiF:Mg,Ti and LiF:Mg,Cu,P thermoluminescent dosimeters for electron interactions spanning the keV-MeV energy range*  
Engineering and Physical Sciences in Medicine (EPSM) 5 – 9 Dec 2010, Melbourne, Australia

2010  **ML Taylor, L Dunn, T Kron, F Height and RD Franich**  
*Characterisation of lung tumour under-dosage for interpretation of clinical trial data,*  
Engineering and Physical Sciences in Medicine (EPSM) 5 – 9 Dec 2010, Melbourne, Australia

2010  **T Kairn, ML Taylor, RD Franich, T Kron and JV Trapp**  
*Origins of the observed asymmetry in out-of-field dose from a linac fitted with an external micro-MLC*  
Engineering and Physical Sciences in Medicine (EPSM) 5 – 9 Dec 2010, Melbourne, Australia

2010  **ML Taylor, T Kairn, L Dunn, JV Trapp, J Kenny, R Knight, R Smith, M Haynes, T Ackerly, T Kron and RD Franich**  
*Three-dimensional dose verification for clinical treatments of small intracranial tumours,*  
Engineering and Physical Sciences in Medicine (EPSM) 5 – 9 Dec 2010, Melbourne, Australia

2010  **ML Taylor, L Dunn, T Kron and RD Franich**  
*Dose inhomogeneity in radiotherapy of lung tumours: Calculation of peripheral underdosage*  
European Society for Therapeutic Radiology and Oncology (ESTRO) 12 – 16 Sept 2010, Barcelona, Spain
2010  ML Taylor, I Dunn, T Kron and RD Franich  
Radiotherapy of paediatric brain lesions: Determination of doses to untargeted organs. European Society for Therapeutic Radiology and Oncology (ESTRO) 12 – 16 Sept 2010, Barcelona, Spain

2009  ML Taylor, LN McDermott, M Haynes, PN Johnston, T Ackerly, T Kron and R Franich,  
Characterisation of peripheral doses from stereotactic photon fields  
European Society for Therapeutic Radiology and Oncology (ESTRO) 30 Aug – 3 Sept 2009, Maastricht, The Netherlands

2009  PN Johnston, ML Taylor, RD Franich, LN McDermott, and T Ackerly  
Developing and commissioning a Monte Carlo model of a linear accelerator and clinical photon beam  
International Meeting of Frontiers of Physics (IMFP) 12 – 16 Jan 2009, Genting, Malaysia

2008  ML Taylor, RD Franich, JV Trapp and PN Johnston  
The effective atomic number of various gel dosimeters  
European Society for Therapeutic Radiology and Oncology (ESTRO) 14 – 18 Sept 2008, Göteborg, Sweden

2008  RD Franich, ML Taylor, T Ackerly and PN Johnston  
Commissioning of a Monte Carlo model of a linear accelerator and clinical photon beam  
Engineering and Physical Sciences in Medicine (EPSM) 16 – 20 Nov 2008, Christchurch, New Zealand

2008  ML Taylor, LN McDermott, RD Franich, T Ackerly, M Haynes, T Kron and PN Johnston,  
Out-of-field doses from stereotactic fields  
Engineering and Physical Sciences in Medicine (EPSM) 16 – 20 Nov 2008, Christchurch, New Zealand

2007  ML Taylor, RD Franich, JV Trapp and PN Johnston  
A Monte Carlo study of the differences between dose to water and dose to polyacrylamide and ferrous-sulphate gel dosimeters in a variety of calibration techniques  
IEEE Nuclear Science Symposium and Medical Imaging Conference 28 Oct - 4 Nov 2007, Honolulu, USA

2007  ML Taylor, RD Franich, JV Trapp and PN Johnston  
Effective atomic number and the characterisation of gel dosimeters  
Engineering and Physical Sciences in Medicine (EPSM) 14 - 18 Oct. 2007, Fremantle, Australia

2007  RD Franich, ML Taylor, T Acklerly JV Trapp and PN Johnston  
A Monte Carlo model of a linear accelerator treatment head for the simulation of clinical photon beams  
Engineering and Physical Sciences in Medicine (EPSM) 14 - 18 Oct. 2007, Fremantle, Australia

2007  ML Taylor, RD Franich, JV Trapp and PN Johnston  
Differences between dose to water and dose to a range of polymer gel dosimeters in common calibration techniques  
Engineering and Physical Sciences in Medicine (EPSM) 14 - 18 Oct. 2007, Fremantle, Australia

2006  ML Taylor, RD Franich, PN Johnston and JV Trapp  
Monte Carlo investigation of standard gel dosimetry calibration  
Australian Institute of Physics Congress (AIPC) 3 – 8 Dec. 2006, Brisbane, Australia

2006  ML Taylor, RD Franich, PN Johnston and JV Trapp  
Monte Carlo quantification of backscatter effects on the absorbed dose in gel dosimeters  
Engineering and Physical Sciences in Medicine (EPSM) 17 - 21 Sep. 2006, Noosa, Australia
### 1.5.4 Invited seminars

<table>
<thead>
<tr>
<th>Year</th>
<th>Title</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>Characterisation of stereotactic fields</td>
<td>RMIT University, Melbourne</td>
</tr>
<tr>
<td>2009</td>
<td>Current applications of Monte Carlo radiation transport methods in the field of medicine</td>
<td>Peter MacCallum Cancer Institute, Melbourne</td>
</tr>
<tr>
<td>2009</td>
<td>On the small fields used in radiotherapy</td>
<td>To a delegation from Victorian institutes and R Mackie, RMIT University, Melbourne</td>
</tr>
<tr>
<td>2008</td>
<td>Peripheral doses and radiocarcinogenesis</td>
<td>QUT, Queensland</td>
</tr>
<tr>
<td>2007</td>
<td>The effective atomic number</td>
<td>Peter MacCallum Cancer Institute, Melbourne</td>
</tr>
<tr>
<td>2007</td>
<td>Quantification of systematic errors in gel dosimeter calibration</td>
<td>The Alfred Hospital, Melbourne</td>
</tr>
<tr>
<td>2006</td>
<td>Monte Carlo quantification of backscatter in gel dosimeters</td>
<td>The Alfred Hospital, Melbourne</td>
</tr>
</tbody>
</table>
CHAPTER TWO

It is necessary, with a view to the science we are investigating, that we first describe the questions which should first be discussed... For those who wish to get rid of perplexities it is first a good plan to go into them thoroughly…

Ἀριστοτέλης (Aristotle)

† From Κεφάλαιον B of Aristotle’s Τα Μετα Τα Φυσικά, translation due to H. Tredennick. This chapter deals with the complexities of stereotactic radiotherapy and poses the questions we wish to answer.
CHAPTER 2

Radiotherapy with small fields

Inherent complexities, clinical efficacy and the potential for detriment

CHAPTER TWO

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2.1 Overview
This study relates to small-field stereotactic radiotherapy, with a particular interest in the potential detriment that may result from the irradiation of healthy tissues.

When ionising radiation is incident upon human tissues, biological damage occurs as a result of a range of processes. In the case of radiotherapy, it is precisely the cell-killing function of ionising radiation that is the desired outcome. These processes are described in Section 2.2. When energy is deposited within human tissues, the tissue is said to have received a ‘dose’ of radiation. This concept and associated clinically-relevant conventions on dose specification are described in Section 2.3. Stereotactic radiotherapy is discussed in detail in Section 2.4, in the context of treatment of both intra- and extra-cranial lesions. The accurate delivery of small-fields for such treatments is inherently complex, because of issues such as charged particle equilibrium, which has a pronounced impact on small-field radiotherapy. As such, relevant background theory and a discussion of the difficulties of the measurement of small-fields and their resulting dose distributions is presented in Section 2.5.

This chapter provides background information regarding the physics of small radiotherapy fields and their clinical use, of relevance to the subsequent chapters. What is clear from the information presented in this chapter is a need for the characterisation of small fields, so as to improve their delivery and hence limit the potential detriment that may occur in the form of toxicity in the vicinity of the targeted region. One might ask: ‘what is meant by characterisation?’ There are gaps in scientific knowledge that are addressed by this study:

– Knowledge of the spectral qualities of small fields, which receive decreased scatter from collimation devices and so on (compared to broad fields).
– Knowledge of the penumbrae of small fields, which is typically difficult to determine because of detector limitations, and can have significant consequences in terms of patient outcome if inaccurate.
– Methods of dose measurement that provide three-dimensional information without the limitations of other dosimeters, such as volume averaging etc.
– Accurate means of dose calculation that remain robust even when using stereotactic fields of sizes approaching that of the secondary electron range in the (heterogeneous) media of interest.
– Knowledge of out-of-field dose from small fields, which may lead to such long-term issues as radiocarcinogenesis.

This chapter thus leads directly into the following two chapters, which are concerned with developing robust procedures for advanced media-matched three-dimensional dosimeters.
(Chapter 3), and accurate dose calculation (Chapter 4). The issue of low-doses well beyond the targeted region (out-of-field doses) and the associated negative consequences shall be dealt with in detail in later chapters.

2.2 The cell killing function of ionising radiation

Photons interact with matter via a range of processes. At clinical (megavoltage) energies, the predominant mechanism of dose deposition in a biological medium is via interaction with electrons of high kinetic energy that have been liberated by initial photons from the linear accelerator (linac). It is these electrons that ultimately deliver a ‘dose’ to tissues. Various mathematical formulations exist that describe these processes. For simplicity, physicists often employ the Bethe-Bloch approximation that treats electron transport through media as a continuous, ‘slowing down’ process rather than the stochastic series of events that actually take place. This does not sufficiently describe the processes that eventually result in molecular modifications in the medium. Cell damage occurs as a result of discrete interactions whereby electrons lose their kinetic energy via ionisation events. There is scientific consensus that the cytotoxic effect of ionising radiation on cells results from damage to deoxyribonucleic acid (DNA) (Latarjet 1972; Hutterman et al. 1978; Teebor et al. 1984; Errera 1985; Thacker 1986). Strands of DNA can be broken directly or indirectly, via interaction with free radicals. The term ‘direct action’ applies to ionisation that occurs within the DNA molecule. The fraction of cell-killing resulting from direct action is of the order of 80 % for high linear energy transfer (LET) radiation, such as alpha particles or heavy ions (Roots et al. 1985). Indirect damage to DNA is caused by free radicals that are generated from the radiolysis of water – the predominant reaction in living systems for low LET radiation, such as x- or γ-rays. The processes of excitation and ionisation of water by radiation are described by the equations below (Alpen 1998):
Free radicals are a highly reactive chemical species. Although most free radicals formed in these reactions recombine to form oxygen and water in a time scale of $\sim 10^{-5}$ seconds, some may interact with other chemical compounds and result in detrimental biological effects. Of the products of water radiolysis, the hydroxyl ($OH^*$) radical (an oxidising species) is the most important radical in terms of damage to DNA (Cadet et al. 1999).

Different tissues have differing sensitivities to ionising radiation. Over a century ago, Bergonié and Tribondeau studied the radiosensitivity of cells, concluding that (i) actively proliferating cells are the most radiosensitive, (ii) the degree of differentiation of cells is inversely related to their radiosensitivity and (iii) radiosensitivity of cells is proportional to the duration of mitotic activity they must undergo (Bergonie and Tribondeau 1906). Cancerous cells are thus relatively radiosensitive, compared to healthy tissues, which is ultimately what makes cancer amenable to treatment with radiotherapy. It is thus the objective of radiotherapy to destroy lesions with ionising radiation while sparing as much as possible the surrounding, healthy tissues. In other words, the aim is to deliver a lethal dose to the cancer whilst adjacent (healthy) tissues receive a sub-lethal dose.

2.3 Dose

2.3.1 A brief conceptual foundation of dose

One may trace the origins of the concept of radiation dosimetry to the medical application of ionising radiation borne of the discovery of the x-ray (Röntgen 1895). Methods for prediction and reproduction of clinical observations are of clear necessity. The concept of ‘dose’, analogous to that in pharmacology, has been introduced into radiotherapy as the key quantity
relating to biological effects. However, ‘dose’ was initially not well defined and was historically thought to be akin to the energy of the incident radiation field. Christen referred to the dose as the energy absorbed by a unit volume (Christen 1914), and this is closer to the contemporary definition of absorbed dose. The key advancement was the recognition that the biological effect of radiation relates to the energy imparted to the tissue rather than that which is incident upon it. The energy imparted to the matter in a volume results from a number of discrete contributions from various processes occurring therein. For photon beams, with which this study is principally concerned, one must consider (i) attenuation of the photons via scattering / absorption processes, (ii) transfer of energy to charged particles, (iii) transport of and energy deposition by charged particles. When an x-ray interacts with matter via either the photoelectric, Compton or pair-production processes, charged particles are liberated and given momentum. These travel through the medium, undergoing a number of interactions until they deposit all their energy and stop. This collisional energy loss leads to the ionisation and excitation events that are ultimately responsible for biological damage. The ‘quantity of energy imparted by ionising radiation to matter in a volume of certain density’ is the fundamental quantity of radiation dosimetry, the determination of which logically requires that a volume and a time interval be specified.

2.3.2 A brief mathematical description of dose

A fundamental quantity in radiation dosimetry is the ‘energy imparted’, $\varepsilon$ (ICRU 1980). The energy imparted to matter in a given volume results from discrete contributions, $\delta\varepsilon$, due to a number of radiation energy loss processes, i.e.

$$\varepsilon = \sum \delta\varepsilon_i .$$ \hspace{1cm} 2.1

The expectation value for the energy imparted may be given by

$$\langle \varepsilon \rangle = R_{in} - R_{out} + \sum Q ,$$ \hspace{1cm} 2.2

where $R$ is the radiant energy (sum of kinetic or quantum energies of ionising particles), the subscripts in and out refer to radiant energy in and out of a volume of interest, and $\sum Q$ corresponds to the release of rest-mass energy of nuclei (Krane 1988).

The absorbed dose at a point within an infinitesimal volume, $dv$, of mass $dm$ is thus given by:
\[ D = \frac{d\langle e \rangle}{dm}. \]

In the context of radiotherapy, specifying the dose that a tumour should receive and reporting dose delivered is a fundamental necessity and is far from being a trivial activity.

2.4 Stereotactic radiotherapy

2.4.1 Overview

Stereotactic radiotherapy is a means of delivering a highly localised dose to a small lesion. This method is frequently applied to intracranial lesions, and as such the following discussions primarily concern intracranial treatments. There are a number of methods for radiation delivery to intracranial lesions, including stereotactic radiotherapy (SRT), stereotactic radiosurgery (SRS), whole-brain radiotherapy (WBRT), intensity-modulated stereotactic radiosurgery and radiotherapy (IMSRS and IMSRT respectively), tomotherapy and a range of other approaches such as electron therapy, proton therapy, the use of internal alpha emitters and others. It is also not uncommon to implement multiple techniques, often as a concomitant boost.

Stereotactic radiotherapy and radiosurgery are routinely employed for the treatment of intracranial lesions. Increasingly, extracranial tumours are being treated in a similar fashion. Figure 2. highlights this trend – with one paper relating to stereotactic radiotherapy published in the early sixties compared to over 1700 papers published in the last four years. In this section, the aim is to provide a broadly encompassing overview of the different aspects of stereotactic radiotherapy, with the objective of giving the reader an understanding of the complexities associated with the use of small fields in terms of dose measurement and calculation, as well as the clinical efficacy of stereotactic techniques. This includes a review of the clinical application of SRT, with a deliberate emphasis on the potential for detriment to the patient – so as to highlight the need for accurate radiation delivery and confident knowledge of the characteristics of the dose distributions resulting from such small fields. A notoriously difficult endeavour, the measurement of small-field dose distributions is also discussed.
A more detailed discussion of the efficacy of stereotactic radiotherapy and radiosurgery, highlighting the importance of accurate clinical dosimetry which is a focus of this thesis, may be found in a review paper by the candidate (Taylor et al. 2011d)

**Figure 2.1** An indication (based on a PubMed search of published literature) of the increasing implementation of both intra- and extra-cranial stereotactic radiotherapy. Note the logarithmic scale.

### 2.4.2 Intracranial stereotactic radiotherapy (SRT) and radiosurgery (SRS): Efficacy and the potential for radiation-induced carcinoma and other complications

The origins of stereotactic intracranial surgery may be traced back to work first presented at the 1906 meeting of the British Medical Association in Toronto. In 1908, after several years of use in studies of the structure and functions of the cerebellum in various animals, Horsley and Clarke published details of a stereotactic instrument that incorporated a frame attached to the skull and a three dimensional coordinate system that facilitated the precise application of an insulated needle for excitation or electrolysis (Horsley and Clarke 1908). Based on the same fundamental principles, stereotactic radiosurgery (SRS) is a single fraction radiotherapy modality for the treatment of intracranial lesions, employing stereotactic apparatus and multiple small beams delivered through non-coplanar isocentric arcs. The word ‘radiosurgery’ is attributed to Leksell, a neurosurgeon (Leksell 1951). Initially, SRS was used primarily for treatment of arteriovenous malformations (AVM) (Steiner et al. 1992; Yamamoto et al. 1995) and other benign brain lesions (Flickinger et al. 1995). More recently, SRS has become increasingly applied for the treatment of malignant brain lesions, including
primary tumours and metastases. Stereotactic radiotherapy (SRT) refers to the same procedure as SRS, but involves multiple dose fractions. SRS and SRT rely on 3D localisation of the lesion, utilising immobilisation devices. The stereotactic apparatus is employed during imaging and treatment for target localisation and head immobilisation. This must be done with a high degree of accuracy, necessitating meticulous quality assurance (QA) processes. Conformity in dose is sought with use of collimated beams, optimised arc angles and multiple isocentres. Alternatively, it is possible to dynamically shape the field during rotation with use of mini-/micro-multileaf collimators.

Stereotactic radiosurgery is typically delivered via either the Leksell Gamma-Knife system (LGK; Elekta), Cyber-Knife (Accuray) or with a conventional megavoltage (MV) linac. The former is a commercialised piece of equipment incorporating a modified $^{60}$Co unit with 201 convergent beams directed through variable circular collimators (Leksell 1983). The Cyber-Knife is a robotic mounted linac, similarly with circular collimators. SRS with a linac is sometimes referred to as ‘x-ray knife’ treatment. This involves the use of multiple non-coplanar arcs of circularly or dynamically shaped fields that converge on the isocentre. A stereotactic frame is fixed to the patient’s head and locked onto the treatment couch. The target coordinates are matched to the machine isocentre with a high degree of precision.

In summary, there are several key points that may be made regarding the efficacy of stereotactic approaches (Taylor et al. 2010b):

- SRT results in comparable survival rates and better normal tissue sparing than conformal radiotherapy (Goyal et al. 2000; Le et al. 2003; Selek et al. 2004).
- The use of linac-based stereotactic techniques (with a multileaf collimator) can be advantageous, in terms of dose homogeneity and normal tissue sparing (Shiu et al. 1997; Tokuuye et al. 1998; Kulik et al. 2002; Combs et al. 2005; Aoki et al. 2006).
- The addition of intensity modulation to stereotactic treatments results in improved dose conformality and improved organ-at-risk sparing (Carnidale et al. 1998; Bues et al. 1999; Pagnini et al. 1999; Benedict et al. 2001; Little et al. 2003).
The brain is known to exhibit sensitivity for acute and delayed radiation damage. Review of published clinical data reveals a number of key trends regarding complications following SRT and SRS (Taylor et al. 2010b):

- There are a range of immediate SRT/SRS potential side-effects, affecting about one third of patients, though these are typically moderate and short term (Werner-Wasik et al. 1999).
- Although accurate localisation reduces the likelihood, there is potential for severe late effects ranging from neurological impairment to death (Lee et al. 1988; Marks and Spencer 1991; Flickinger et al. 1995; Ianssen et al. 2004; Jensen et al. 2005; Korytko et al. 2006).
- Little is known about long-term neuropsychological effects. Clinical findings show children exhibit cognitive decline subsequent to fractionated radiotherapy of brain tumours; data for adults is comparatively scarce, with preliminary finding suggesting some cognitive function, such as memory, may be particularly vulnerable (Roman and Sperduto 1995).
- There is a risk of radiation-induced cancer (particularly meningiomas (Gomori and Shaked 1982)) resulting from intracranial treatments in general (Modan et al. 1974; Shore et al. 1976; Ron et al. 1988; Sadetzki et al. 2002); however, the likelihood of such tumours becoming manifest following stereotactic techniques is relatively low (Sheehan et al. 2006).
- There are reported cases of radiation-induced tumours from stereotactic radiosurgery, the majority of which are glioblastomas (Brada et al. 1993; Yu et al. 2000; Kaido et al. 2001; Shamisa et al. 2001; McIver and Pollock 2004; Minniti et al. 2005).

Stereotactic radiotherapy and radiosurgery may also be employed to extracranial regions. Generally referred to as stereotactic body radiotherapy, though the term extracranial stereotactic radiotherapy is often still applied, is discussed in the following section.

2.4.3 Stereotactic body radiotherapy (SBRT) and the need for accurate dose delivery:
The potential for radiation toxicity

As mentioned earlier, stereotactic radiotherapy generally implies treatment of intracranial lesions. An obvious extension is to apply similar treatment techniques to small tumours at other anatomic locations; such treatments are often referred to as ‘extracranial stereotactic radiotherapy’ or ‘stereotactic body radiotherapy’ (SBRT). A review of the relevant scientific
literature indicates that extracranial treatments are of most interest in relation to the lung, liver and the spine.

There are several key differences between conformal or intensity-modulated radiotherapy and SBRT. In the former case, doses of up to 3 Gy/fraction are typically given over 10-30 fractions, whilst for SBRT up to 30 Gy/fraction may be given in just a few (< 5) fractions. Margins are also of the order of millimetres for SBRT, whereas IMRT margins are typically of the order of centimetres. It is important to note this latter point, since often treatment planning systems have a dose grid resolution of the same order of magnitude as the margins in the case of SBRT.

One critical element of SBRT is the use of a suitable immobilisation methodology. The earlier forays into SBRT were facilitated by apparatus such as an extracranial stereotactic frame proposed by Hamilton et al for treatment of spinal lesions (Hamilton et al. 1995) and a body frame with vacuum bag implemented by Lax et al for treatment of lesions of the liver and lung (Lax et al. 1994). Ultimately, image-guidance may be considered the ideal approach, with applications in not only initial patient setup but also real-time monitoring of the target (or surrogate marker) during treatment.

For lung treatments, a range of immobilisation and positioning devices have been employed: the Elekta Body Frame (Elekta Oncology, Stockholm) with accuracies ranging from 1.8 to 5 mm (Wulf et al. 2000; Fukumoto et al. 2002; Nagata et al. 2002; Hof et al. 2003), the MI BodyFIX (Medical Intelligence, Schwabmuenchen) with accuracies ranging from 2.5 to 3 mm (Fuss et al. 2004) and the Leibinger Body Frame (Leibinger, Freiburg) with accuracies of 2 to 4.4 mm (Wulf et al. 2001). For liver treatments, the Elekta Body Frame has been used with an accuracy of ≤ 4.4 mm (Wulf et al. 2000), the MI BodyFIX has been employed with a reported accuracy of ≤ 3.2 mm(Fuss et al. 2004) and the Leibinger Body Frame has been used for liver treatments with a reported accuracy of 1.8-4.4 mm (Herfath et al. 2001). Tokuuye et al found motion was significantly reduced just by making the patient lie ventrally on the couch and strapping the jaw and arms down (achieving an accuracy of approximately 5 mm)(Tokuuye et al. 1997). For spinal treatments a range of approaches have been taken. These include use of the MI BodyFIX with approximately millimetre accuracy (Chang et al. 2004), use of a body cast with ~3 mm accuracy (Lohr et al. 1999) and approaches using frameless real-time tracking of fiducial markers achieving accuracies of approximately 2 mm (Murphy 1997).
Stereotactic body radiotherapy is facilitated by such approaches to immobilisation, with further distinctions from other techniques in methods and importance of dose prescription/verification and hypofractionation. The ultimate objectives remain the same: the dose to the tumour volume must be maximised, whilst minimising doses to normal tissues; the following discussion concentrates on the clinically reported acute and delayed side-effects of SBRT.

The reader is referred to the associated review paper by the candidate for a comprehensive discussion of the issues and efficacy of stereotactic body radiotherapy, focusing on the lung, liver, spine and pancreas (Taylor et al. 2010b).

2.4.4 Concluding thoughts
Stereotactic radio-therapy and –surgery for the treatment of tumours both intracranial and at other anatomical locations is widely employed because of the highly localised doses achievable. Furthermore, it is a highly patient-driven modality, because of its non-invasive nature. However, the approaches described invariably result in the irradiation of significant healthy tissue, despite the small fields involved. SRS (single fraction) and SRT (few fractions) are associated with high doses per fraction compared to other techniques and, as such, accurate localisation is critical. Consequences for irradiated tissue are more significant.

There are many contributing factors that influence the extent of complications in a given treatment. The focus of the present work is that of small-field dosimetry, which – if inaccurate – can lead to complications for the patient. Quality assurance (QA) processes are routine in clinical radiotherapy departments and it would be unusual for a given QA to be performed incorrectly. Rather, the focus of the current paper is to address issues associated with the accuracy of current dose measurement and calculation methodologies as applied to stereotactic radiotherapy. Consider, for example, SBRT of the lung. There is a strong contemporary interest in motion compensation; patient fixation devices typically have accuracies of 2-5 mm. However, even if a tumour is guaranteed to be ‘stationary’ and modern treatment approaches facilitate precise delivery of planned doses – if the accuracy of the calculated dose is poor then this will have direct consequences for the patient. Doses to the periphery of lung tumours may be of the order of 10 % lower than at the centre, which is often not accurately predicted by treatment planning systems (Taylor et al. 2010a). It is worth bearing in mind that the use of multiple convergent fields is of course advantageous not only in the reduction of integral healthy tissue dose but also results in a reduction in peripheral
under-dosage. The study by Taylor et al (2010a) indicates that for circumstances where multiple beams or arcs are employed the aforementioned ~10% under-dosage at the periphery of lung tumours drops to the order of 5%. This is poorly predicted by conventional treatment planning algorithms such as pencil beam convolution, although better predicted by the analytical anisotropic algorithm (Härdinger et al. 2005). This was highlighted recently by Timmerman et al (2009), who reported on the Radiation Therapy Oncology Group 0236 Phase II trial, whereby the prescribed 20 Gy per fraction dose (totalling 60 Gy) was found to be only 18 Gy per fraction (totalling 54 Gy) – an error that arose because of dose calculation inaccuracy. This highlights the necessity for accurate dose calculation. However, even if accurate dose calculation in treatment planning could be guaranteed, it is still nonetheless subject to the accuracy with which doses were measured during commissioning. Dose calculation and dose measurement are of critical importance.

This necessitates accurate knowledge of dosimetry – particularly of field edges and penumbra, which is difficult in the case of small fields, where the periphery occupies a large fraction of the field area. The complexities with dose prescription, measurement and calculation make understanding the dose characteristics of small fields a challenging task. These issues are discussed in the following sections.

2.5 The difficulty of dose prescription

One of the more complex issues in stereotactic radiotherapy is the choice of prescription point or volume. The system of prescribing and reporting described by the International Commission on Radiation Units and Measurements (ICRU) in their reports 52 and 60 is not commonly used for stereotactic procedures (ICRU 1993; ICRU 2000). While the concepts of clinical target volume (CTV), internal target volume (ITV) and planning target volume (PTV) are well accepted, the use of a reference point for reporting is rare.

The reason for this is illustrated by Figure 2.2. If one prescribes to a location in the target such as the isocentre or the point of maximum dose, one would expect that no point in the target much less than the prescription dose; typically not more than 5% less (ICRU 2000). In that case, the edge of the target would align with the 95% isodose curve where the dose fall-off is still relatively shallow. If one selects a lower isodose curve for prescription, the dose gradient is much sharper, leading to better conformity. The sacrifice in this case is reduced
target homogeneity – as the maximum dose will typically exceed the prescription dose by over 20%.

In different countries there is a different emphasis regarding the objective to be achieved when prescribing stereotactic radiotherapy (Hiraoka and Nagata 2004; Nagata et al. 2007; Timmerman et al. 2007b; Timmerman et al. 2007c; Fakiris et al. 2009; Nagata et al. 2009). In Japan, the emphasis is on dose homogeneity, in which case prescribing to an ICRU reference point is appropriate. In North America, the preferred approach is to prescribe to an isodose curve covering the target (or the large majority thereof). The latter method is also more common in intensity modulated radiotherapy (IMRT), whereby the inverse treatment planning process uses dose volume constraints that are more easily associated with prescription to isodose volumes. The Scandinavian approach in particular deliberately employs quite inhomogeneous dose distributions (Lax 1993; Baumann et al. 2006).

Ultimately, it is quite difficult to compare the outcomes of clinical series that utilise the same nominal dose but employ different prescription systems. In practice, many approaches are possible, as illustrated in Figure 2.2. It is essential that reporting of dose delivered to targets in stereotactic procedures includes a clear description of the prescription rules. As many of the extracranial targets are also subject to motion, this must be taken into consideration when prescribing (ICRU 2000; Admiraal et al. 2008).

Figure 2.2 A sketch of a tumour and isodose curves illustrating different concepts of dose prescription.
2.6 The complexities of small fields

2.6.1 Overview

Small, conformal fields are necessary for the treatment of small lesions. The three-dimensional dose distributions delivered by techniques such as SRS, SRT and IMRT need to conform tightly to the planning target volume (PTV). This is particularly so in the case of SRS where the relatively high doses in a single fraction demand strict conformality. The historical limitations in the implementation of small fields may have included technical difficulties of small target localisation and the integration of diagnostic and therapeutic procedures, in addition to a lack of dosimetric data for small fields. Contemporary technology in the field of radiotherapy has overcome many of these technical limitations. However, despite being described as early as 1952 by Leksell, there is still concern regarding the use of small fields (generally below about 4 x 4 cm\(^2\)) because of a lack of detailed knowledge about the characteristics of the radiation fields. To deliver small-field treatments with confidence, precise and accurate measurement of the dose profiles, percent depth-dose curves and output factors for small fields is necessary for input into the clinical planning software. There are difficulties associated with this as a result of ‘detector volume averaging’ – a smoothing of the penumbra resulting from the finite volume of the detector, and the lack of electronic equilibrium in small fields.

2.6.2 Radiation equilibrium: A concise theoretical discussion

2.6.2.1 Radiation equilibrium: An overview

Calculation of absorbed dose is significantly simplified if a state of ‘radiation equilibrium’ exists in the region of interest. For a detailed discussion of the theory of radiation equilibrium, the interested reader is referred to Ch. IV of Attix (2004), Ch. II of Metcalfe \textit{et al} (1997; 2007) or Ch. I (Vol. I) of Kase \textit{et al} (1987); though there are many other good references.

Generally, authors define radiation equilibrium as the circumstance whereby the amount of radiant energy entering a certain volume is in balance with the amount leaving the volume. If the volume considered is infinitesimal, this may expressed mathematically via the divergence theorem\(^\dagger\) (for the net flux of content passing through a surface surrounding a region of space), i.e.

\[ \nabla \Psi = 0, \]

\[ 2.4 \]

\(^\dagger\) This null case is in fact referred to as divergenceless.
where $\Psi$ is the vectorial energy fluence. This itself may be broken into components corresponding to charged ($\Psi_c$) and uncharged particles ($\Psi_u$), i.e.

$$\Psi = \Psi_c + \Psi_u.$$  \hfill 2.5

In reality, the finite nature of media means that equilibrium conditions are rarely completely met; however, often for (one or more components of) a radiation field, a state of equilibrium may be met, albeit approximately, with a high degree of accuracy. In a finite homogeneous medium, equilibrium may exist at a given point for a particular radiation provided there is uniform production of such particles within all distances from the point up to the maximum range of the particles. An immediately apparent example would be a point within a large homogeneous volume consisting of a uniformly distributed radioactive source, where the distance from the point to the boundary of the volume is of a magnitude less than the range of the particles and their progeny. In the case of external photon beam radiotherapy, charged particle equilibrium may be approximately achieved (i.e. $\nabla \Psi_c = 0$) at regions located beyond the maximum charged particle range within that medium. The International Commission of Radiation Units and Measurements (ICRU 1980) defines charged particle equilibrium as existing when “the energies, number and direction of the charged particles are constant throughout the volume of interest”.

### 2.6.2.2 Full radiation equilibrium (RE)

The absorbed dose may be defined as:

$$D = \frac{1}{\rho} \lim_{V \to 0} \left( \frac{\langle \varepsilon \rangle}{V} \right) = \frac{1}{\rho} \left( \nabla \Psi + \frac{d}{dV} \langle \sum Q \rangle \right).$$  \hfill 2.6

where the expectation value $\langle \varepsilon \rangle$ is the mean of the energy imparted in an infinitesimal volume $V$, $\rho$ is the mass density and $\sum Q$ corresponds to the release of rest-mass energy of nuclei (Krane 1988). In conditions of radiation equilibrium, this simplifies to:

$$D = \frac{1}{\rho} \left( \frac{d}{dV} \langle \sum Q \rangle \right).$$  \hfill 2.7

Under conditions of radiation equilibrium (RE), $R_{\text{in}} - R_{\text{out}} = 0$, thus:
\[
\langle \varepsilon \rangle = \langle \sum Q \rangle ,
\]

and therefore:

\[
D = \frac{1}{\rho} \left( \frac{d\langle \varepsilon \rangle}{dV} \right) = \frac{d\langle \varepsilon \rangle}{dm} = \frac{d\langle \sum Q \rangle}{dm} ,
\]

where \( m \) is mass. What this means is that the absorbed dose is equal to the expectation value of the energy released by the radioactive sources (per unit mass), at a point in the medium where radiation equilibrium exists.

2.6.2.3 Charged particle equilibrium (CPE)

Where radiation equilibrium exists, so too, therefore, does ‘charged particle equilibrium’ (CPE), or simply ‘electronic equilibrium’ (sufficient for our purposes). Equivalently to radiation equilibrium, charged particle equilibrium exists for a volume if each charged particle of a certain type and energy exiting the volume is replaced by a particle of the same type and energy entering. Of particular interest is the case whereby finite homogeneous media are irradiated with uncharged ionising particles (such as photons from a medical linear accelerator). CPE is said to exist for the volume \( V \) provided the following general conditions on \( V \) are met (Burch 1955; Dutreix et al. 1965):

- The media is homogeneous (in terms of atomic composition).
- The media is homogeneous (in terms of mass density).
- There exists a uniform field of (indirectly ionising) radiation, which is subject to negligible attenuation through the medium.
- There are no net electric or magnetic fields that may perturb the path of charged particles.

Although external radiation beams incident on a given body generally result in anisotropic radiation distributions, the anisotropy will be homogeneous throughout the volume \( V \), and so CPE will be produced. The net ‘energy transferred’ in a given volume is the kinetic energy received by charged particles in \( V \) (not including kinetic energy transferred between charged particles), and may be written as:
\[ \langle \xi^n \rangle = \langle \xi \rangle + \langle R_{\text{out}} \rangle_u - \langle R_{\text{out}} \rangle_{u^{\text{nonrad}}} + \langle R \rangle_{u^{\text{rad}}} \],

where the subscript \( u \) refers to uncharged radiation, and the superscripts \( \text{nonrad} \) and \( \text{rad} \) refer to non-radiative and radiative losses respectively. With the condition that the volume \( v \) is sufficiently small to allow the escape of photons generated via radiative losses from charged particles,

\[ \langle R_{\text{out}} \rangle_u = \langle R_{\text{out}} \rangle_{u^{\text{nonrad}}} + \langle R \rangle_{u^{\text{rad}}} \],

and thus combining Equations 2.10 and 2.11 yields:

\[ \langle \xi \rangle = \langle \xi^n \rangle \],

and therefore

\[ \frac{d}{dm} \langle \xi \rangle = \frac{d}{dm} \langle \xi^n \rangle \].

Equation 2.13 is a key result, because the left hand side is the definition of absorbed dose, \( D \) (see Equation 2.9) and the right hand side is the definition of the ‘collision kerma’, \( K_c \), i.e.,

\[ ^{\text{CPE}} D = K_c \].

This is an important relationship because it relates dose (a measurable quantity) to the collision kerma (a calculable quantity, proportional to the photon energy fluence). The parameters \( \langle \xi^n \rangle \) and \( K_c \) do not incorporate radiative losses. If Bremsstrahlung is negligible, the absorbed dose is equal to the kerma, \( K \), as shown in Roesch’s (1958) original work.

Issues of CPE are of particular relevance where inhomogeneities exist. Consider two juxtaposed slabs of media identical in composition but differing significantly in density, irradiated with a photon beam. The range of secondary electrons in one medium will be significantly greater than that in the other. This means that in order to obtain CPE, a significantly larger volume (proportional to the density difference) of the low-density medium must be irradiated to generate an equivalent number of secondary electrons in a much smaller
volume of high-density medium. Since this is not always the case, there will be a discrepancy resulting in a difference in dose. This problem is evident in the well-known shape of a depth dose curve, which exhibits a ‘build-up’ region resulting from the air-water interface. The impact of the problem of heterogeneities as a compounding effect on the complexities of small fields will be discussed in greater detail in Chapter 5.

2.6.2.4 Lateral disequilibrium

Of particular relevance to small fields is lateral electronic equilibrium. Consider first a broad beam: lateral equilibrium exists along the central axis of the beam because electrons ejected out of the volume are replaced by a roughly equal number of electrons from neighbouring volumes. The edges of the fields do not receive these ‘replacement’ electrons from one side and as a result there is an electronic disequilibrium in these regions. Lateral disequilibrium is more significant for higher energy photons. The greater the energy of the incident beam, the greater the kinetic energy of laterally ejected electrons and hence the higher the number of electrons ranging outside the boundaries of the beam. Figure 2.3 illustrates the problem of lateral electronic disequilibrium.

![Diagram of lateral charged particle disequilibrium](image)

**Figure 2.3** An illustration of lateral charged particle disequilibrium. The two inner regions irradiated by the photon beam exhibit charged particle equilibrium because secondary electrons leaving the regions are equally replaced. However, the outer regions are not in equilibrium, because there is a lack of replacement particles from adjacent regions.
As one may imagine, there is a significant problem relating to electronic disequilibrium as the lateral range of electrons extends beyond the radius of the field. As a result, small fields can be inherently difficult because, unlike broad beams, the doses within small fields are less well known. Furthermore, the density of the medium also influences the degree of disequilibrium. The range of electrons is inversely proportional to the density of the medium in which they travel, hence, for low density media, disequilibrium will exist even for relatively large field sizes. As a result, because of the densities and energies typical of radiotherapy, one must be cautious with fields smaller than about 4 x 4 cm$^2$.

The algorithms used to compute dose in contemporary radiotherapy treatment plans typically assume electronic equilibrium. This can result in the erroneous calculation of dose distributions, particularly in the vicinity of inhomogeneities and with small fields. This issue will be described in greater detail in Chapter 4 in the broad context of dose calculation. Treatment planning software requires measured depth-dose curves, profiles and so on, as input. The measurement of small fields for this purpose, and for the purpose of delivery verification, is inherently difficult.

2.6.3 Measurement of small-field dose characteristics

There are various challenges with the implementation of small fields for radiotherapy, with one significant issue being the measurement of small fields. To perform measurements of sufficient accuracy, the detector should be media-matched and not perturb the radiation field. A high degree of spatial resolution is required and, as such, a detector with a very small sensitive volume is required. The use of a detector of finite size leads to a detector volume averaging effect. In the case of very small fields, significant errors can occur if the size of the field approaches that of the active volume of the detector. A notable effect (which can occur for any field of sharp dose gradient) is broadening of the penumbras of the dose profiles. The clinical consequence of this is increased field margins employed in treatments, and therefore systematic exposure of larger volumes of healthy tissue in the region of the targeted tumour. It also leads to miscalculation of dose volume histograms as well as tumour control and normal tissue complication probabilities. The measurement of small fields using conventional dosimeters and associated issues are discussed more comprehensively in the following chapter.

The ideal dosimeter for stereotactic radiotherapy measurements would necessarily possess properties such that it would not be subject to volume averaging issues, as well as being
media-matched, so as not to perturb the radiation field. Consequently, gel dosimeters – which comprise both the detector and phantom material – are a very promising tool for investigation of small fields. In Chapter 3, methods for small-field dose measurement are discussed, with a focus on gel dosimetry because of its capacity for the accurate three-dimensional measurement of small fields.

A further approach to the determination of small field dose characteristics is the use of Monte Carlo calculation. This explicitly models the transport of radiation, overcoming many of the limitations of contemporary treatment planning algorithms. There is a general scientific consensus that Monte Carlo dose calculation may be used as a standard by which to compare other calculation or measurement methods. Monte Carlo radiation transport is discussed in greater detail in Chapter 4.

The in-field characteristics of stereotactic fields are investigated in depth in Chapter 5, in the context of both intracranial and extracranial stereotactic radiotherapy, drawing on the methods for dose measurement and calculation described in Chapters 3 and 4 respectively.

### 2.6.4 Issues beyond the primary field

Despite the small field sizes involved, stereotactic radiotherapy nevertheless results in the delivery of radiation (and therefore dose) to regions outside of the primary field. Such doses are referred to as out-of-field or peripheral dose. The low-dose regimes involved require a different approach to dose measurement, with gel dosimeters not being suitable because of the high degree of sensitivity required. Doses to untargeted regions may have detrimental consequences for the patient, such as radiation-induced carcinogenesis. Such out-of-field doses are not specific to small field treatments, and hence a detailed discussion of out-of-field doses from stereotactic fields and the associated potential consequences for patients shall be left to Chapter 6. Anecdotal evidence from discussions with clinicians indicates a general feeling that the out-of-field doses from small-field treatments are likely to be so small that they can be safely ignored. This misconception is addressed later in this thesis.
2.7 Final comments

There is the potential for both acute and long-term detriment in the immediate periphery of the targeted volume in stereotactic radiotherapy. The majority of secondary cancers form in the margins of the treatment volume. In the case of intracranial stereotactic radiotherapy, a significant number are also found in the lower-dose regions of the brain through which the beam passes. Conformality to the tumour volume and the dose characteristics of small fields are thus significant issues.

Clinical dosimetry is thus critical for the efficacious delivery of intra- and extra-cranial SRT and SRS. There is, however, a greater uncertainty associated with clinical dosimetry for small fields relevant to stereotactic techniques (Alfonso et al. 2008).

This is because there is a high level of complexity in the measurement and calculation of these fields. In the present study, three-dimensional gel dosimetry and Monte Carlo dose calculation (discussed in Chapters 3 and 4) are employed to overcome some such limitations and hence quantify these dose characteristics.
CHAPTER THREE

Water is the principle material of the world. †

Θαλής ο Μιλήσιος (Thales of Miletus)
CHAPTER 3

Advanced dosimetric methods

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3.1 Overview of chapter

The objective of this chapter is to demonstrate the suitability of three-dimensional dosimetry – in particular dosimetric gels – for the characterisation of stereotactic radiotherapy fields. Specifically, investigations in this chapter are undertaken from a theoretical perspective and pertain mostly to the fundamental radiological characteristics of the dosimeters.

In the present study, a number of dosimeters have been employed, including ionisation chambers, radiation sensitive films and thermoluminescent dosimeters. These tools are widely used in both experimental and clinical contexts, and a comprehensive discussion of their efficacy and accuracy is not the objective of this work. However, to evaluate the dose distributions delivered to an anthropomorphic head phantom in three dimensions, dosimetric gels have been employed. Gel dosimeters are more novel and far less widely implemented in a clinical context. As a result, an investigation of several aspects of gel dosimetry was conducted to support its use in this study.

In this chapter, an overview of the various available methods of dose measurement has been provided, and gel dosimetry is discussed in comparatively greater detail. A discussion of the relevant radiochemical processes, accuracy and use of gels in radiotherapy is provided based on a review of scientific literature.

To develop the usability of gels, innovative results are presented in this chapter relating predominantly to the water equivalence of gel dosimeters. Energy-dependent effective atomic numbers of gel dosimeters have been calculated here for the first time, for total and partial interaction processes of photons and electrons, surpassing the limited single effective atomic number approximations typically employed. From these works two key outcomes may be noted: the first being that gel dosimeters match water (radiologically) well over a broad energy range and, secondly, that the routinely employed method for single-valued parameterisation of effective atomic number is flawed. A study of the water equivalence of gel dosimeters under calibration conditions (where surrounding materials may affect the dose absorbed) has also been undertaken using Monte Carlo calculation. There has previously been no publication of a standard protocol for gel calibration. The novel works described in this thesis identify (from a range of published approaches) the optimum calibration methods in terms of minimisation of systematic error due to deviation from water equivalence.
3.2 The difficulty of measuring small-field dosimetric characteristics using conventional dosimeters

3.2.1 Overview
Contemporary treatment techniques allow for accurate, highly conformed dose distributions, and so any uncertainty in the delivery process may result in under / over dosage. For this reason, verification of dose delivery is of great importance. The principal aim of this study is to quantify the dose delivered to both the tumour volume and untargeted structures, which necessitates a discussion of the dosimetry methods available. Calorimeters and chemical dosimeters provide absolute dose information, but no spatial information. There are a range of zero- and one-dimensional dosimeters that provide accurate dose data at a single spatial location, and radiation-sensitive films that provide two-dimensional dose information. These have been well studied and are typically considered to be reliable measurement tools. However, the advent of techniques for delivery of very complex dose distributions means that the ideal dosimeter would provide three-dimensional dose information. Gel dosimeters satisfy this criterion; however, they are not widely implemented clinically and are the subject of much research. An overview of various dose measurement modalities is provided heretofore and, being the most promising dosimeter, gels are discussed separately and more rigorously in the subsequent section of this chapter.

3.2.2 The difficulty of small-field measurement: Volume averaging
Stereotactic radiosurgery of small tumours was proposed almost sixty years ago (Leksell 1951), but difficulties with the implementation of small fields for radiotherapy still remain, with one significant issue being the measurement of small fields. To perform measurements of sufficient accuracy, the detector should be media-matched and not perturb the radiation field. A high degree of spatial resolution is required and, as such, a detector with a very small sensitive volume is required.

The use of a detector of finite size leads to a detector volume averaging effect. In the case of very small fields, significant errors can occur if the size of the field approaches that of the active volume of the detector. A notable effect (which can occur for any field of sharp dose gradient) is broadening of the penumbras of the dose profiles. The clinical consequence of this is systematic exposure of larger volumes of healthy tissue in the region of the targeted tumour. It also leads to miscalculation of dose volume histograms (DVH) as well as tumour control and normal tissue complication probabilities (TCP and NTCP respectively).
3.2.3 Available dosimeters and their potential limitations

3.2.3.1 Ionisation chambers

Ionisation chambers are the standard radiation dosimeter in a clinical medical physics department. Absolute dosimetry with ionisation chambers for small photon fields is often limited by the lack of electronic equilibrium in the radiation field and the size of the chamber cavity volume (Sibata et al. 1991; Heydarian et al. 1996). It is important that the chamber cross-section be smaller than the homogeneous dose regions in which it is placed (Bjarnegard et al. 1990; Boyer 2001); chamber positioning should be known to better than 1 mm (Low et al. 1998b). The finite size of an ionisation chamber introduces a volume averaging effect which can lead to overestimation of penumbra (Rice et al. 1987; Westermark et al. 2000). Micro-ionisation chambers have been developed to help overcome the volume limitation. A study of a micro-chamber, Farmer chamber and waterproof scanning chamber showed that the larger the chamber, the greater the under-response at the field’s centre for small fields (Low et al. 2003). Calibration involves the use of broad beams, which means that this dosimetric data may not be directly applicable in the case of small fields. Stopping power ratios facilitate conversion of dose in the chamber cavity to dose in surrounding water. The depth dependence of water / air stopping power ratios has been studied via Monte Carlo simulation showing that, for a 6 MV photon spectrum, discrepancies of around 1 % may exist between broad and narrow fields (Andreo and Brahme 1986; Heydarian et al. 1996; Verhaegen et al. 1998), with greater disparity for higher energies (Sanchez-Doblado et al. 2003). A study of a new parallel-plate micro-chamber showed that the dosimeter was under-responsive for small fields, as verified by comparison with Monte Carlo (Francescon et al. 1998). Martens et al showed that the PinPoint type ionisation chamber over-responds to low energy Compton scattered photons and is limited to fields greater than 2 cm (Martens et al. 2000). Water-proof sleeves for ionisation chambers can result in discrepancies of up to 0.8 % depending on the material and beam energy (Ross and Shortt 1992). All these works ultimately indicate that the applicability of ionisation chambers to small field measurements may be limited and a combination of measurement modalities may be appropriate.

3.2.3.2 Semiconductor dosimeters

The use of smaller detectors may introduce other problems. For instance, semiconductor dosimeters such as silicon diodes and metal oxide semiconductors – field effect transistors (MOSFET) may be used for small field dosimetry. These have the significant advantage of small size and real-time readout. However, diode detectors are not without limitations. These include temperature dependence (Grusell and Rikner 1986) and dose rate dependence (Wilkins et al. 1997), between which there also exists a correlation (VanDam et al. 1990;
Heukelom et al. 1991). There is also a directional dependence that arises from the junction geometry (Bjork et al. 2000; Higgins et al. 2003). There is typically an over-response to low energy components of the spectrum; diodes have been shown to overestimate output factors by up to 7 % because of low-energy photons (Westermark et al. 2000). For this reason, backscatter filters are sometimes used (Grusell and Rikner 1986). Correction factors are often needed for the field size, focus to surface distance and phantom thickness (Heukelom et al. 1991). MOSFET dosimetry is achieved via assessment of the radiation damage to the device; the consequence of this is a radiation sensitivity that changes over time and finite life. In general, the characteristics of diodes must be checked, as they differ even for the same type of diode produced by the same manufacturer (Leunens et al. 1990; Li et al. 1995; Alecu et al. 1999).

3.2.3.3 Thermoluminescent detectors
Kron gives a detailed overview of the application of thermoluminescent detectors (TLD) in dosimetry (Kron 1994; Metcalfe et al. 1997). TLD have the advantage of small size and are routinely used in clinical environments (Horowitz 1984; Kron 1994). The most common material used to construct TLD is lithium fluoride doped with magnesium and titanium (LiF:Mg,Ti), or, more recently with magnesium, copper and phosphorous – resulting in greater sensitivity (Horowitz 1993a; Delgado et al. 1995). Sensitivity depends on composition and thermal history, and may vary between and even within batches. Sensitivity has been shown to decrease at a rate of about 1.5 % per 10 Gy of absorbed dose (Horowitz 1993a). Supralinearity is also an issue and must be corrected for. TLD do not appear to exhibit significant dose-rate dependence up to $10^8$ Gy/s (Tochilin and Goldstein 1966). The TL signal does, however, vary with the radiation quality in a manner that is most significant for low energy photons (Metcalfe et al. 1997). The use of high Z-number dopants may lead to over-response because of the greater interaction probability of low-energy photons. Above 1 Gy, the energy response changes according to the energy spectrum of photons and is not readily corrected for, potentially resulting in a loss of precision for high doses. Radiation attenuation within the TL material may also have an effect, as does the readout process and thermal history. Ultimately, the factors relating dose to light emission are many and complex, which means that TLD are often restricted to relative dosimetry. TLD precision down to ± 0.2 % is possible (Martenssen 1969), but typically a reproducibility of ± 2 % for a single rod is achievable with effort (Metcalfe et al. 1997).
3.2.3.4 Diamond detectors

Being very small and suited to use in regions of high dose gradient, diamond detectors have been of recent interest in dosimetry. Simply, these consist of a diamond housed in a small cylinder with a bias applied via two gold contacts - the resistance being inversely proportional to the dose rate of the incident radiation. Theoretical aspects have been studied by Hoban et al (1994). A good overview of the advantages of diamond detectors is provided by Laub et al (1999). They exhibit resistance to radiation damage of 0.05 % kGy\(^{-1}\) (Planskoy 1980), a sensitivity of approximately 0.05 µC Gy\(^{-1}\) (Vatnitsky and Jarvinen 1993) and a stability of 0.67 % SD (over 13 weeks) (Hoban et al. 1994). It has been shown that to obtain sufficient response stability, pre-irradiation of several Gy is required if the detector has not been used for more than one hour. An extra dose is required if the bias was left on while irradiation was interrupted – even for a few minutes. The most apparent problem is dose rate dependence, necessitating the use of correction factors (Laub et al. 1999).

3.2.3.5 Radiosensitive film

Films are one of the earliest applied methods of detecting x-rays and their use in a clinical environment is standard practice. One problem with film is the over-response to low-energy photons resulting from the high atomic number of the active material. There are further processes that may result in darkening of the film during processing that mean film is not readily usable for absolute dosimetry. Underexposure may occur when measuring low-energy photons (Muench et al. 1991; Kron et al. 1998) with radiochromic films. Broadly, disadvantages include energy dependence, orientation of radiochromic films, processing conditions, film density variation and inhomogeneities due to air pockets inside the film jacket (Cheng and Das 1996). The obvious limitation of film is the inability for in vivo measurement and the restriction of two dimensional planar dosimetry. Attempts to obtain 3D detail by stacking radiographic films within a phantom (Robar and Clark 2000) are simple methods to obtain 3D dose information, but are limited by the geometry of the positioning structure and the loss of tissue-equivalence.

3.2.4 Published works dealing with the measurement of small fields using various dosimeters

There are a number of published studies describing the measurement of small fields with various dosimeters. Garcia-Vicente et al (2005) investigated the detector size effect in conformal radiotherapy (CRT) and found that organs at risk (OAR) received higher doses when a 5.5 mm detector was used to measure profiles as compared to when a 2 mm detector
was used. The NTCP of the brain stem in hypophysis chordoma treatments was doubled when the larger detector was used. Laub and Wong (2003) investigated the effect of detector size on the dosimetry of small fields and steep dose gradients in the context of intensity modulated radiotherapy (IMRT). They found discrepancies of 10% when comparing measurements taken with film to calculated profiles based on ionisation chamber measurements used in commissioning the IMRT tool. Discrepancies of around 6% were found (at isocentre) when using a 0.6 cm$^3$ Farmer chamber. In the same experimental arrangement, differences of about 2% were found when using a 0.015 cm$^3$ pinpoint ion chamber.

Dawson et al (1984) studied the penumbra of $^{60}$Co, 6 MV and 31 MV x-rays using three commercially available detectors (a silicon diode and two ionisation chambers) and a series of in-house ionisation chambers of internal diameters between 0.3 and 1.4 cm. They demonstrated that the width of the penumbralae increase linearly with the internal diameter of the ionisation chamber. True penumbralae were determined via extrapolation. Metcalfe et al (1993) took a similar approach, extrapolating back from measurements taken with multiple detectors of different sensitive volumes. They measured the penumbral width at $D_{max}$ with a diode, film and TLD. The sensitive widths of these measurement systems were 2.5, 2.0 and 1.0 mm respectively and the 80-20% penumbra was measured to be 3.6, 3.6 and 3.4 mm respectively. Westermark et al (2000) undertook measurements using a diamond detector, liquid ionisation chamber, plastic scintillator and two Si diodes. One of the diodes was a double-diode using two parallel opposed active volumes with compensating interface perturbations. The volumes of the scintillator and ionisation chamber result in a broadened penumbra. Deviations in output factors varied up to around 10% amongst the detector types. The diamond detector matched the ionisation chamber within 1% for field sizes ranging from 3 x 3 cm$^2$ to 15 x 15 cm$^2$.

Sibata et al (1991) corrected for the ionisation chamber detector size effect in beam profile measurements by extrapolation to zero detector size and a simple convolution method. Higgins et al (1995) also implemented an analytical deconvolution algorithm (similar to those used in radiology applications) to correct for the influence of the finite detector volume on the measured dose. Chang et al (1996) undertook a computational convolution approach to investigate the detector averaging effect. This was found to match penumbral widths using the backwards extrapolation approach described earlier. Garcia-Vicente et al (1998) determined the spatial convolution kernel for several detectors experimentally, and later used an analytical solution of the integral equation for a general profile fitting function using Gaussian convolution kernels (Garcia-Vicente et al. 2000). Van’t Veld et al (2001) used the latter model and measured data to determine the detector line spread functions of an
ionisation chamber exposed to various energy sources. They found that, following correction, larger volume detectors (such as the IC15, Wellhöfer) can then be used for high resolution relative dosimetry. More recently, Sahoo et al (2008) employed two semi-empirical methods to determine true profiles by elimination of the detector volume averaging effect. The first method shifts the profile based on published deconvolution methods, while the second shifts the measured profile according to the value of an analytical function related to the second derivative of the real profile at a given point.

Figure 3. shows a comparison of different detector types as applied to small-field measurements. The main figure shows the relative central axis dose factors for stereotactic fields as a function of field diameter (or diameter of equivalent area) for a 2mm plane-parallel ionisation chamber (McNiven et al. 2006), silicon electron diode (Scanditronix, Wellhofer Germany), Kodak EDR2 radiographic film (Kodak Inc., Rochester, NY), micro-MOSFET (Wollongong, Australia), Type 31006 PTW PinPoint cylindrical ionisation chamber (PTW-Freiburg, Germany) and GafChromic Type HS Radiochromic film (ISP Corp.,Wayne, NJ). Measurements are in each case normalised to the standard 10 x 10 cm\(^2\) reference field. Beneath the main figure is a plot of the same data presented relative to the 2 mm plane-parallel ionisation chamber. Note that for 0.5 cm fields discrepancies vary from a factor of 1.1 up to 1.7, and with increasing field size the disparity between the different measurement techniques decreases. This highlights the complexity of small-field measurement.
Figure 3.1 The main figure shows a comparison of different detector types as applied to small field measurement, based on data from McNiven et al (2006). Shown are the relative central axis dose factors for stereotactic fields as a function of field diameter (or diameter of equivalent circle) for a 2mm plane-parallel ionisation chamber, silicon electron diode, Kodak EDR2 radiographic film, micro-MOSFET, Type 31006 PTW PinPoint cylindrical ionisation chamber and GafChromic Type HS Radiochromic film. Measurements are in each case normalised to the standard 10 x 10 cm² reference field. Beneath the main figure is a sub-plot of the same data presented relative to the 2 mm plane-parallel ionisation chamber.

3.2.5 Concluding thoughts

An overview has been given of a broad range of dosimeters, each suited to different applications, each typically yielding zero or two dimensional spatial information (zero-dimensional dosimeters can often be scanned for one-dimensional information). The ideal dosimeter for small-field dosimetry would be a media-matched (discussed in the following section), dose-integrating device that provides three dimensional information about the spatial distribution of dose. Gel dosimeters exhibit many of the desirable qualities that approach these criteria. There are, however, various issues associated with gel dosimetry that have thus far limited their clinical implementation. Of these, issues of composition and tissue
equivalence, as well as systematic errors in calibration have been chosen as a particular focus in this work. The following sections of this chapter are devoted to novel investigations concerned with the latter topics.

3.3 The importance of ‘media matching’ in dosimetry

There is a significant amount of theory devoted to the interpretation of dosimeter readings. The reason for this is simple: the dose to a dosimeter is never the ultimately desired quantity – rather, it is the dose to the region occupied by the dosimeter in whatever medium the dosimeter is placed. Unfortunately, dosimeters typically do not exhibit the exact same radiological properties as the medium of interest. This is because their composition generally differs from that of the medium. As a result, whilst dosimeters function to measure dose, their presence may also perturb it.

Following the nomenclature of Attix (2004), if the wall \((w)\) and the sensitive volume \((g)\) of the detector match (in terms of composition and mass density), then the doses delivered to each are such that:

\[
D_w = \overline{D}_g.
\]

An improvement upon the latter case would be if the wall and sensitive volume were identical, and then matched to the medium of interest \((x)\). If such matching could be performed perfectly, then

\[
D_x = D_w = \overline{D}_g.
\]

Cavity theory (Bragg 1912; Gray 1936) allows \(w\) and \(g\) to differ, which potentially provides the flexibility of needing only to match \(w\) and \(x\). Matching the sensitive volume to the medium of interest is typically complicated by further dosimetric requirements on \(g\).

Deviation from these ideal circumstances necessitates corrective steps in terms of the geometric design of the dosimeter or calculations based on knowledge of the spectrum and stopping power ratios in the applied context.
Ultimately, the ideal dosimeter would possess radiological properties identical to that of the medium of interest, would not perturb the radiation field, and would have the capacity to yield multidimensional dosimetric information. The most promising dosimeter that closely meets these criteria is radiosensitive gel. Composed mostly of water (the dose to which is considered to be well known), gel dosimeters show great potential, acting as both the phantom and dosimeter material. However, their clinical implementation has been limited so far. In this work, the radiological properties of gel and, in particular, their water or tissue equivalence as assessed by the ‘effective atomic number’ concept are a focus of study. Gel calibration methods are also considered, as not only the gel but also the containment vessels influence the conditions of media-matching and non-perturbation. These issues are investigated thoroughly in the following sections.

3.4 Three dimensional dosimetry: Radiosensitive gels

3.4.1 An overview

Gel dosimetry dates back to the 1950s, when radiation doses were investigated with use of radiation sensitive dyes infused in gel matrices (Day and Stein 1950). In early studies, the radiation-induced changes were studied via spectrophotometry (Andrews et al. 1957), but contemporary gel dosimetry typically employs magnetic resonance imaging. Gels possess certain advantages over other more ‘standard’ dosimeters, such as ionisation chambers, radiosensitive films and thermoluminescent dosimeters. To obtain fully three-dimensional dose information with the latter detectors is not feasible. This is because only a limited number of one-dimensional points or two-dimensional planes may be measured at one time, and the simultaneous use of multiple detectors or stacking of film can be detrimental by reducing the effective water equivalence and influencing the dose distribution. Gel dosimeters, on the other hand, possess radiological properties similar to that of water and integrate dose regardless of direction of incidence, yielding dose information over a three-dimensional volume. There are two categories of gel dosimeter: ferrous-sulphate doped (Fricke) gels and polymer type gels.

3.4.2 Ferrous-sulphate doped (Fricke) gel dosimeters: An overview

In 1927 Fricke and Morse published a paper describing the use of dilute ferrosulphate solutions as a means of dose measurement (Fricke and Morse 1927). A key advancement since Fricke’s work was the proposal by Gore (1984) to employ magnetic resonance imaging
to facilitate three-dimensional radiation dosimetry, where the aqueous Fricke solution is integrated into a gel matrix.

Fricke gels are prepared in air, and are typically composed of deionised water, ferrous ammonium sulphate (the source of ferrous ions), sulphuric acid and gelatin or agarose. More recently, Chu et al (2000) described Fricke solution and xylenol orange integrated into a polyvinyl alcohol (PVA) cyrogel / hydrogel. The proposed advantage of this method is reduced post-irradiation ion diffusion, however, in-house studies have shown that diffusion is still a limiting factor.

Schreiner (2004) has summarised some of the radiochemical processes relevant to Fricke dosimetry. The physical principle which enables the dosimetric use of Fricke gels is the dose dependant transformation of the ferrous Fe$^{2+}$ ions into ferric Fe$^{3+}$ ions. Irradiation initiates water decomposition and the hydroperoxy radical is produced:

$$H^+ + O_2 \rightarrow HO_2^*$$

The reactions oxidising ferrous ions to ferric ions (Fricke and Hart 1966) are given below:

$$Fe^{2+} + OH^* \rightarrow Fe^{3+} + OH^-$$
$$Fe^{2+} + HO_2^* \rightarrow Fe^{3+} + HO_2^-$$
$$HO_2^- + H_2O^+ \rightarrow H_2O_2 + H_2O, and$$
$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^+ + OH^-$$

The change in concentration of ferric ions is proportional to the energy absorbed per unit mass, as described by the following equation:

$$\Delta[Fe^{3+}] = \frac{D \cdot G(Fe^{3+}) \cdot 10 \rho}{N_A \cdot e},$$

wherein $D$ is the dose, $G(Fe^{3+})$ is the chemical yield of Fe$^{3+}$ ions per heV, $\rho$ is the density in kg.litre$^{-1}$, $N_A$ is Avogadro’s number and $e$ is the number of Joules per eV. The gel macromolecules provide additional pathways for ion conversion, and as such there is a greater yield of ferrous ions than for the aqueous Fricke solution.
The relaxivity of Fe$^{3+}$ ions can be probed via nuclear magnetic resonance (NMR), and is linear with dose within the range of doses relevant to radiotherapy. Fricke gels also exhibit dose-dependent changes in optical density. Podgorsk and Schreiner (1992) showed that the Fricke solution requires tens of Gy to exhibit measurable radiation-induced changes. Fricke gels, however, are significantly more sensitive than in solution (Schulz et al. 1990; Hazle et al. 1991), but are less sensitive than polymer-type gel dosimeters. This generally does not present a significant problem unless working in very low dose/dose-rate regimes.

Contemporary dose delivery often involves fields of very high dose gradients. The major limitation of Fricke gel dosimetry is diffusion of ferrous and ferric ions within the gel. This imposes a time constraint, restricting the available time between irradiation and imaging. A number of authors have reported on this problem; see for instance (Olsson et al. 1992; Balcolm et al. 1995; Harris et al. 1996; Pederson et al. 1997; Baldock et al. 2001; Chu and Wang 2001). This limitation was the primary impetus for the development of polymer-based gel dosimeters.

3.4.3 Polymer gel dosimeters: An overview

The diffusion of ferrous and ferric ions in Fricke gels presents time constraints for post-irradiation imaging – a problem that has led to the increased development and implementation of polymer gel dosimeters. These consist of monomers dissolved in a hydrogel, which undergo dose-dependent polymerisation.

Polymer gels are predominantly water (around nine tenths), with a gelling agent (gelatine or agarose) and a monomer (an organic hydrocarbon). When irradiated, radiolysis of water occurs, generating (highly reactive) radicals from the dissociation of H$_2$O molecules which can then react with the monomers. The binding of a radical to an electron of the double bond of a monomer initiates polymerisation. These polymers can have reactive double bonds which also react with the radicals. Propagation occurs, whereby the loose ends of polymer chains continue to react with monomers, forming progressively larger macromolecules.

Peroxide radicals are generated if there is oxygen within the gel. These react quickly with other radicals, inhibiting the polymerisation process. As such, polymer gels are generally prepared in an inert gas atmosphere to avoid oxygen. Recently, normoxic polymer gel dosimeters have been introduced that employ antioxidants, allowing gel preparation in the presence of oxygen (Fong et al. 2001). Polymerisation can also be terminated by the reaction
of two polymer radicals with each other. The rate of polymerisation has been shown to decrease with increasing gelatine concentration (Lepage et al. 2001a).

Early polymer gels were made with acrylamide and N-N’-methylenebisacrylamide (Bis) (Maryanski et al. 1993) as monomers (note that Bis also acts as a cross-linker). This is illustrated in Figure 3.2. Other monomers have been employed by other researchers and these have their own characteristics; some of these are illustrated in Figure 3.3.
Figure 3.2 The molecular structure of (a) acrylamide, (b) N-N’-methylenebisacrylamide (Bis) and (c) polyacrylamide. Note in (c) that acrylamide molecules have linked together to form a long polymer chain (circled in red, large-dash), and the Bis molecules facilitate cross-linking between polymer chains (circled in blue, short-dash). This figure has been adapted from Gustavsson (2004).
The molecular structure of several monomers used in different polymer gel dosimeter formulations: (a) methacrylic acid, (b) 2-hydroxyethyl acrylate, (c) acrylic acid and (d) 2-hydroxyethyl methacrylate. Adapted from (Lepage et al. 2001a).

The formation of polymers results in an optical change within the gel (increased opacity) that allow optical evaluation of the gels. The polymers in the gel also influence the mobility of \( \text{H}_2\text{O} \) molecules and therefore affect the nuclear magnetic resonance (NMR) spin-spin relaxation rate, facilitating evaluation via magnetic resonance imaging (MRI).

### 3.5 Evaluation of gel dosimeters

#### 3.5.1 Magnetic resonance imaging (MRI)

##### 3.5.1.1 Fricke gel dosimeters

Irradiation of a Fricke dosimeter results in the oxidation of ferrous Fe\(^{2+}\) ions to ferric Fe\(^{3+}\) ions. Fe\(^{2+}\) and Fe\(^{3+}\) ions possess different magnetic moments. Gore (1984) proposed that this feature could be exploited to facilitate the evaluation of radiation induced changes in a Fricke dosimeter via nuclear magnetic resonance (NMR) relaxation measurements. The spin-spin and spin-lattice relaxation times (\( T_2 \) and \( T_1 \) respectively) of the hydrogen nuclei in the gel are affected by the concentration of the different ions, which means that the NMR relaxation is dose-dependent. It is common to determine the spin-spin and spin-lattice relaxation rates (\( R_2 = T_2^{-1} \) and \( R_1 = T_1^{-1} \) respectively) and relate this back to the dose absorbed.
Audet and Schreiner (1996) presented a model for R1 dose response:

\[
R1 = \left[ G(Fe^{3+}) \left(r^{3+} - r^{2+}\right) \frac{10 \rho}{N_A e} \right] D + R_0,
\]

wherein \(D\) is the dose, \(G(Fe^{3+})\) is the chemical yield of \(Fe^{3+}\) ions per heV, \(\rho\) is the density in kg.litre\(^{-1}\), \(N_A\) is Avogadro’s number, \(e\) is the number of Joules per Ev, \(R_0\) is the relaxation rate of the unirradiated dosimeter and is a constant for a given gel concentration. The quantities \(r^{3+}\) and \(r^{2+}\) are the ‘relaxivities’ of the two ions† (these are known quantities). For a given formulation, one can therefore simplify this equation to:

\[
R1 = dD + R_0,
\]

where \(d\), the coefficient of the dose, is called the ‘dose sensitivity’ of the dosimeter. This is experimentally evaluated by determining the gradient of a plot of \(R1\) as a function of the dose, \(D\).

### 3.5.1.2 Polymer gel dosimeters

Polymerisation of gel dosimeters is dose-dependent and, as such, evaluation of the extent of polymerisation is indicative of the dose received. Because of the different relaxation behaviour of the protons in different chemical arrangements within the gel, such evaluation may be performed using MRI.

Lepage et al (2001b) suggested the idea of considering protons within various ‘pools’. There are protons associated with free water and monomer molecules, protons associated with the polymeric chains and protons bound to the gel matrix. The mobility of the protons within these pools differs and so does that rate of thermal motion of the molecules containing them. This influences the spin-spin interaction and therefore the different proton pools will have different relaxation rates, facilitating quantitative study.

† *Nota bene* the relaxivity of the ferric ion, \(r^{3+}\), is actually an effective relaxivity that must be determined for the gel system, because the ferric ion hydration is affected by the gelling agent.
The total relaxation rate is the weighted average of the spin-spin relaxation rates of the different proton pools in the whole sample, and therefore will change with the amount of monomer converted to polymer (DeDeene 2004):

\[ R2 = f_{\text{free}} R2_{\text{free}} + f_{\text{polymer}} R2_{\text{polymer}} + f_{\text{gel}} R2_{\text{gel}}. \]

The protons in the gel pool are assumed to be unaffected by dose (i.e. remain unchanged in the irradiated and unirradiated sample). The ‘free’ protons from the water and monomer pool are transferred to the polymer pool. This results in an overall reduction in the relaxation time of the system.

3.5.1.3 Practical issues with MRI of gel dosimeters and the problem of MRI accessibility for gel dosimetry in Australia

In normal clinical MRI for diagnostic purposes, uncertainties in T2 of up to around 10% are generally considered acceptable. In gel dosimetry, many of the problems associated with clinical MRI (such as patient movement – both internal and external) are non-issues, thus allowing a much improved level of uncertainty to be achieved. An MRI pulse sequence is developed or carefully selected for a particular gel formulation, scanning time and image resolution such that imaging artefacts and stochastic noise are minimised. Field inhomogeneities, non-linearities in the gradient and eddy currents may result in geometrical distortions of the obtained images. Ultimately, MRI is not a quantitative tool.

One significant limitation on the use of MRI for gel dosimetry in Australia is simply accessibility – something which may come as a surprise to scientists in other countries. Patient diagnostics generally take precedence over research. As such, research time generally must be paid for, access if often ad hoc, or research must be undertaken out of hours, which may in cases be prohibited by the administering department.

The attractiveness of a low-cost, easy-access alternative has driven a strong interest in alternative imaging methods for gel dosimeters (which is not restricted to Australia), such as x-ray computed tomography or optical tomography methods.
3.5.2 X-ray computed tomography (CT) imaging

As an alternative to MRI, Hilts et al. (2000) raised the possibility of employing x-ray computed tomography (CT) for read-out of polymer gel dosimeters. This is facilitated by the density change that occurs in polymer gel dosimetry, which results in different photon attenuation (Trapp et al. 2002) and hence gels exhibit a dose-dependent change in Hounsfield number, albeit with a very low sensitivity. Adding antioxidants (for normoxic gel formulations) has been shown to reduce the dose sensitivity even further, compared to the hypoxic formulations (Jirasek et al. 2006). However, there may be flexibility to design gel dosimeters specifically intended for read-out via CT. For instance, adding a co-solvent has recently been shown to increase x-ray CT sensitivity (Koeva et al. 2009).

In addition to the limitation of low sensitivity, the other obvious problem with x-ray CT read-out of gel dosimeters is that additional dose is delivered to the dosimeter. This generates further polymerisation of the gel, which restricts the use of many image averages per slice as a means of resolution improvement. Baxter et al. (2007) investigated the CT dose and corresponding change in Hounsfield number for a range of imaging protocols for polyacrylamide gel. For volumetric imaging, the CT dose was of the order of several cGy and the change in CT number was 0.1 to 0.15. For single slice, the dose ranged from 0.7 up to 2.1 cGy, and the CT number change ranged from 0.04 to 0.13.

Another imaging modality that may overcome some of the limitations of x-ray CT is optical computed tomography (OCT).

3.5.3 Optical imaging

As a relatively inexpensive alternative to MRI, Gore et al. (1996) suggested the use of optical computed tomography (OCT) as a read-out method for polymer gels. There are two main types of OCT: a laser-scanning type and a broad-beam type. Both reconstruct a large number of projections through the sample to obtain a three-dimensional dose distribution, relying on dose-dependent changes in light transmission properties of the irradiated gel. The laser type OCT scanners are typically much slower than the broad-beam scanners. The downside of the latter scanners, however, is that they can exhibit greater scattering artefacts.

The high diffusion rates of Fricke type gels make polymer gels an attractive alternative – particularly for normoxic type gels which are relatively simple to manufacture – but OCT of polymer gels is more problematic. Unlike xylenol-orange Fricke gels, which tend to attenuate light through absorptive processes, polymer gels remove light from the beam path through
scattering processes. This can give rise to imaging artefacts. To illustrate this, an example was performed in-house (see Figure 3.4): a MAGIC normoxic polymer gel was manufactured and irradiated using a Varian 600C with a 5 x 5 cm$^2$ field. When read out with a Modus Medical ‘Vista’ Optical CT Scanner, a ‘cupping’ artefact was observed that results from scatter at the periphery of the irradiated region in the polymer gel.

Figure 3.4 An example of the ‘cupping’ artefact that occurs when polymer gels are scanned with a broad-beam optical CT scanner. The example shown in this figure was performed in-house using a Modus Medical ‘Vista’ Optical CT Scanner. (a) Shows a surface reconstruction of a MAGIC-type polymer gel (in a cylindrical container) irradiated with a 6 MV, 5 x 5 cm$^2$ field. (b) Indicates a line profile taken across a slice in the middle of the gel. The two spikes towards the edges of the line profile correspond to the interface with the container (reflecting the poor refractive index matching between the container of gel and the liquid bath in which it was placed). Rather than a relatively flat profile in the high dose region, we see a ‘cupping’ effect which arises because of the scatter effects. Before dosimetric information may be derived from such data, scatter corrections must be applied – something which has been achieved with only limited success in published literature.

Oldham et al (Oldham et al. 2003; Oldham and Kim 2004) have described in detail the artefacts that may be encountered in OCT of polymer gels, and the interested reader is referred to their work and the references therein. Rather than focus on dealing with the potential complications of gel read-out, the work described in this chapter deals with other aspects of gel dosimetry. Namely, the radiological properties of gel dosimeters and the accuracy of gel calibration. The strong interest in gel dosimetry for small-field applications is evidenced by a number of recent publications.
3.6 Gel dosimetry for small-field measurement: A summary of published works and comparison with alternative dosimeters

The ideal dosimeter for stereotactic radiotherapy measurements would necessarily possess properties such that it would not be subject to volume averaging issues, as well as being media-matched, so as not to perturb the radiation field. Consequently, gel dosimeters – which comprise both the detector and phantom material – are a very promising tool for investigation of small fields. Read-out of the gels may be performed using magnetic resonance imaging (MRI), optical computed tomography (OCT) or x-ray computed tomography (CT). There have been a number of publications detailing the application of gel dosimetry to the small fields involved in stereotactic radiotherapy.

The majority of works describing gel dosimeters for stereotactic field characterisation are applied to Gamma-Knife, and most of these involve MRI readout ([Coffey et al. 1993; Guo et al. 1996; Cosgrove et al. 2000; Ertl et al. 2000; Watanabe et al. 2002; Isbakan et al. 2005; Papagiannis et al. 2005; Sandilos et al. 2006; Isbakan et al. 2007; Pourfallah et al. 2009]). Most studies compared gel measurements for field sizes of the order of millimetres to TPS and other dosimeters, often observing discrepancies. Watanabe et al. (2005) used BANG-type gel dosimeters to calculate the tumour control probability (TCP) and the normal tissue complication probability (NTCP) for Gamma-Knife treatments. TCP values based on measured data were up to 7% smaller than those based on calculated data, while NTCP values were 7-24% higher (for two-thirds of treatments).

Linac-based stereotactic fields with conical collimators have also been investigated. For instance, Pappas et al. (2001) used VIPAR-type gel dosimeters (read out with MRI), radiographic film and a PinPoint ionisation chamber to investigate 5 and 10 mm stereotactic fields. A spatial resolution of 0.13 mm was achieved with the gel, and a significant difference was found between penumbral measurements. The penumbrae from 5 and 10 mm collimators were 1.34 and 1.70 as measured with gel, 2.23 and 2.45 mm as measured with film and 2.25 and 2.52 mm as measured with the PinPoint chamber.

Linac-based stereotactic radiotherapy with fields shaped using multileaf collimators have also been studied ([Grebe et al. 2001; Pappas et al. 2001; Audet et al. 2002]). Wong et al. (2007) used PAG-type gel dosimeters to study 6 x 6 mm$^2$ and 18 x 18 mm$^2$ fields. The penumbral dose was shown to drop off more rapidly with the gel measured data compared to data obtained using radiochromic film and diode measurements. Gels have also been used to verify doses in unusual contexts, particularly where conventional treatment planning systems may
be inaccurate. For instance, Geso et al (2008) used PAG-type gel dosimeters and Gafchromic film to measure the dose enhancement in the vicinity of an aneurism clip – as relevant to intracrani al stereotactic radiotherapy. Dose increases of the order of 20% were observed close to the clip surface. Results were verified using Monte Carlo dose calculations.

Gels have even found use in dosimetry of very small stereotactic fields applied to rat brains (Novotny et al. 2002a; Novotny et al. 2002b; Charest et al. 2009) and in the characterisation of synchrotron fields (Boudou et al. 2004; Boudou et al. 2007).

It is common for gels to be employed in the assessment of stereotactic treatments, typically comparing measurements to other dosimeters (Bjoreland et al. 2008; Babic et al. 2009), and one makes the observation that – for small stereotactic fields – there is often significant variation in measured characteristics between detector types. Pappas et al (2008) undertook measurement of small fields with a pinpoint ion chamber, a diamond detector and a silicon diode array, using measurements taken with a polymer gel dosimeter as the reference data. Profiles were obtained for 7.5, 15 and 30 mm small fields that were delivered with a BrainLAB conical collimation device mounted on a Varian 600C Clinac. Measurements of the full-width half-maximum (FWHM) obtained using gel were shown to match the nominal fields well, compared to other dosimeters; see Figure 3.5.

Figure 3.5 (a) The agreement between nominal beam diameters and those measured (FWHM) with VPL radiosensitive gel. The $y = x$ line indicates perfect agreement. (b) A comparison of beam diameters as measured with various dosimeters, expressed as a ratio with the measured data plotted in (a). The PinPoint detector suggests larger penumbra, while the diamond and silicon diode (DOSI) detectors give lower estimates of the penumbra. Based on data from Pappas et al (2008).
The large number of studies employing gel dosimetry clearly reflect the recognition of their potential for three-dimensional small-field dosimetry. However – as evidenced by the aforementioned papers – despite being used widely for such applications since the mid-nineties, gel dosimetry is rarely used as part of routine clinical practice. There are a number of limitations associated with gel dosimetry that must be overcome for this to be achieved. For instance, it is often not practical to have a laboratory space within a clinical physics department that facilitates chemical handling and the manufacture of gel dosimeters. The reproducibility of gel dosimeters is also an issue, requiring additional volumes of gel to be made within the same batch for the purposes of calibration. Read-out of gel dosimeters using MRI requires not only development of an associated protocol, but MRI time and access are often difficult or expensive to obtain. The advent of optical computed tomography for gel readout may help solve the latter problem. However, broad-beam optical scanners are generally designed for light-absorbing gels such as XO Fricke gels, which suffer from rapid ion diffusion, and the use of polymeric gel dosimeters is not straightforward, since these are light-scatterers and hence generate artefacts that hide the true dose information.

**Figure 3.6** This shows the measured output factors for 5 mm, 7.5 mm and 10 mm beams from a CyberKnife unit. The majority of dosimeters underestimate the output factors, relative to measurements made with gel (VIPAR). For the Gafchromic film (Wilcox and Daskalov 2007; Pantelis et al. 2008), diode (Yu et al. 2004; Francescon et al. 2005; Wilcox and Daskalov 2007; Francescon et al. 2008) and PinPoint chamber (Francescon et al. 2005; Francescon et al. 2008; Pantelis et al. 2008) measurements the error bars represent the standard deviation in different published values while the error bars for the gel (Pantelis et al. 2008) and TLD measurements (Yu et al. 2004) correspond to the uncertainty of the published measurements.
Figure 3.6 compares output factors corresponding to 5 mm, 7.5 mm and 10 mm beams from a CyberKnife unit for different detector types. In the case of the 5 mm field, there is good agreement (within uncertainty) between the gel, Gafchromic film and diode. In the case of the diode, there appears to be (statistically insignificant) overestimation of the output factor; this is most likely a consequence of the reduced water equivalence of the Silicon detector, which has been shown to result in such overestimation (Araki 2006). The PinPoint detector tends to underestimate the output factors, which is a consequence mostly of volume averaging effects.

There are a number of dosimeters available for measurement of small field characteristics, and although the discussion of dosimeters has been relative to gels, this does not imply that gels are a ‘gold standard’. Each dosimeter possesses its own attractive properties and limitations. Table 3.1 gives a qualitative overview of the advantages and disadvantages of various detector types for the measurement of small-field dose distributions. Ultimately, gel dosimeters are in principle highly suited to the measurement of small fields. One significant strength is the level of media-matching; however, this has not been rigorously established (particularly with regard to effective atomic numbers). A further issue noted is that of calibration – there is no standardised accepted methodology. These issues are investigated in depth in this chapter.
### Table 3.1 A qualitative overview of the advantages and disadvantages of the different dosimeters as applied to small field dosimetry.

<table>
<thead>
<tr>
<th>Dosimeter</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>General comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionisation chamber</td>
<td>High precision; wide variety of chambers available; real time measurement; no dose rate dependence; standard dosimeter that is well documented and investigated.</td>
<td>One-dimensional (1D); geometry restricts applications; typically inappropriate for stereotactic fields because of volume averaging effects.</td>
<td>Standard clinical tool for calibration; acquisition of data for planning, QA.</td>
</tr>
<tr>
<td>Radiosensitive film</td>
<td>Two-dimensional (2D) dose information; integrative; good spatial resolution</td>
<td>Single-use; energy and (to a lesser extent) dose dependence; geometry may restrict applications.</td>
<td>Standard clinical tool for measurements in solid phantoms, qualitative dosimetry, QA.</td>
</tr>
<tr>
<td>Semi-conductor</td>
<td>Small size; real-time measurement; arrays for 2D information</td>
<td>Degradation (finite life and changing radiation sensitivity); energy, temperature, dose rate and directional dependence; requires recalibration.</td>
<td>Diodes increasingly common (MOSFET less so); can be used for water tank measurements and in vivo.</td>
</tr>
<tr>
<td>TLD</td>
<td>Small size; various materials and forms available; large number can be used; small size and lack of cables etc allows greater flexibility in measurement geometry; standard LiF good for stereotactic spectral qualities.</td>
<td>Precision typically lower than ionisation chambers; read-out is delayed and relationship between dose and light emission is very complex; sensitivity may change with history</td>
<td>Measurements in phantom (slab or anthropomorphic) and in vivo; personal dosimetry; may be used for inter-clinic comparisons.</td>
</tr>
<tr>
<td>Diamond detector</td>
<td>Small size; real time measurement; no directional dependence.</td>
<td>Dose-rate dependence; requires pre-irradiation for stability (if not used for &gt; 1 hr); directional dependence.</td>
<td>Have been used for measurement of penumbra and stereotactic fields; have been used as TLDs.</td>
</tr>
<tr>
<td>Radiosensitive gel</td>
<td>Water equivalent; simultaneously acts as phantom and dosimeter; three-dimensional dose information; high spatial resolution; large number of types available; integrative; multiple readout methods; high flexibility in geometry.</td>
<td>Requires lab for manufacture or as-needed purchase from commercial vendors; each batch requires calibration; single-use; MRI readout may not be feasible at some clinics; optical readout of polymer-type gels nontrivial.</td>
<td>Limited clinical application; have been used for stereotactic fields; commercially available; published ‘recipes’ allow in-house manufacture.</td>
</tr>
</tbody>
</table>
3.7 The radiological properties of gel dosimeters and ‘water equivalence’

As discussed earlier, media-matching of dosimeters is advantageous. Gel dosimeters are unique in that they function as both the dosimeter and phantom material. Water or tissue equivalence is a typical requirement of phantom materials. This implies that the radiological properties of the phantom material match those of water sufficiently within the desired regime of applicability. The term ‘tissue equivalence’ is widely used, and perhaps misused, in the field of radiation dosimetry. For two different materials to scatter and absorb photons and electrons in the same way, five quantities must be the same: (i) mass attenuation coefficients ($\mu/\rho$), (ii) mass energy absorption coefficients ($\mu_{en}/\rho$), (iii) electron mass stopping powers ($s/\rho$), (iv) electron mass angular scattering powers ($\theta^2/\rho l$) and (v) mass density ($\rho$). To be more precise, their partial, as opposed to total, coefficients and powers must be identical.

The formulation of materials which are tissue equivalent is traditionally approached in one of two ways. The first is in terms of elemental equivalence. Mixtures of water, urea, glycerol and so forth are produced so as to try and mimic the formula for soft tissue; see for instance (Rossi and Failla 1956). This method is not widely employed and there is comparatively little relevant literature. The second method, however, is frequently adopted. The ‘effective atomic number’ approach involves calculation of, usually, a single value which is taken to characterise photon interactions in the medium.

Since the original work of Moseley (1913), the atomic number, $Z$, has been identified as being fundamentally connected with various properties of the elements. Of particular interest is the dependence of photon interactions on the atomic number of a material, as shown in early photon absorption studies (Bragg and Peirce 1914; Owen 1919; Richtmyer and Warburton 1923). The latter authors have shown that the interaction cross section per atom is proportional to the atomic number raised to some power, i.e.

$$\sigma \propto Z^m$$

where $m$ is a constant that varies depending on (amongst other things) the interaction process. This $Z$-dependency gives rise to the notion of an ‘effective atomic number’, $Z_{\text{eff}}$, of mixtures and compounds that have composite elemental composition.

For historical reasons, only the effective atomic number for photoelectric processes is considered; for a long period only low energy x-rays were produced in medical applications. This practice demands revision for at least two reasons. Contemporary applications involve
MeV particles and ‘tissue equivalence’ must thus be considered over a broader range of energies (and _ergo_ a greater number of interaction processes). Furthermore, the strong Z-dependence of the photoelectric effect means that small errors in the effective atomic number generate significant errors in the ultimate quantity of interest, and so the accuracy and appropriateness of the values used must be well investigated.

It is commonplace in the field of gel dosimetry to support statements of tissue equivalence by calculation of a single effective atomic number using a simplistic, energy-independent power-based formula. In the subsequent section of this chapter it is shown that there is significant variability of the effective atomic number over the range of energies relevant to radiotherapy.

3.8 The effective atomic number of dosimetric gels

3.8.1 Background

There are a range of gel dosimeters in contemporary usage and the selection of a gel formulation involves many considerations, one of which is the degree to which the radiological properties of the gel match those of water. In this regard, it is common to compare parameters such as density, mass attenuation, stopping powers, scattering powers and ‘effective atomic number’. In a number of papers, a single $Z_{\text{eff}}$ is calculated to support water equivalence of gels used in radiotherapy dosimetry (e.g. (Farajollah et al. 1999; Pantelis et al. 2004; Venning et al. 2005a; DeDeene et al. 2006; Jirasek et al. 2006; Luci et al. 2007)). The commonly used $Z_{\text{eff}}$ calculation of Mayneord (1937) was originally developed based on low energy attenuation measurements, though it is frequently quoted in MeV gel dosimetry publications. Extrapolation to the high energy regime requires consideration of energy dependence.

In this thesis, a novel approach is employed for the calculation of $Z_{\text{eff}}$ of gel dosimeters that accounts for energy-dependence, allows use of a spectrally-weighted mean for applications requiring single-valued $Z_{\text{eff}}$ and demonstrates the questionable usefulness of routine methods.

A frequently employed method for determination of atomic number is that used by Mayneord in a discussion of the Röntgen (see Equation 3.) (Mayneord 1937), used in the context of gel dosimetry since the work of Kron et al (1993). The relative electron fraction of the $i^{th}$ element $Z_i$ is given by $f_i$, such that $\sum f_i = 1$. Mayneord used a value of 2.94 for the exponent $m$, and this method may be found in contemporary radiotherapy textbooks (Kahn 2003).
A further frequently referenced paper is Spiers’ (1946) work on the absorption of energy in tissues wherein the mass absorption coefficient of a compound is derived. To do so, Spiers uses Walter’s (1929) expression for the photoelectric absorption coefficient, and employs the same expression for effective atomic number as Mayneord. The absorption of x- and γ-rays is a combination of multiple processes. Other authors have attempted to describe heterogeneous media in terms of a single effective atomic number using a single exponent, for example Murty (1965), however the differing dependency of the exponent $m$ and hence $Z_{eff}$ on the interaction process and material composition means that this cannot be done without compromising accuracy.

The influence of different interaction processes on the total photon interaction cross section in a given material varies with energy. Hine (1952) highlights that there should be a different effective atomic number for each of the chief interaction processes. With reference to Equation 3., Hine uses values for $m$ of 3.1 and unity for photoelectric and pair production respectively. Weber and van den Berge (1969) suggest the use of two effective atomic numbers – one associated with the photoelectric effect and another with coherent scattering, using values for $m$ of 3.4 and 1.7 respectively. White’s (1977) results involve multiple energy-dependent values of $m$ that reflect earlier comments by McCullough (1975). Henriksen and Baarli constructed a simple argument against the use of an equation of the form of Equation 3., suggesting a different power relationship, but this suffers from the same limitations (1957). In later work, White (1978a) employed the relatively complex ‘extended $\bar{Y}$ method’ and tabulated a number of $Z_{eff}$ values that vary with the photon energy and the interaction process. Ultimately, a number of studies have involved the use of multiple exponents to estimate the effective atomic number, but none are suitable over a large energy range (Jackson and Hawkes 1981). This suggests that comparisons of radiological properties should be made over a range of energies with consideration of all interaction processes.

A qualitative comparison of radiological properties should include consideration of $Z_{eff}$ (or equivalently interaction cross sections) over a relevant energy range. Energy dependent data has been presented elsewhere for biological and other materials of relevance to dosimetry (Kumar and Reddy 1997; Prasad et al. 1997) (n.b. older studies employ outdated cross section data (Jayachandran 1971; Rao et al. 1985; Parthasaradhi et al. 1989)). In this study, we present the effective atomic number for fifteen types of ferrous-sulphate and polymer gel
dosimeters as a function of energy between 10 keV and 10 MeV. For comparative purposes, the effective atomic number for water, soft tissue, muscle and bone are also evaluated. Data is presented relative to water so as to allow direct comparison over relevant energy or interaction regimes. The significant variability of these curves over the keV-MeV energy range (see Figure 3.7) should persuade the reader that the use of a single $Z_{eff}$ value is likely to be problematic if this energy dependence is not considered. For those applications benefiting from the simplification a single value allows, we recommend the use of an appropriately chosen value or weighted mean based on the source spectrum in question.

A more detailed discussion of the evaluation of effective atomic numbers of gel dosimeters that establish radiological properties as being suitable for application in characterisation of stereotactic fields may be found in two key papers by the candidate (Taylor et al. 2008; Taylor et al. 2009b).

### 3.8.2 Gel dosimeters investigated

Data is presented for a Fricke gel dosimeter (Keall and Baldock 1999) and the hypoxic polymer gel dosimeters PAG (polyacrylamide gelatine) (Maryanski et al. 1993), BANG-1 (Maryanski et al. 1994) and BANG-2 (Maryanski et al. 1996; Farajollaha et al. 1999) (bis-acrylamide nitrogen gelatine), PABIG (polyethylene glycol diacrylate bis gelatine) (Sandilos et al. 2004) and VIPAR (N-vinyl pyrrolidone argon gel) (Pappas et al. 1999; Kipouros et al. 2001; Pappas et al. 2003). Also studied are the normoxic polymer gel dosimeters MAGIC (methacrylic acid, ascorbic acid in gelatine initiated by copper) (Fong et al. 2001), HEAG (hydroxy-ethyl-acrylate gel) (Gustafsson et al. 1994), MAGAS (methacrylic acid, gelatine gel with ascorbic acid), MAGAT (methacrylic acid, gelatine gel and tetrakis hydroxyl methyl phosphonium chloride) (DeDeene et al. 2002a; Hurley et al. 2005; Venning et al. 2005b), PAGAT (polyacrylamide, gelatin and tetrakis hydroxyl methyl phosphonium chloride) (Venning et al. 2005a), nPAG (normoxic polyacrylamide gel), nMAG (normoxic methacrylic gel) (DeDeene et al. 2006), ABAGIC (ascorbic acid, bis-acrylamide, in gelatine initiated by copper) (DeDeene et al. 2002b) and NIPAM (N-isopropylacrylamide) (Senden et al. 2006b). Water and various human tissues (ICRU 1989) are also presented for comparison.
3.8.3 Effective atomic numbers of gel dosimeters for photon interactions

The transport of photons through matter is related to energy and atomic number (Barkla and Sadler 1907; Barkla and Sadler 1909) with use of the mass attenuation coefficient. In the present work, energy dependent $Z_{\text{eff}}$ values are calculated from the mass attenuation data compiled by Hubbell et al (1995). For the composite materials studied here, the total mass attenuation coefficients are determined additively considering their fractional weightings. The total cross section is simply derived (see for example, Hubbell (1999)) from the mass attenuation coefficients. The present work draws on the x-ray mass attenuation data (Hubbell 1982) without the renormalisation proposed by Scofield (1973), as it has been shown that agreement with experiment is improved without renormalisation (Saloman et al. 1988).

$Z_{\text{eff}}$ may be determined via exploitation of the smooth correlation between atomic cross section and atomic number (Parthasaradhi 1968). The tabulated mass attenuation coefficient data was obtained for the first thirty elements and the corresponding cross section values were calculated. A matrix of cross sections was constructed spanning atomic numbers $Z = 1$ to 30 for photon energies ranging between 10 keV and 10 MeV. The cross sections for the gel dosimeters studied were calculated via linear additivity. These gel cross section values were then contrasted with the cross section matrix as a function of $Z$, and an effective $Z$ number for each energy was obtained by interpolation of $Z$ values between the adjacent cross section data. Care must be taken at low photon energies in the region of the K-absorption edge where discrete jumps in $Z_{\text{eff}}$ may be apparent that correspond to photoelectric absorption at K-shell binding energies. For compounds of higher atomic number there exist relatively pronounced discontinuities in $Z_{\text{eff}}$ and, for this reason, $Z_{\text{eff}}$ must be applied cautiously with high $Z$ elements ($Z > 50$). All materials studied here have $Z \leq 30$ and in this regard are not problematic.

The effective atomic number as a function of photon energy (from 10 keV to 10 MeV) has been calculated for nine normoxic and five hypoxic polymer gel dosimeters, a Fricke gel dosimeter and three biological materials. Figure 3.7 shows the effective atomic number of water as it varies with energy. To evaluate the degree of water equivalence, we have taken the ratio of the $Z_{\text{eff}}$ values of the various materials with the $Z_{\text{eff}}$ values of water over the full energy range. This ratio, $Z_{\text{eff,R}}$, is plotted in Figure 3.8 and Figure 3.9.
Figure 3.7 The effective atomic number ($Z_{\text{eff}}$) of water as a function of energy between 10 keV and 10 MeV.
Figure 3.8 $Z_{\text{eff},R}^\text{Water}$: The ratio of $Z_{\text{eff}}$ values of various materials with those of water as a function of energy, shown for (i) Fricke and the normoxic dosimeters (ii) MAGAT, MAGIC and NIPAM, (iii) nMAG, nPAG and ABAGIC and (iv) MAGAS, PAGAT and HEAG.
Figure 3.9 $Z_{\text{eff,R}}$: The ratio of $Z_{\text{eff}}$ values of various materials with those of water as a function of energy, shown for the hypoxic dosimeters (i) BANG-1, BANG-2, PABIG, (ii) PAG and VIPAR as well as the biological materials (iii) tissue (soft), muscle (striated) and (iv) bone (cortical).
The effective atomic numbers are presented here over a broad energy range to facilitate detailed comparison. Single values may nonetheless be convenient and, depending on the application and extent of approximation allowable, one may consider specific values or average within certain energy bands etc. Provided the spectral content of the photon source is known, one may generate a single effective atomic number by appropriate weighting. As an example, performing such weighting yields a $Z_{\text{eff}}$ value for MAGIC of 3.41 for the 6 MeV photon spectrum defined by Mohan et al. (1985). As one would expect, this coincides with the effective atomic number at an energy of around 2 MeV, which is approximately the mean energy of the spectrum from a 6 MV medical linear accelerator. This compares to a value of $Z_{\text{eff}} = 7.37$ calculated elsewhere (Sellakumar et al. 2007) using Equation 3, where the authors chose a value of $m = 3.5$. The latter power originates from the dependence of the photoelectric effect, which varies with the photon wavelength to the power of approximately three and four at low and high energies respectively. For this example, the power method underestimates the percentage discrepancy between $Z_{\text{eff}}$ of water and that of MAGIC (1.5 % for the weighting method and 0.7 % for the latter method). The effective atomic numbers of gel dosimeters calculated using the Mayneord method are invariably higher than those calculated using the more robust method presented here, even within the intended regime of applicability (where discrepancies are typically at least 20 %).

By consideration of the mean disparity, the effective atomic number of BANG-1 is most similar to water, as shown in Figure 3(i). HEAG and VIPAR, shown in Figure 3.8 (iv) and Figure 3.9 (ii) respectively, also match that of water closely, both having no constituents of Z > 8. Of the polymer gels, MAGAT is the least similar in $Z_{\text{eff}}$ to water, as shown in Figure 3.8 (ii). Observation of Figure 3.8 (i) shows that Fricke, the gel matching water least well, has $Z_{\text{eff}}$ values systematically greater than that of water over the full energy range studied.

### 3.8.4 Effective atomic numbers of gel dosimeters for electron interactions

A comprehensive study of the effective atomic numbers of gel dosimeters corresponding to electron interactions has thus far not been published. As discussed in the previous section, for photon interactions, it is common to derive the effective atomic number of a compound by summation of the constituent elemental atomic numbers raised to the power $m$ (where $m$ is a constant) and weighted according to their fractional electron content. It should be noted, however, that this simple, single Z-exponent method is typically not appropriate over extended energy ranges (White 1978a; Jackson and Hawkes 1981). The availability of such exponent data is comparatively limited for electron interactions, and the importance of H, C,
N and O (the primary constituents of gel dosimeters) is often ignored in their derivation (White 1977).

The interaction of electrons is of key importance whether as primary or secondary particles. The various current and future applications of gel dosimetry necessitate consideration of radiological properties in different energy regimes. In this study, effective atomic numbers are determined for a range of gel dosimeters, as well as for water and several biological materials for comparative purposes, for electron energies between 10 keV and 100 MeV. Effective atomic numbers are calculated for total and partial interaction processes using ICRU stopping powers (ICRU 1984b). The mass stopping power of the composite material is then determined via linear additivity of stopping powers of the constituent elements, taking into consideration their fractional weighting. This is then contrasted with a matrix of stopping powers that spans the elements $Z = 1$ to 30 for energies between 10 keV and 100 MeV. The effective atomic number at a given energy may then be obtained by interpolation of $Z$ values between adjacent stopping power data. The uncertainty due to such interpolation is $< 0.2 \%$.

The uncertainties in the collisional stopping powers employed are 2 \% to 3 \% below 100 keV and 1 \% to 2 \% above. The uncertainties in the radiative stopping powers are 5 \% below 2 MeV, 2 \% to 5 \% between 2 MeV and 50 MeV and 2 \% above 50 MeV; the relative contribution of the radiative process is negligible at lower energies where the uncertainties are higher. Effective atomic numbers are calculated in this way for collisional, radiative and total electron interaction processes.

Table 3.2 gives the effective atomic numbers for five hypoxic and nine normoxic polymer gel dosimeters, a Fricke gel dosimeter, water and soft tissue. The effective atomic number varies by approximately 30 \% over the energy range studied (10 keV $\leq E \leq$ 100 MeV). This is also evident from Figure 3.10 which shows the variation of $Z_{\text{eff}}$ with energy for each interaction process for a representative gel (PAG), plotted alongside the percentage discrepancy between $Z_{\text{eff}}$ of PAG and $Z_{\text{eff}}$ of water. Table 3.3 shows the mean, minimum and maximum values of $Z_{\text{eff}}$ for the partial and total interaction processes over the considered energy range.
For a representative gel (PAG): (a) the variation of effective atomic number with energy for collisional, radiative and total electron interaction processes; (b) the percentage difference between $Z_{\text{eff}}$ of PAG and $Z_{\text{eff}}$ of water, $\Delta Z_{\text{eff}}$.

It is common practice to use $Z_{\text{eff}}$ as one of the parameters (generally in conjunction with other parameters; see for instance (Constantinou 1978; White 1978b)) to indicate water/tissue equivalence. $Z_{\text{eff}}$ values for water are typically lower than those for the gels (up to approximately 2%), with the discrepancy decreasing as energy increases (see Figure 3.10 (b) for an example). As one would expect, this discrepancy, $\Delta Z_{\text{eff}}$, is greater between the $Z_{\text{eff}}$ values of gels and tissue than gels and water. For the radiative interaction process the difference is fairly constant, $Z_{\text{eff}}$ for gels are approximately 3% higher than for tissue, decreasing gradually with increasing energy. The discrepancy for the collisional process increases with energy; $\Delta Z_{\text{eff}}$ is over 1% from 10 keV to 100 keV, 2% at 1 MeV, 3.5 – 4% at 10 MeV and 4.5 – 5% at 100 MeV. Because of the dominant influence of the collisional process, this also reflects the discrepancy in the total interaction process, until approximately 10 MeV at which point the influence of the radiative process results in a reduction of the discrepancy between $Z_{\text{eff}}$ for gels and tissue between 10 MeV and 100 MeV (such that $\Delta Z_{\text{eff}}$ remains between 3 and 4%). Ultimately, the discrepancy between $Z_{\text{eff}}$ for tissue and for gels is of the same magnitude as the difference between tissue and water.
Table 3.2 The total effective atomic numbers of gel dosimeters, water and biological materials at a selection of energies between 10 keV and 100 MeV calculated from total stopping power data.

<table>
<thead>
<tr>
<th>Energy (MeV)</th>
<th>0.01</th>
<th>0.1</th>
<th>0.2</th>
<th>0.6</th>
<th>1</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
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</tr>
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<td>MAGAS</td>
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<td>3.73</td>
<td>3.81</td>
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Table 3.3: The mean, minimum and maximum effective atomic numbers (with standard deviation) for gels, water and biological materials, calculated for collisional, radiative and total electron interaction processes between 10 keV and 100 MeV.

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<th>RADIATIVE</th>
<th>TOTAL</th>
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3.9 Systematic variations in polyacrylamide gel calibration due to container influence and deviations from water equivalence

3.9.1 Overview

As a water-equivalent three-dimensional integrating dosimeter, gels would appear, in principle, to be the ideal dosimeter. In the previous sections the radiological properties of gel dosimeters have been examined, with a specific emphasis on the effective atomic number, since this is not dealt with sufficiently well in published scientific literature. Another practical issue to be considered if the use of gel dosimeters is desired is that of gel calibration. Inspection of the literature highlights that there are a wide number of methods employed, and the absence of a standard methodology.

The work presented in this section of the chapter is a detailed Monte Carlo investigation into the accuracy of published calibration techniques. A concise overview of the key findings of this work is presented here, and the interested reader is referred to a much more comprehensive discussion of the investigated methods and results that may be found in two publications by the candidate (Taylor et al. 2007; Taylor et al. 2009a):

3.9.2 Introduction

Gel dosimeters are often used for relative dosimetry; however for quantitative information it is necessary to calibrate each batch of gel individually. In principle, this is undertaken by irradiating gel with varying doses, with the assumption that the doses received are equivalent to that in water under the same conditions. A dose calibration curve is then constructed by association of the presumed dose at such points with the corresponding relaxation rate values obtained via MRI, or with Hounsfield units from x-ray computed tomography, attenuation coefficients from optical computed tomography, or similar. The importance of calibration is self evident and, in the case of gel dosimeters, uncertainty in calibration has been the subject of various studies (Ballock 1999, Trapp 2004a).

Of particular note is the fact that there has been little consideration of the effect of backscatter from containers on the absorbed dose in gel dosimeters. Michael et al (2000) concluded that the presence of glass containers and Nitrogen pockets therein had no significant effect on the total absorbed dose within a vial of gel. However, alternative calibration techniques and the local effects of containment vessels coupled with the compounded effects of juxtaposition of multiple containers have not been previously investigated in detail.
Numerous practical techniques for gel calibration exist, described in detail by Taylor et al. (2007; 2009a); in summary:

- Multiple small vials in a water phantom that are given different doses (Maryanski et al. 1994; Baldock et al. 1998; Baldock et al. 1999)
- A large volume flask of gel placed in air, into which numerous small fields of varying doses are directed (Maryanski et al. 1994; Maryanski et al. 1996; Oldham et al. 1998a).
- A long gel-filled test tubes placed within a water phantom and irradiated through the bases so that a depth-dose distribution exists along the length of the tube (allowing multiple calibration points to be obtained from a single test tube) (Oldham et al. 1998b).
- Gel-filled test tubes placed 5 cm deep in a water phantom with their axes perpendicular to the irradiation field (McJury et al. 1999; DeDeene et al. 2001; Vergote et al. 2004).

3.9.3 Summary of method
Accurate measurement of effects such as backscatter and cross-talk is not feasible and, as such, the investigation is highly amenable to Monte Carlo dose calculation. The water equivalence of five gels in five different calibration arrangements is modeled here using the Electron Gamma Shower (EGSnrc) code V4-2-2-5 (EGSnrc 2006). It is well accepted that Monte Carlo generates accurate dose calculations, even in zones of electronic disequilibrium, such as interfaces between materials of high and low density. In this work, several of the aforementioned gel calibration arrangements are modelled to determine the extent to which containment vessels affect the absorbed dose in gel dosimeters. This allows an informed choice between the common dose calibration methods to minimise the systematic errors introduced by calibration. The radiotherapy beam modeled is a 6 MeV endpoint bremsstrahlung spectrum (Mohan et al. 1985). Refer to Taylor et al for a detailed description of the simulation geometries (2007; 2009a). Briefly, the different methods incorporate small vials, test tubes and a large flask. The small vials are 55 mm long, have a 25 mm internal diameter and are made with 1 mm thick borosilicate glass with a polyethylene cap. The test tube is similar, though 200 mm long. The large flask is modeled as a Perspex tub of inner diameter 130 mm and height 45 mm with a wall thickness of 6 mm. A 6 MV beam is used in all cases. A schematic of the modeled geometry is provided in Figure 3.11.
Figure 3.11 Overview of modelled geometries; a key is also provided. (a) Method A: a small Pyrex vial at 50 mm depth in water. (b) Method B: a large acrylic container filled with gel, irradiated with a small field. (c) Method C: a perpendicularly-oriented Pyrex test tube at 50 mm depth in water. (d) Method D: a similar orientation, with a smaller test tube. (e) Method E: A large test tube, coaxial with the beam, positioned at the surface of a water phantom.
3.9.4 Results

For each method of calibration modeled, difference plots are provided that show the ratio of the dose in gel to the dose in water; this highlights the differences that are the subject of the present study (see Figure 3.12 to Figure 3.16). The plots given are depth dose curves and radial plots that show the range of influence of inhomogeneities. In each case Fricke is used as the representative gel. For comparison to other gel formulations, Table 3.4 and Table 3.5 quantify the difference between calculated dose to water and dose to gel \( \left( \frac{D_{gel} - D_{water}}{D_{water}} \right) \) for clinically appropriate volumes. The data presented in Table 3.4 and Table 3.5 are dose values averaged over a small volume (~80 mm\(^3\)), so as to reflect clinical practice, where relaxation rates from MRI or attenuation coefficients from optical computed tomography etc. are volume-averaged at certain locations. These voxel values are then associated with the known values of dose to water such that a calibration curve can be constructed. The results we present here highlight the differences between dose to water and dose to gel which thus indicates any systematic uncertainty introduced by this practice. The low dose ratios observed at locations corresponding to the containers are due to the higher density of the container materials.

3.9.4.1 Method A: Small vial

Figure 3.12 (a) shows the ratio of a depth dose curve in Fricke gel to a depth dose curve in water (the field size is 100 mm). Figure 3.12 (b) shows the ratio of the radial dose distributions of gel and water at a depth corresponding to the mid-point of the vial. The abrupt drop at a depth of 5 cm corresponds to the glass base of the vial (which faces the oncoming beam). Taking an area of about 80 mm\(^2\) around the centre of the vial at its mid-point and averaging the voxel values would yield a value lower than the dose to water by 0.4 (± 0.2) % for Fricke, the same for PAG, 0.7 (± 0.2) % for MAGIC, 0.3 (± 0.2) % for BANG-1 and 0.8 (± 0.2) % for BANG-2.

3.9.4.2 Method B: Large flask

Based on the calibration technique outlined by Oldham et al (Oldham et al. 1998a), we have modeled a large flask with and without a nitrogen gap. For greater generality, the results shown in Figure 3.13 correspond to the model with no nitrogen gap (thus filled entirely with gel), however other simulations indicate its effect (particularly at the point of maximum dose, \( D_{max} \)) is negligible, as shown in Figure 3.14. Figure 3.13 (a) shows the ratio of depth dose curves in Fricke and in water, corresponding to a 2 cm diameter circular field incident on the centre of the flask. Figure 3.13 (b) shows the ratio of the radial distributions in Fricke and
water at a depth corresponding to $D_{\text{max}}$ (the field size is 40 mm). The equivalent information is shown for a large flask of gel with a nitrogen gap in Figure 3.14 (a) and (b). The dose in the build up region is several percent higher in the gel than the water, matching to within 1% between depths of 1 and 2 cm. Between 2 cm and 5 cm the calculated dose in gel matches water within about 2%. Taking an area of $80 \text{ mm}^2$ at $D_{\text{max}}$, with a voxel thickness of 2 mm, shows the mean dose to Fricke is the same as that to water, within an uncertainty of about 0.3%. For PAG this difference is $0.2 (\pm 0.1) \%$, for MAGIC it is $0.5 (\pm 0.2) \%$, for BANG-1 it is $0.1 (\pm 0.2) \%$ and for BANG-2 there is zero difference with an uncertainty of about 0.2%.

3.9.4.3 Method C: Large perpendicular test tube

Figure 3.15 (a) shows the ratio of the central axis dose profile in Fricke gel and in water alone for a 20 cm long test tube oriented perpendicular to the beam with its centre at a depth of 5 cm within a water phantom (the field size is 300 mm across). In this case a radial dose profile would not yield useful information. The objective of this method is to obtain a large number of points (over the length of the tube) so as to average the voxel values and reduce uncertainty in the corresponding dose value. Taking an area of $13 \text{ mm}^2$ and averaging the values in this way (taking care to avoid the ends of the tube) indicates that the dose to Fricke is 0.4 ($\pm 0.1$) % lower than the dose to water. Similarly, the difference for PAG is 0.7 ($\pm 0.1$) %, for MAGIC it is 0.9 ($\pm 0.1$) %, for BANG-1 it is 0.6 ($\pm 0.1$) % and for BANG-2 the difference is 0.7 ($\pm 0.1$) %.

3.9.4.4 Method D: Small perpendicular test tube

Figure 3.15 (b) shows the ratio of the central axis dose profile in Fricke gel and in water alone for a 10 cm long test tube with a diameter of 10 mm, oriented perpendicular to the beam with its centre at a depth of 5 cm within a water phantom (200 mm field size). There is significant statistical noise because of the smaller voxel sizes (~0.016 cm$^3$) used to define the geometry. Averaging over a lateral area of $13 \text{ mm}^2$ over the length of the tube, the difference between dose to Fricke and dose to water is 0.2 ($\pm 0.2$) %. For PAG this difference is 0.4 ($\pm 0.3$) %, for MAGIC it is 0.3 ($\pm 0.2$) %, for BANG-1 it is 0.0 ($\pm 0.2$) % and for BANG-2 the difference is 0.1 ($\pm 0.2$) %.

3.9.4.5 Method E: Long coaxial test tube

Figure 3.16 (a) shows the ratio of a depth dose curve in Fricke gel to a depth dose curve in water alone for a 20 cm long test tube the base of which is at the surface of a water phantom,
oriented parallel to the beam. The radial dose distribution varies with depth and the ratio of
the radial dose for Fricke and water is thus presented at depths of 5, 10 and 15 cm. These are
shown in Figure 3.16 (b), (c) and (d) respectively. Choosing an area of 80 mm$^2$ around the
centre of the test tube at each of these depths and average the dose values yields multiple
calibration points, but ones typically increase in disparity with the dose to water, as indicated
in Table 3.5.

**Figure 3.12** Ratio of calculated dose to Fricke gel compared to dose in water for Method A: a small
vial at a depth of 5 cm. (a) shows the ratio of depth dose curves and (b) shows the ratio of radial dose.
Gel-filled regions are shaded for clarity.

**Figure 3.13** Ratio of calculated dose to Fricke gel compared to dose in water for Method B: a large
flask in air. (a) shows the ratio of depth dose curves and (b) shows the ratio of radial dose. The notable
peak occurs as a result of the increased secondary electron fluence immediately beyond the (relatively
high density) container wall.
Figure 3.14 Ratio of calculated dose to Fricke gel compared to dose in water for Method B: a large flask in air with a Nitrogen gap (evident at 4.5 cm depth). (a) shows the ratio of depth dose curves and (b) shows the ratio of radial dose.

Figure 3.15 (a) corresponds to Method C, showing the ratio of dose to gel and dose to water along the central axis of a large (200 mm long, 20 mm diameter) test tube. (b) corresponds to Method D, showing the ratio of dose to gel and dose to water along the axis of a small (100 mm long, 10 mm diameter) test tube. Gel-filled regions are shaded for clarity.

Table 3.4 Percentage difference between calculated dose to gel and dose to water.

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<th></th>
<th>Method B</th>
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<td>0.4</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1</td>
<td>0.7</td>
<td>0.1</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Fricke</td>
<td>0.4</td>
<td>0.2</td>
<td>0.0</td>
<td>0.1</td>
<td>0.4</td>
<td>0.1</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>MAGIC</td>
<td>0.7</td>
<td>0.2</td>
<td>0.5</td>
<td>0.3</td>
<td>0.9</td>
<td>0.1</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>BANG 1</td>
<td>0.3</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
<td>0.6</td>
<td>0.1</td>
<td>0.0</td>
<td>0.2</td>
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<tr>
<td>BANG 2</td>
<td>0.8</td>
<td>0.2</td>
<td>0.0</td>
<td>0.2</td>
<td>0.7</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
</tr>
</tbody>
</table>
Figure 3.16 (a – d) all correspond to Method E, a long test tube coaxial with the beam. The ratio of depth dose curves is shown in (a), and the ratio of radial dose distributions are shown in (b), (c) and (d) corresponding to depths of 5, 10 and 15 cm respectively.

Table 3.5 Differences between calculated dose to gel and dose to water for a long test tube coaxial with the beam (Method E).

<table>
<thead>
<tr>
<th>Depth in test tube</th>
<th>5 cm</th>
<th>10 cm</th>
<th>15 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAG</td>
<td>0.7</td>
<td>0.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Fricke</td>
<td>0.4</td>
<td>0.2</td>
<td>0.6</td>
</tr>
<tr>
<td>MAGIC</td>
<td>0.4</td>
<td>0.2</td>
<td>1.6</td>
</tr>
<tr>
<td>BANG 1</td>
<td>0.5</td>
<td>0.3</td>
<td>1.1</td>
</tr>
<tr>
<td>BANG 2</td>
<td>0.5</td>
<td>0.2</td>
<td>1.1</td>
</tr>
</tbody>
</table>
Table 3.6 Statistical data for each calibration method, analysed by gel type.

<table>
<thead>
<tr>
<th>Calibration method</th>
<th>Diff (%)</th>
<th>St. Dev</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method A (small vial)</td>
<td>0.5</td>
<td>0.2</td>
<td>0.2, 0.8</td>
</tr>
<tr>
<td>Method B (large flask)</td>
<td>0.2</td>
<td>0.2</td>
<td>-0.1, 0.4</td>
</tr>
<tr>
<td>Method C (large perpendicular test tube)</td>
<td>0.7</td>
<td>0.2</td>
<td>0.4, 0.9</td>
</tr>
<tr>
<td>Method D (thin test tube)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.0, 0.4</td>
</tr>
</tbody>
</table>

Table 3.7 Statistical data for each calibration method, analysed by calibration type.

<table>
<thead>
<tr>
<th>Gel dosimeter</th>
<th>Diff (%)</th>
<th>St. Dev</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAG</td>
<td>0.4</td>
<td>0.2</td>
<td>0.1, 0.8</td>
</tr>
<tr>
<td>Fricke</td>
<td>0.3</td>
<td>0.2</td>
<td>-0.1, 0.6</td>
</tr>
<tr>
<td>MAGIC</td>
<td>0.6</td>
<td>0.3</td>
<td>0.2, 1.0</td>
</tr>
<tr>
<td>BANG-1</td>
<td>0.3</td>
<td>0.3</td>
<td>-0.2, 0.7</td>
</tr>
<tr>
<td>BANG-2</td>
<td>0.4</td>
<td>0.4</td>
<td>-0.3, 1.0</td>
</tr>
</tbody>
</table>

3.9.5 Discussion

It is clear that the majority of calibration methods evaluated in the present study, provided they are performed in a precise manner, accurately reflect the dose given to water within the 1 % uncertainty limit typically specified in the context of radiotherapy. For all methods excepting the long coaxial test tube, the 95 % confidence interval for the percentage difference between the calculated dose to gel and the dose to water is contained in the interval [-1.0 %, 1.0 %].

While results for different methods and different materials are not necessarily from consistent distributions, it is useful to impose some statistical analysis of the data. Nine analyses were undertaken as shown in Table 3.6 and Table 3.7 considering each calibration method and gel material individually. Note that although the data are only reported to one significant figure, confidence intervals were calculated exactly prior to rounding. In all cases the distribution was consistent with a normal distribution.
For the calibration methods, the mean is significantly different to zero at the 95% confidence level for 3 methods, but the 95% confidence interval spans zero for the large flask method. For the different gel materials, the PAG and MAGIC gels gave results significantly different to zero at the 95% confidence level, while the other 3 did not. In all 5 cases the confidence interval was [-1.0 %, 1.0 %].

For all the combinations of gel type and calibration geometry, the various differences lie a large number of standard deviations from -1 %, and the probability that a difference will occur beyond this is negligible (i.e. the differences are close to zero – far from -1 % even if you consider the tail end of σ). Applying a normal distribution, the probability that a random occurrence of the difference lies beyond 1 % is less than 1 % for the vast majority of the arrangements. The exceptions are MAGIC and BANG-2 in Method A, MAGIC in Method C and PAG in Method D, for which the probability of the difference exceeding 1 % is 7 %, 16 %, 16 % and 2 % respectively.

Users of those combinations of gel and geometry yielding the possibility of >1 % dose differences should consider incorporating these differences into calibration correction factors. Method E (a long test tube coaxial with the beam) exhibits results quite different to the other techniques. As shown in Table 3.5, differences between dose to gel and dose to water begin within 1 % at one sigma at a depth of 5 cm, and increase with depth to up to 2.2 % at 15 cm. This is due to the cumulative effect of the different attenuating properties over the relatively long path length in gel. Readers may employ the data presented here to help influence their choice of calibration technique, by preferentially considering those which exhibit the least difference to water.

As shown in Table 3.4 and Table 3.5, broadly, the Fricke formulation exhibits the least difference with water. For most of the calibration methods studied, the influence of the container on the dose to gel is small, so long as measurements are taken at specific points. The radial dose plots indicate that the dose varies laterally. The magnitude of the disparity is influenced by the volume over which the dose is averaged.

Knowledge of the radial distributions as presented in this work makes it possible to minimize the error introduced. The volume may be chosen such that build-up effects and the low dose regions caused by attenuation may compensate for one another. The small vial technique is sometimes performed so that multiple vials are irradiated simultaneously in an array, so as to reduce total beam time. The radial plots indicate the closest proximity a neighboring vial may be placed such that the cross-talk is minimized.
There are observable trends associated with the different methods. Ranking the methods in terms of increasing disparity, it is clear that Method B using a large flask is the optimal technique. In terms of set-up, this method is also likely to be more straightforward than the other techniques. The presence of a small nitrogen pocket has a negligible effect on the measurement at $D_{\text{max}}$. It is the least difficult to position for both irradiation and subsequent measurement. All other techniques shown here involve vessels of gel submerged in a water phantom, which likely involve more complex positioning structures and so forth given the necessity for accurate localization. The next best method is the small test tube placed perpendicular to the beam at a depth of 5 cm within a water phantom (Method D). After this, a small vial, coaxial with the beam, placed 5 cm deep within a water phantom where the dose gradient is relatively linear (Method A). Exhibiting a slightly greater difference is the method involving a large test tube perpendicular to the beam at a depth of 5 cm (Method C). The technique resulting in doses to gel least close to that of water is the method whereby a long test tube is placed at the surface of a water phantom coaxial with the beam, such that a dose distribution is achieved along its length (Method E).

We have employed Monte Carlo radiation transport modeling to evaluate the water equivalence of five different gel formulations under varying conditions corresponding to five different methods of calibration. From this we can identify that BANG-1 and Fricke are the most water equivalent gel formulations and the ‘large flask’ and ‘small vial’ methods exhibit the smallest differences.

3.10 Summary
There are many types of dosimeter that may be employed for the measurement of dose in the context of radiation therapy. The three most commonly employed dosimeters in a typical clinic are ionisation chambers, radiosensitive films and thermoluminescent dosimeters. All dosimeters have various advantages and disadvantages. For stereotactic fields, a review of the literature has shown that typically a number of dosimeters are employed to characterise small fields – and often there are significant discrepancies between dosimeters when measuring the same field.

Here, gel dosimeters – which act as both dosimeter and phantom material – have been identified as showing great promise for the measurement of three-dimensional dose distributions in stereotactic radiotherapy.
In this chapter, an overview of aspects of gel dosimetry has been given, including their manufacture, mechanisms for radiation response and read-out. However, clinical implementation of gel dosimeters has been very limited by comparison to other methods. There are a number of reasons for this, which include very practical issues such as a lack of chemical handling and preparation facilities in clinical physics departments.

In the present work, the focus has been on investigation of the composition and radiological interaction properties of the various gel dosimeters available – in particular their effective atomic number. In this thesis, effective atomic numbers have been calculated in a novel fashion for gel dosimeters, indicating energy dependence and the very limited regime of applicability of the power-law method that is typically employed in published literature. One important finding is that the subtle differences in effective atomic number between water and gels may be considered negligible for most radiotherapy applications.

Furthermore, no standard protocol for gel calibration has been published. As such, the second half of this chapter has focused on assessing, via Monte Carlo methods, systematic variations in gel dosimeter calibration due to container influence and deviation from water equivalence for a range of gels and calibration methodologies. From this, optimum methods have been identified that minimise systematic error.

Gel dosimetry has been identified as being highly suited to the characterisation of stereotactic radiotherapy fields, and its use is demonstrated for verification of clinical treatments as described in Chapter 5.

At the cutting edge of dose calculation – rather than measurement – of stereotactic fields is Monte Carlo radiation transport, which is discussed in significant detail in the following chapter.
CHAPTER FOUR

The apparition of these faces in the crowd;
Petals on a wet, black bough. †

_Ezra Pound_

† Perhaps this concise poem written in haiku style about the underground Parisian metro seems chosen randomly, but the elegant simplicity of imagist poetry – of which Pound is my most admired proponent – seems appropriate for a chapter devoted, essentially, to mathematical calculation. Indeed Pound himself was quoted as saying with reference to this poem that the faces of those in the metro were best put into a poem not with a description, but with an equation.
CHAPTER 4

Theoretical dose calculation

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4.1 Overview

There are a wide range of mathematical descriptions of the different interactions of ionising radiation in materials, each with different limitations and approximations. The calculation of dose deposited by radiation as a result of such interactions in the context of radiotherapy is of critical importance. Treatment planning systems (TPS) employ algorithms to calculate doses in patients as part of the treatment optimisation process, sacrificing some level of accuracy in order to achieve rapid calculation times and hence ensure efficient patient throughput in a clinical context. There are a range of potential issues:

- Approximations in TPS algorithms often result in insufficiently accurate treatment of charged particle equilibrium.
- This has consequences for small fields (in particular where the size of the field approaches the range of secondary electrons) and for heterogeneities.
- Calculation of small fields with TPS is still reliant upon broad-beam measured data for input, and is thus limited by the accuracy of the dosimeter employed and suitability of extrapolation to small fields.

Ideally, for the characterisation of stereotactic fields, it is necessary to have an accurate means of calculating dose distributions (and, if possible, other quantities such as fluence, spectra, etc). Monte Carlo radiation transport methods are widely accepted as the most accurate means of calculating dose and other relevant quantities.

This chapter essentially describes the development of a capability for accurate characterisation of stereotactic fields – spectral and dosimetric:

- Dose calculation algorithms implemented in commercial treatment planning systems are described, with an emphasis on noting their limitations.
- The Monte Carlo method of simulating radiation transport is described in more detail, being considered the most accurate approach for dose calculation.
- The Electron Gamma Shower (EGSnrc) code is employed for many applications in this study, and consequently is described thoroughly.
- The key result of this chapter is the development and commissioning of a Monte Carlo model of a Varian 600C medical linear accelerator with mounted BrainLAB™ mini-multileaf collimator.

The methods developed in this chapter are employed for numerous investigations characterising stereotactic fields, described in later chapters.
4.2 Dose calculation in clinical treatment planning systems and the limitations thereof

4.2.1 Calculation of dose

As has been discussed, the absorbed dose is the relevant parameter for planning and reporting a radiotherapy treatment. Contemporary radiotherapy treatment planning systems (TPS) provide the capacity to computationally determine the dose delivered to a patient, superseding the relatively laborious and limited hand-planning techniques. Because three-dimensional measurement of dose within a patient is not feasible, in a clinical setting there is no choice but to model in some way the dose given in a treatment plan. Recent developments in imaging modalities have improved the capacity for target delineation. With this come attempts to improve delivery precision; contemporary methods such as IMRT select treatment arrangements via an optimisation method within the range of available degrees of freedom in delivery. Initially, treatment planning involved the use of empirical techniques, which clearly limits the treatment geometries that can be employed confidently. Despite knowledge of transport equations, analytical dose algorithms sometimes lack the generality required for use in many treatment geometries. Monte Carlo methods represent the gold standard in dose calculation, modelling the interactions of all primary radiations and those generated from subsequent cascades. This, however, is not widely adopted in a clinical context because of the high demand on the central processing unit (CPU) time. Hence, the option most frequently employed is to adopt semi-analytical algorithms. Invariably, these incorporate approximations and hence are limited in their accuracy. The AAPM / ASTRO working group categorises dose computation algorithms as correction-based broad-beam algorithms, correction-based pencil beam algorithms, superposition or convolution kernel-based algorithms and Monte Carlo algorithms (IMRT-CWG 2001).

4.2.2 Density scaling and approaches to heterogeneities

The dose information used in treatment planning is predominantly derived from dose to water data. Dose in other media and the presence of inhomogeneities is often treated using ‘density scaling’. Dating back to 1954, one theory suggests that when a medium of constant elemental composition but varying density is subjected to a constant photon fluence, the fluence of secondary particles is also constant (Fano 1954). The primary assumptions here are that the cross sections per unit mass are independent of the density of the medium, and that the primary photon attenuation, density effect and the generation of secondary photons are negligible processes. O’Connor presented a theory suggesting that the ratio of fluences of secondary to primary radiations is constant in two media of different density but same atomic
composition, provided that relevant geometrical distances (such as field sizes) are scaled inversely to the density (O’Conner 1957). Though widely implemented, analysis of the accuracy of the density scaling method in its treatment of inhomogeneities by comparison with Monte Carlo has shown that discrepancies ranging up to 50% may exist (Woo and Cunningham 1990).

There are a range of approaches to heterogeneity corrections, a comprehensive review of which may be found in Ahnesjo and Aspradakis (1999). Many approaches consider densities only along the path of the primary photon, approximating the medium as a series of slabs that are laterally infinite. Applicable for water-like media only, the ‘effective path length’ method involves scaling the broad beam dose distribution according to the factor that the primary fluence at the point of calculation has changed by, as compared with the homogeneous case. Sontag and Cunningham showed that this method is not accurate for highly heterogeneous media, nor for interfacial regions (Sontag and Cunningham 1977). The ‘power-law method’ was first suggested by Batho and then generalised by Sontag and Cunningham, using correction factors based on build-up depth shifted tissue-maximum-ratios (Batho 1964; Sontag and Cunningham 1977). However, this method has been shown to be of limited applicability, being inaccurate for large inhomogeneities (Wong and Henkelman 1982) and for small fields (Thomas 1991). The equivalent tissue-air-ratio method (Sontag and Cunningham 1978) drew on computed tomography (CT) data, employing the density scaling theorem and thus being subject to the associated limitations thereof.

4.2.3 Modelling scattered radiation
Calculation of the scatter dose is of understandable importance. Less computationally demanding than full Monte Carlo modelling, ‘implicit modelling’ of scattered particles may be performed. The most widely implemented approach to this is the ‘kernel’ method. This functions on the principle of superimposed, weighted responses to point irradiations – ‘kernels’. Each individual kernel represents the dose deposition due to secondary radiations resulting from a point irradiation, typically calculated via Monte Carlo. This can be done for a range of monoenergetic primary photons and the results stored in a database; superposition of these for a beam of known spectrum can then yield kernels. A variation of the point kernel method is the pencil-beam method, a correction-based algorithm, which represents the dose deposition in a semi-infinite medium from a point monodirectional beam (Mohan et al. 1986; Mohan and Chui 1987; Ahnesjo et al. 1992). These are calculated via Monte Carlo either directly or by superposition of point kernels. The point kernel and pencil-beam methods are illustrated in Figure 4.
The pencil-beam method is the most frequently employed, however, the method is not without limitations, relying on broad beam scaling corrections for heterogeneities. The primary problem is the lack of lateral electron transport (Nilsson and Knoos 1992); superposition accounts for the range of electrons ejected by primary photon interactions, however, linear electron paths are assumed and are scaled by the density only, ignoring lateral deflection due to scattering (Hoban et al. 1990). In regions of insufficient charged particle equilibrium, there are discrepancies in the calculated dose that increase significantly with energy (Knoos et al. 1995). On the low energy scale, overestimations of dose exist that are attributed to the approximation for the integration volume for scatter calculations (Hurkmans et al. 1995).

The kernel superposition approach is relatively time efficient compared to full Monte Carlo modelling, however, reasonable throughput in clinical practice requires that the calculations be as fast as possible. As a result, numerous algorithms exist that attempt to speed up the process. Of particular note is the ‘collapsed cone convolution’ of point kernels method (Ahnesjo 1989), which has been shown to improve the match with measured and Monte Carlo dose distributions, as compared with the standard pencil-beam method (Partridge et al. 2006). A range of commercially available IMRT treatment planning systems and their associated dose calculations algorithms are given in Table 4., and their clinical performance has been compared by Fogliata et al (2007).
Table 4.1 A range of commercial treatment planning systems (TPS) and their calculation algorithms. References: \( ^a \) (Nizin \textit{et al.} 2001), \( ^b \) (Chui \textit{et al.} 1994), \( ^c \) (Spirou and Chui 1998), \( ^d \) (Ulmer and Harder 1995), \( ^e \) (Ulmer and Harder 1996), \( ^f \) (Alber and Nusslin 1999), \( ^g \) (Alber and Nusslin 2001), \( ^h \) (Bortfeld \textit{et al.} 1993), \( ^i \) (Gustafsson \textit{et al.} 1994), \( ^j \) (Gustafsson \textit{et al.} 1995), \( ^k \) (McNutt 2002), \( ^l \) (Wu \textit{et al.} 2003), \( ^m \) (McNutt 2002), \( ^n \) (Hardemark \textit{et al.} 2004) and \( ^o \) (Xiao \textit{et al.} 2000).

<table>
<thead>
<tr>
<th>TPS</th>
<th>Calculation algorithm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corvus (5.0)</td>
<td>Pencil beam ( ^a )</td>
</tr>
<tr>
<td>Eclipse (7.5 14.3)</td>
<td>Anisotropic analytical algorithm ( ^b,c,d,e )</td>
</tr>
<tr>
<td>Hyperion (2.1.4)</td>
<td>Monte Carlo ( ^f,g )</td>
</tr>
<tr>
<td>KonRad (2.2 18)</td>
<td>Pencil beam ( ^h )</td>
</tr>
<tr>
<td>Oncentra Master Plan (1.5)</td>
<td>Pencil beam ( ^i )</td>
</tr>
<tr>
<td>Pinnacle 3 EUD (7.4f)</td>
<td>Collapsed cone ( ^k,l )</td>
</tr>
<tr>
<td>Pinnacle 3 Phys (7.4f)</td>
<td>Collapsed cone ( ^m,n )</td>
</tr>
<tr>
<td>PrecisePLAN (2.03)</td>
<td>Pencil beam ( ^o )</td>
</tr>
<tr>
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</tr>
<tr>
<td>Radionics X-Knife</td>
<td>Pencil beam</td>
</tr>
<tr>
<td>iPlan</td>
<td>Pencil beam</td>
</tr>
</tbody>
</table>

4.2.4 The \textit{iPlan}™ Dose calculation algorithm

At the William Buckland Radiotherapy Centre (The Alfred Hospital, Melbourne), small fields are delivered by a Varian 600C Clinac with mounted BrainLAB m\_3 mini-multileaf collimator (MMLC). Plans are generated with iPlan (BrainLAB, Feldkirchen) dose calculation software. The iPlan software employs a pencil beam dose calculation algorithm. Pencil beams have been discussed briefly in the previous section, with an emphasis on their limitations. The iPlan algorithm is discussed more specifically in this section, as it is the planned doses that will be compared to that measured experimentally and calculated via Monte Carlo methods.

The iPlan pencil beam algorithm uses photon beam data calculated by Mohan \textit{et al} (1985; 1986; 1987). In this method, the incident beams are subdivided into small ‘beamlets’. For each beamlet, a radiological path length correction is applied to correct for density inhomogeneity. A fast Fourier transform (FFT) is applied for the beam kernel convolution with the fluency distribution of the beam.

The convolution between pencil beam kernels and photon fluence assumes that pencil beam kernels are translation invariant in \( x \) and \( y \) directions (a homogeneous medium is assumed). For doses near inhomogeneities this assumption can fail. Further approximations are
incorporated into the equation for the tissue maximum ratio (TMR). The TMR characterises the dose as a function of depth, similarly to the common percentage depth dose (PDD), with the main difference being (effectively) independence of SSD. However, the corresponding equation incorporates assumptions that introduce an error, the size of which increases for increasing depth and decreasing field size.

Ultimately, a range of dose calculation algorithms exist, each of which is subject to various approximations and limitations. Of particular note is the broad assumption of electronic equilibrium, which reduces the accuracy of the dose calculations for small fields and for regions in the vicinity of high-low density interfaces. For this reason, it may be necessary to verify the accuracy of such calculated dose distributions, whether experimentally or via Monte Carlo modelling.

4.2.5 A comment on limitations in the context of out-of-field dose calculation
Treatment planning systems (TPS) are normally commissioned using measured data that extend only a few centimetres beyond the field edge, with penumbra defined as 80% to 20% of the maximum dose for the field. Dose extending outside the field is not intended to be used for the overall calculation of the dose distribution or contribute to the inverse optimisation procedure. Therefore, one would expect the dose distributions predicted by the iPlan TPS to be inaccurate in regions far from the primary field. Even low-dose regions in close proximity to the main treatment field have been shown to be calculated inaccurately by treatment planning systems. Jang et al (2008) showed this recently for intensity-modulated radiotherapy by comparison to Monte Carlo dose calculation.
4.3 The principles of Monte Carlo radiation transport

Analytical (i.e. non-numerical) calculation of the integro-differential equations that describe the development of electromagnetic showers in matter is prohibitively difficult without significant approximations. Briefly referred to in the previous section, Monte Carlo radiation transport is the only broadly applicable solution. Monte Carlo simulation is widely accepted as the best means of dose calculation because it explicitly models many of the interaction processes ignored or simplified by treatment planning software algorithms.

In a general sense, when the Monte Carlo technique is employed for the purpose of studying physical phenomena, as opposed to purely mathematical applications, it can be best described as a numerical solution to a (macroscopic) problem that models the (microscopic) interaction of objects with other objects or environments via simple object-object or object-environment relationships. A solution is determined via random sampling of the microscopic interactions until a convergent result is obtained (Bielajew 2001). The generation of random numbers for this purpose is thus the key element of a Monte Carlo simulation. True random number generation is in practice not implemented because of its inherent complexity and the difficulty of interfacing it with the Monte Carlo code. As such, it is ‘pseudo’ random numbers which are generated – something which in itself constitutes a field of mathematical study. The pseudo-random quality of Monte Carlo simulations emulates the true stochastic nature of radiation interactions. A sampling method (devoted to which there is again much theory) is then implemented to select and reject generated values according to defined probability distributions. Uncertainty estimation in Monte Carlo simulation is crucial. The stochastic nature of the process means that calculated values are subject to statistical variance.

4.4 Monte Carlo calculation of small-field dose characteristics

4.4.1 Dose calculation for treatment planning

Monte Carlo radiation transport methods represent the best means of dose calculation, however, are not widely adopted in a clinical context because of the high demand on the central processing unit time. Semi-analytical algorithms are more common in clinical treatment planning systems. While of acceptable accuracy for many applications, the use of TPS-calculated dose distributions for very small fields is sometimes dubious. This is compounded in the vicinity of inhomogeneities. Monte Carlo methods provide the potential for more accurate calculation of stereotactic field quanta.
4.4.2 General purpose Monte Carlo radiation transport codes

Monte Carlo radiation transport simulation explicitly models the interaction of individual particles. There is a general scientific consensus that Monte Carlo dose calculation may be used as a standard by which to compare other calculation or measurement methods. There are numerous available Monte Carlo radiation transport codes that may be employed for the investigation of stereotactic fields. These include the Electron Gamma Shower (EGS) codes and in particular the BEAMnrc (Rogers et al. 1995) extension of EGSnrc (Kawrakow and Rogers 2006), the Monte Carlo N-Particle (MCNP) code (Team 2003), and GEANT4 (Agostinelli et al. 2003). The latter two codes were originally developed for high-energy applications. As indicated in Figure 4.2, in the context of stereotactic radiotherapy the EGS codes are most frequently employed. Aside from confidence in the accuracy of the transport algorithms, the reason for the widespread use of this code in particular is likely to be due to the easy implementation of the BEAMnrc package, which makes component-by-component modelling of a linear accelerator readily achievable.

Figure 4.2 A breakdown of thirty-seven relevant scientific papers (employing general Monte Carlo codes) indicates that the Electron Gamma Shower codes are the primary codes employed in the study of stereotactic fields, with EGS4 being employed most frequently in the early 2000s and EGSnrc being employed in the late 2000s.

4.4.3 Studies employing EGSnrc and EGS4 for small-field dose calculation

The majority of papers dealing with Monte Carlo calculations in the context of stereotactic radiotherapy from the late 1990s to early 2000s employed EGS4. It has been common for EGS4 to be used to verify small field measurements undertaken with various detectors (Heydarian et al. 1996; Westermark et al. 2000; Haryanto et al. 2002; Tsougos et al. 2004), often identifying quite significant discrepancies (tens of percent) compared to routinely-employed dosimeters such as ionisation chambers and film (De Vlamynck et al. 1999;
Cheung *et al.* 2000) (Deng *et al.* 2003; Paskalev *et al.* 2003). Poor calculation by treatment planning systems has been demonstrated (Scielzo *et al.* 1998) and the spectral characteristics of stereotactic fields have also been evaluated (Verhaegen *et al.* 1998) – a key aspect of stereotactic radiotherapy field characterisation, and one which is discussed at length in Chapter 5.

Readers are referred to the relevant review paper by the candidate for greater detail (Taylor *et al.* 2011d), but in general one may make several key observations:

- EGS was the Monte Carlo code of choice for stereotactic radiotherapy applications in the 1990s.
- Comparisons of EGS to treatment planning calculations revealed discrepancies of up to 5% and 20% for PTVs in homogeneous and heterogeneous regions respectively.
- Dosimeter measurements have been compared to EGS for field sizes of the order of millimetres, with the Monte Carlo code used to identify issues of detector volume averaging.

EGSnrc is the most widely used full Monte Carlo code for contemporary studies in stereotactic radiotherapy. Numerous authors have investigated small fields via Monte Carlo methods, comparing findings to experimental measurements for linac-based stereotactic fields (Sanchez-Doblado *et al.* 2007; Ding *et al.* 2008; Heydarian *et al.* 2008; Zhao *et al.* 2008) and Cyber-Knife fields (Araki 2006; Francescon *et al.* 2008). In many cases, dosimeters are shown to measure small-field characteristics very poorly, with discrepancies in the order of tens of percent for fields in the mm – cm range (Capote *et al.* 2004; Ding *et al.* 2006; Scott *et al.* 2008). Extrapolation to ‘zero’ field size has been demonstrated via Monte Carlo methods (Cheng *et al.* 2007). Evidence for the characteristics of small fields being highly sensitive to the electron beam incident on the bremsstrahlung target has been established (Scott *et al.* 2009) (Sanchez-Doblado *et al.* 2007) – a concept which shall be discussed in greater detail when describing the model constructed in the present study. EGSnrc has also been used to highlight the limitations of treatment planning systems, which may exhibit inaccuracies of the order of tens of percent compared to Monte Carlo, particularly in the vicinity of heterogeneities (Jones *et al.* 2003; Jones and Das 2005; Lydon 2005; Ding *et al.* 2007; Sterpin *et al.* 2007; Moiseenko *et al.* 2010).

The interested reader is referred to the review paper by the candidate for more detail (Taylor *et al.* 2011d), but in summary one may note several key findings:

- EGSnrc is currently the most frequently employed full Monte Carlo code for stereotactic radiotherapy applications.
– EGSnrc has highlighted poor treatment planning system dose calculations, particularly in the vicinity of heterogeneities.
– EGSnrc has been used to verify detector measurements of stereotactic fields, and has informed the correction of output factors for small field sizes.

4.4.5 Studies employing other available codes for small-field dose calculation
Other codes have also been employed for the study of stereotactic fields, albeit with less frequency than the EGS-based transport codes. Boudou et al (2005) used MCNPX to investigate the potential for synchrotron-based SRT (with beam energies of 50-85 keV). Moskvin et al (2002) verified PENELOPE for Monte Carlo calculation of Gamma-Knife SRS fields against measured data and calculations by other authors (using EGS4). Two years later, Moskvin et al (2004) investigated the effects of inhomogeneities using PENELOPE and a heterogeneous phantom (again, for their Gamma-Knife unit), and found that the TPS underestimated dose by up to 7%. Lax et al (2006) compared pencil beam and cone-convolution algorithms to PENELOPE calculations (for a Varian 2300CD), finding that the pencil beam in particular significantly overestimated dose. Panettieri et al (2007) compared three TPS algorithms to PENELOPE Monte Carlo calculations for a Varian 2100CD. The TPS was found to overestimate dose by up to 10% in the periphery of the gross-target volume.

4.4.6 Monte Carlo codes optimised for radiotherapy applications
The complexity of non-equilibrium dosimetry means that Monte Carlo calculated small-field dose distributions would be the clinical ideal; however, prohibitively long computation times restrict routine clinical use. The discussion thus far has deliberately focused on general purpose Monte Carlo codes which are capable of modelling a large number of particle types and interaction modes over a very broad energy range. The advent of simplified Monte Carlo TPS algorithms that employ some simplifications and approximations are likely to be an improvement over other contemporary TPS algorithms. These include hybrid approaches in treatment planning systems whereby some component of the calculation is undertaken with Monte Carlo whilst others are undertaken using more computationally efficient algorithms (Freud et al. 2007; Freud et al. 2008). Another strategy is to employ a Monte Carlo code which has been entirely optimised for radiotherapy applications. See the TG105 report for greater detail on the clinical implementation of Monte Carlo (Chetty et al. 2007). Table 4.2 summarises available Monte Carlo codes optimised for radiotherapy. Ultimately, it is
probable that a high-efficiency full Monte Carlo model that explicitly simulates all aspects of radiation transport will remain the ultimate desideratum. Such a code, if one could be made to run within a clinically-acceptable timeframe, would be attractive because of its flexibility, in the sense that functionality beyond the most common treatment conditions would be available.

Rogers and Mohan (2000) suggest comparisons in terms of geometry (both homo- and hetero-generous), uncertainties and issues of approximations in the underlying physics. Figure 4.3 shows a comparison of simulation times for various full Monte Carlo and treatment planning optimised Monte Carlo codes, relative to EGS4, achieved when using a simple standard geometry specified by Rogers and Mohan. This indicates the speed that may be achieved with the TPS Monte Carlo implementations.

**Figure 4.3** A comparison of the simulation times of various treatment planning optimised and full Monte Carlo radiation transport codes. The data is based on that compiled by Chetty et al (2007). The times presented are relative to EGS4 (which were performed using the PRESTA algorithm and in a Cartesian geometry, DOSXYZ). The simulations were undertaken for the simple geometry specified by Rogers and Mohan (2000), under which conditions the codes generally agreed within 1%. Note the logarithmic scale.
Table 4.2 A summary of different Monte Carlo codes optimised for radiotherapy applications.

<table>
<thead>
<tr>
<th>Code</th>
<th>Ref.</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEREGRINE</td>
<td>(Cox et al. 1997)</td>
<td>Simulates radiation through collimators using pre-calculated source input. Source obtained using BEAM modelling of linac head. Transport through beam shapers involves several approximations (Schach von Wittenau et al. 2000).</td>
</tr>
<tr>
<td>MCDOSE</td>
<td>(Li et al. 2000; Ma et al. 2002)</td>
<td>Based on EGS4. Modifications (for efficiency) are mostly to electron transport algorithms. Uses source model for accelerator head; input into patient-specific beam modifiers (tongue-and-groove effect in mini-multileaf collimators ignored). Shown to match EGS4 well in various geometries (Li et al. 2000).</td>
</tr>
<tr>
<td>VMC, XMVC, VMC++</td>
<td>(Kawrakow et al. 1996; Fippel 1999; 2000)</td>
<td>Voxel Monte Carlo (VMC) originally intended for electron beams; photons incorporated later (XVMC). Kawrakow and Fippel later developed VMC++, with modifications such as relativistic spin and ‘exact’ multiple scattering (Kawrakow and Bielajew 1998). VMC-based codes being incorporated into commercial TPS packages by several vendors, including Elekta, BrainLAB, Nucletron and Varian.</td>
</tr>
<tr>
<td>MCV</td>
<td>(Siebers et al. 2000)</td>
<td>Monte Carlo Vista (MCV) implemented as part of commercial TPS (Pinnacle, Philips Radiation Oncology Systems). Accelerator head modelled with BEAM, stored and used as input for patient-specific geometries. Patient-specific calculations may be performed using DOSXYZnrc (an EGSnrc usercode), VMC++ or MCVRP – a code developed by Philips (based on EGS4).</td>
</tr>
<tr>
<td>RTMCNP</td>
<td>(DeMarco et al. 1997)</td>
<td>Radiotherapy-oriented MC code, functions as a pre-processor for MCNP4. Only implemented for research applications so far. Source library is used, and RTMCNP converts patient CT into lattice geometry with set number of defined media. Patch used to modify standard transport algorithms.</td>
</tr>
</tbody>
</table>
Ultimately, while such codes will likely be a significant improvement over traditional TPS algorithms, one must be cautious not to make the inference that Monte Carlo dose calculation in a treatment planning system necessarily refers to explicit modelling of all particles and their progeny.

The reason for the strong interest in Monte Carlo methods as applied to stereotactic radiotherapy is the increased confidence it gives in the accuracy of calculated dose distribution, which can be very complex for small fields. Acceptable for some applications, there does exist published Monte Carlo data regarding beams of radiation from medical linacs.

4.5 Linac beam data in the public domain: The Mohan spectra

4.5.1 Overview

Imperative to the characterisation of a treatment beam is knowledge of the spectral qualities. Such data can be employed to determine subsequent dose distributions in the medium of interest. Unfortunately, direct experimental measurement of beam spectra is prohibitively difficult (namely due to the high particle fluxes involved). However, the energy spectra may be determined readily via Monte Carlo radiation transport modelling of a linac. The seminal work in this area was presented by Mohan et al (1985) a quarter of a century ago, and the data therein is still frequently used and referred to today. As such, where generality and reproducibility are deemed to be of high importance in the original works detailed in this thesis, the ‘Mohan spectra’ have often been employed. When this is not the case, an in-house, dosimetrically-matched Monte Carlo model has been employed, and this is discussed in latter sections.
4.5.2 The Mohan spectra

Mohan et al used Electron Gamma Shower (EGS) Version 3 to model Varian Clinac-4, -6, -18, -20 and -2500 linear accelerators. They employed energy cut-offs of 0.01 MeV for photons and 1 MeV for electrons. Energy spectra were scored in a plane perpendicular to the central axis at a specified distance from the target. Annular bins of various sizes were used to score the data. Figure 4.4 shows the energy spectra for 4, 6, 10 and 24 MV linacs. The mean energies are given in Table 4.3.

While the Mohan spectra are useful in some contexts because of their wide availability and the generality and reproducibility that facilitates, thorough characterisation of the beams (which is the objective of this study) necessitates construction of a fully-detailed dosimetrically-matched linac model. This endeavour, undertaken using the Electron Gamma Shower Monte Carlo code, is discussed in detail in the following sections.

<table>
<thead>
<tr>
<th>Radial bin (cm)</th>
<th>Nominal (MV)</th>
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<tbody>
<tr>
<td></td>
<td>4</td>
</tr>
<tr>
<td>0-2</td>
<td>1.51</td>
</tr>
<tr>
<td>2-3</td>
<td>1.41</td>
</tr>
<tr>
<td>3-5</td>
<td>1.38</td>
</tr>
<tr>
<td>5-10</td>
<td>1.34</td>
</tr>
<tr>
<td>10-15</td>
<td>1.27</td>
</tr>
<tr>
<td>15-20</td>
<td>1.17</td>
</tr>
</tbody>
</table>
Figure 4.4 The energy spectra calculated by Mohan et al (1985) for (a) 4 MV, (b) 6 MV, (c) 10 MV and (d) 24 MV beams. In each case, the spectrum is taken for a radial bin of 0-3 cm about the central axis for a 10 x 10 cm$^2$ field, with the exception of the 24 MV beam which has a radial bin of 0-2 cm.
4.6 The Electron Gamma Shower code

4.6.1 Overview
The Electron Gamma Shower (EGS) code is a general purpose package for the Monte Carlo simulation of coupled electron-photon transport in arbitrary, user-defined geometries for energies ranging from a few keV up to hundreds of GeV. In this study, EGSnrc has been employed. EGSnrc is an enhancement of EGS4 (Nelson et al. 1985), and a detailed description of the code may be found in the EGSnrc manual (Kawrakow and Rogers 2006). The transport of photons, electrons and positrons may be simulated in any element, compound and mixture, with particle steps that are random in length rather than discrete. This section of the chapter gives an overview of various aspects of the code, including its validation and suitability for the applications described in this work.

4.6.2 Pseudo-random number generation in EGSnrc
Being the fundamental element of a Monte Carlo code in general, it is first worth mentioning the random number generator. The default random number generator in EGSnrc is RANLUX (James 1994; Luscher 1994), and has a period of over $10^{165}$. The random number generator is portable, and as such results are machine-independent. Multiple levels of ‘luxury’ are available (between 0 and 4). A luxury level of 0 may exhibit some errors; however, for luxury levels above 0 no problems have been reported. With luxury levels of 1 and 4, RANLUX uses around 20 % or 60 % of the total CPU calculation time respectively. A luxury level of 4 requires roughly double the CPU calculation time than for a luxury level of 1 (Kawrakow and Rogers 2006).

4.6.3 Radiation interactions
EGSnrc models a range of photon interaction processes, which are summarised in Table 4.4. The simulation of electron and positron transport is more complicated than for photons. As it slows down through matter, a fast electron (and all the secondary particles created by it) undergoes scores of interactions within its medium. Modelling electron transport with an interaction-by-interaction approach is thus inordinately computationally demanding. However, in the majority of cases, a single collisional event with an atom results in only small changes to the particle’s energy and direction. This thus allows the ‘condensed history’ approach for charged particle simulation, which involves condensing large numbers of transport and collisional processes into a single ‘step’ (Berger 1963). This simplification is ultimately what facilitates the Monte Carlo simulation of charged particles in a reasonable
time frame, but it gives rise to the concept of a ‘step-size’, which can influence the result obtained and thereby introduce artefacts. The cumulative effect of collisions during a given step is taken into account by sampling energy and directional changes from multiple scattering distributions at the end of the step. In EGSnrc, an energy threshold (defined according to the context and desired accuracy) separates these statistically grouped interactions and what are known as ‘catastrophic’ interactions. Bremsstrahlung processes that generate photons above a certain threshold energy $k_c$, and inelastic collisions that generate atomic electrons with kinetic energies above $T_c$, are simulated explicitly and secondaries transported. Sub-threshold events are subject to grouping, and the associated electron transport equations employ what is known as the ‘continuous slowing down approximation’ (CSDA). The electron interactions modelled by EGSnrc are summarised in Table 4.5.

4.6.5 Accuracy of the code
Monte Carlo radiation transport is widely accepted as an accurate means of modeling dose distributions, particularly in regions of electronic disequilibrium such as interfaces of high and low density media. In the field of radiotherapy, EGSnrc is extensively used for Monte Carlo calculations, and has found to be accurate at the sub-percent level in the context of external beam radiotherapy (Chibani and Li 2002; Doucet et al. 2003). Validation of the code is not the purpose of this study, however, there are a number of works that have been carried out which investigate the accuracy of the physics in EGSnrc. In the first instance, the reader is pointed to a list of approximately three hundred papers detailing validation of different aspects of the Electron Gamma Shower code (Kawrakow 2005). In the Monte Carlo investigations carried out here, a step size of 0.25 (maximum fractional energy loss, ESTEPE) was employed. EGSnrc has been shown to produce step-size independent results at a sub 0.1 % level even at interfaces of high Z media in fine geometries (Kawrakow 2000; Verhaegen 2002). The work undertaken in this study employs the PRESTA-II electron-step algorithm with the EXACT boundary crossing algorithm such that the electron transport will go into single-scattering mode within three elastic mean free paths of the boundary, giving the necessary accuracy at peak efficiency.
Table 4.4 A summary of the photon interactions handled by EGSnrc.

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pair production</td>
<td>– Pair production in the field of the nucleus (photon materialises into an electron-positron pair, facilitated by a third body, a nucleus, required for conservation of energy and momentum). Threshold $2m_e c^2$.&lt;br&gt;– Triplet production in the field of atomic electrons; EGSnrc does not explicitly model triplet production, but rather uses the total pair-triplet cross section to sample distances to subsequent pair production collisions. Threshold at $4m_e c^2$.&lt;br&gt;– Reader is referred to reviews on the pair production interaction process for detailed descriptions (Davies et al. 1954; Motz et al. 1969) and a simplistic discussion is presented by Raymond (1972).</td>
</tr>
<tr>
<td>Incoherent scattering</td>
<td>– A.k.a. Compton scattering (Compton and Allison 1935).&lt;br&gt;– Ejection of atomic electron by incident photon; the wavelength of the recoiling photon is altered by an amount dependent upon how much energy is given to the electron.&lt;br&gt;– EGSnrc incorporates binding effects (an advancement on EGS4) and Doppler broadening according to the impulse approximation (Ribberfors 1975).</td>
</tr>
<tr>
<td>Photoelectric</td>
<td>– Dominant interaction at low energies.&lt;br&gt;– Incident photon absorbed by an atom and an electron is ejected with energy equal to that of the photon minus the binding energy of the electron. Atom is left with a vacancy in the ionised shell, and relaxes through fluorescence and emission of Auger and Coster-Kronig electrons.</td>
</tr>
<tr>
<td>Coherent scattering</td>
<td>– Otherwise known as Rayleigh scattering.&lt;br&gt;– Elastic scatter of photons from atoms.&lt;br&gt;– Coherent scattering in EGSnrc uses total coherent scattering cross sections from Storm and Israel (1970) and the atomic form factor from Hubbel and Øverbø (1979).&lt;br&gt;– For molecules, the independent atom approximation is implemented in EGSnrc, although it should be noted that there is some evidence for sensitivity to molecular structure (Johns and Yaffe 1983).</td>
</tr>
</tbody>
</table>
Table 4.5 A summary of the electron interactions handled by EGSnrc.

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bremsstrahlung</td>
<td>Modelled in EGSnrc with the NIST bremsstrahlung cross section database (Seltzer and Berger 1985; Seltzer and Berger 1986), Employed Coulomb-corrected extreme relativistic cross sections above 50 MeV (Koch and Motz 1959), partial wave analysis calculations below 2 MeV (Pratt et al. 1977) and spline interpolation for the range of energies between 2 and 50 MeV.</td>
</tr>
<tr>
<td>Møller &amp; Bhabha scattering</td>
<td>Møller (1932) cross section describes electron-electron scattering and the Bhabha (1935) cross section describes positron-electron scattering. In EGSnrc, binding effects are ignored in the treatment of electron and positron inelastic scattering with atomic electrons.</td>
</tr>
<tr>
<td>Positron annihilation</td>
<td>As positron energy tends to zero, cross section for annihilation tends to infinity (positrons always annihilate at rest if they have not already). Higher order processes (in nuclear field) are less likely than the one-body process, thus EGSnrc restricted to modelling two-photon annihilation.</td>
</tr>
<tr>
<td>Bethe-Bloch continuous energy loss</td>
<td>Assumption: energy is lost continuously along particle path according to the Bethe-Bloch theory (Bethe 1930; Bethe 1932; Bloch 1933). EGSnrc employs the formulae recommended by Berger and Seltzer (1964) and the International Commission on Radiological Units (ICRU 1984b). Restricted stopping power approach employs a mean ionisation energy and EGSnrc employs a density effect correction Sternheimer and Peierls’ (1971).</td>
</tr>
<tr>
<td>Scattering</td>
<td>EGSnrc models electron and positron elastic scattering with the option for inclusion of spin effects or elastic scattering based on the screened Rutherford cross section. For multiple elastic scattering, EGS4 implements Molière’s (1948) theory, but EGSnrc employs an exact formulation for multiple scattering dependent upon the underlying elastic scattering cross sections. EGSnrc also incorporates spin effects in its treatment of multiple scattering.</td>
</tr>
<tr>
<td>Electron steps and boundary crossings</td>
<td>Between catastrophic events, charged particles are transported in short straight-line paths along which energy is lost continuously via collisional interactions and bremsstrahlung (Kawrakow 2000). At the end of each path-length, the multiple scattering angle is determined according to a theoretical distribution. In heterogeneous media, EGSnrc employs an exact boundary crossing algorithm, whereby simulation uses single elastic scattering whenever an electron comes closer to a boundary than some defined distance.</td>
</tr>
</tbody>
</table>
4.6.6 Modelling of linear accelerators using EGSnrc: The BEAMnrc code

BEAMnrc is a Monte Carlo simulation system (Rogers et al. 1995) for modelling radiotherapy sources which was developed as part of the OMEGA project to develop 3-D treatment planning for radiotherapy (with the University of Wisconsin). BEAMnrc is built on the EGSnrc Code System. The code is designed to deal with a range of geometric structures with different symmetries and so on, as suited to the different components of a linear accelerator. It also has the capacity to track each particle’s history and allows the total dose to be separated out into components corresponding to different sources of scattered radiation.

4.7 Modelling the Varian 600C medical linear accelerator with mounted mini-multileaf collimator

4.7.1 Overview

Monte Carlo simulation of radiation transport has been employed in a medical context for a number of decades. Although the complexity of the simulated sources and geometries has historically been limited by computational power, nowadays simulation of the transport of radiation through a medical linear accelerator (linac) is readily achievable. Using Monte Carlo methods to simulate radiation transport through a linac treatment head is an accurate method for the calculation of complex dose distributions, fluences, energy spectra and so on, with the capacity to identify different scattering components. The advent of advanced treatment delivery techniques and the limitations of the dose calculation algorithms in contemporary treatment planning systems mean that the capacity to accurately calculate delivered doses is a useful further clinical verification tool.

A wide variety of Monte Carlo radiation transport codes are now available. One such code, EGSnrc (Kawrakow 2000), is interfaced with BEAMnrc (Rogers et al. 2007), allowing straightforward modelling of, in particular, radiotherapy linear accelerators. Although there is strong interest in Monte Carlo modelling of linear accelerators, the clinical implementation of Monte Carlo methods is not widespread in Australia at present.

If the calculated dose distributions are to be considered to accurately represent those delivered, the simulated beam must be validated against an appropriate set of measured data. This section of the chapter describes the commissioning of a BEAMnrc model of the Varian 600C with mounted BrainLAB MMLC. The geometry of the model is based primarily on specifications provided by Varian. Many parameters are selected via a process of optimising
the match between simulated and measured dose distributions. Justification of the use of certain parameters or simplifications is based on data already in the public domain, and as such a comprehensive literature review is presented in this section.

4.7.2 Key components of the linear accelerator model and simulation parameters

4.7.2.1 Machine specifications

The Varian 600C is a standing gantry accelerator with a maximum field size of 40 x 40 cm². It has a standing-wave guide accelerator structure with a 2.5 MW magnetron and diode type gun. The geometry and material specifications were obtained from Varian under a non-disclosure agreement (NDA), and as such the details provided in this section are limited. Figure 4.5 is an illustration of the basic components of the accelerator that are replicated in the model. An electron beam is made incident upon the upper surface of a target. The (primarily bremsstrahlung) photons produced are first collimated by the primary collimator. Inset into the primary collimator is a flattening filter, which has a complex contour, and functions to flatten the fluence profile of the resulting radiation field. The beam then passes through an ionisation chamber, which is composed of a complex number of layers of plastic, metallic casing and electrodes for charge collection. This is simplified in the model. The mirror is also explicitly modelled, though its influence is likely to be negligible. The Y-jaws sit above the X-jaws, and serve to shape the beam. Below this is a light field reticule. Mounted at a distance of 49.2 cm from the source is the BrainLAB mini-multileaf collimator (MMLC). BEAMnrc facilitates ‘tagging’ components of the model with LATCH bits. This allows the total dose to be separated out into components based on where the contributing particles have interacted, for instance one may select to only evaluate dose resulting from jaw scatter, et cetera.
Figure 4.5 Simplified 2D illustration of the basic components of the linear accelerator. The waveguide etc is not explicitly modelled. Instead, an electron beam (with user-specified characteristics) is made directly incident upon the top of the target. The LATCH numbers for each component are also shown in this figure. This figure is intended to illustrate the concept of treating accelerator components individually, and is not to scale.

4.7.2.2 The primary electron beam

The spot size and energy of the primary electron beam incident on the target is a critical parameter that influences dose and fluence distributions. BEAMnrc allows for multiple source types, the most appropriate of which in this context is a parallel circular beam of electrons with a Gaussian radial distribution, with the option for either a monoenergetic or spectral source.

The assumption of monodirectionality is justifiable because the angular divergence from central axis is typically between 1 and 5 milliradians (Karzmark et al. 1993), the cosine of which is effectively unity.
The beam energy spread is typically restricted to ± 10 % about its central value (Karzmark et al. 1993), and is much smaller in modern linacs with a bending magnet. For a Varian 1800 dual photon linac, the full-width half-maximum of the Gaussian distributed energy spectrum for both 6 MeV and 18 MeV has been shown to be 3 % (Tanabe and Hamm 1985). Where spectral information of the electron source is unavailable, a monoenergetic beam yields acceptable results. The simplest way to determine the energy of the initial electron spot is via an iterative modelling approach that circumvents direct measurement. As a first step, one may estimate the initial energy of the electron beam, which is most likely slightly lower than the nominal energy (6 MeV) in the case of the Varian 600C (Hinson et al. 2008). By simulating a 10 x 10 cm$^2$ field incident upon a voxelated water phantom, depth dose curves may be compared to the equivalent data from water tank measurements. At $D_{\text{max}}$ and beyond, local dose discrepancies should be within 1 to 2 %, and the initial energy should be iteratively adjusted until this condition is met. There is some evidence that smaller field sizes may exhibit greater sensitivity to variations in the primary electron energy, thus allowing more precise refinement (for instance, Siantar et al (2001) suggest 2 x 2 cm$^2$).

Measurement of the spot size and shape is a difficult undertaking. Lutz et al used a slit camera constructed from tightly packed thin strips of lead and cardboard with radiographic film placed beneath the device, though found quantitative measurements of small spot sizes to be difficult, making use of the camera more appropriate for the measurement of relative changes over time (Lutz et al. 1988). Shortly after Lutz et al, Munro and Rawlinson (1988) used large lead collimators, a diode detector and tomographic reconstruction to determine the source size in a range of linacs. They found that the sources (excluding $^{60}$Co) were elliptical with various eccentricities, and had spot sizes between 0.7 and 3.3 mm full-width half-maximum (FWHM). Jaffray et al (1993) employed a similar method, finding spots sizes between 0.5 and 3.4 mm at FWHM. Loewenthal et al (1992) used two Cu-W alloy blocks to create a long slit and obtained a series of images by translating the slit horizontally. The images were then examined with a microdensitometer. Using an analytical model they found the spot size to be 1.5 ± 0.1 mm for both 8 and 18 MV. Von Wittenau et al (2002) used a tungsten rollbar technique to characterise the source spot edge function, and thus size and shape, of a megavoltage linac. Treuer et al (2003) used a micro multileaf collimator and grid field dose measurements using film dosimetry to determine the spatial intensity distribution of the photon source of an Elekta SL25.

Determination of a spot size for use in the BEAMnrc model does not necessarily involve direct measurement. Some of the literature described earlier indicates that the shape of the spot may be elliptical; however, in practice a circular beam spot is sufficient to generate the
experimentally observed photon dose distributions. Depending on the type of beam transport system, the shape of the ellipse may change from being tilted one way, to circular, to being tilted another way, but presuming there are no nonlinear forces its area will not change. It is evident from consideration of the beam optics that the absence of a bending magnet in the Varian 600C reduces the potential for energy spread, radial displacement and radial divergence that may otherwise occur (though the energy slit and doubly-achromatic bending magnets employed by Varian for horizontal waveguide linacs do generate electrons beams well focused spatially/energetically). Once there is an optimal match between measured and simulated depth dose curves from variation of the primary electron energy, the FWHM of the Gaussian beam fluence profile may be determined. Again, this does not necessarily require direct measurement, but may be evaluated by an iterative method of varying the radius of the spot within the simulation so as to best match output with measured results. The results of the aforementioned spot size measurements indicate that 1.5 or 2 mm is an appropriate initial estimate of the FWHM. Dose profiles for large fields from water tank measurements may then be compared to the simulation results, and the FWHM can be varied until profiles match. Depth dose curves should still match, and if this is not the case the energy and FWHM must be adjusted again until this is achieved. A recent study by Sham et al (2008) showed that for very small diameter beams relevant to radiosurgery, the modelled dose distributions critically depend on the diameter of the circular focal spot used in the simulation.

Applying this methodology, the electron beam of the Varian 600C model was chosen to have an energy of 5.65 MeV, with a Gaussian radial distribution of FWHM 2.2 mm. This energy is close to the experimentally reported value (Hinson et al. 2008) of maximum photon energy for a 600C, 5.7 MeV. The FWHM of the spatial distribution is within the expected range based on the aforementioned studies.

4.7.2.3 Target

To produce a beam of photons, the electron beam is made incident upon a target at the top of the linac head. The target design is of key importance and is discussed in detail here. The spectrum of photons generated by MeV electrons incident on the target is complex, being composed of a discrete spectrum of positron annihilation photons and characteristic x-rays superimposed on a continuous bremsstrahlung spectrum. Collisional interaction in the target predominantly results in heat generation, with a small fraction resulting in fluorescence. \( L \)-shell binding energies are small and of little interest compared to \( K \)-shell fluorescence. An electron (or photon) of kinetic energy greater than 69.5 keV can eject a Tungsten (for example) \( K \)-shell electron via collision. Transitions to the \( K \)-shell result in the emission of
characteristic x-rays. Fluorescence emission is a secondary transition process following a primary event. As a result, there is no angular correlation with the incident particle and as such fluorescence emission is isotropic in energy and intensity. Bremsstrahlung, however, is highly anisotropic, with the photons emitted in a direction strongly correlated with that of the incident electron. In a linac, bremsstrahlung is the more relevant process. The energy of the incident electrons is reduced rapidly by Coulombic interaction with the force fields of atomic nuclei, which results in the emission of bremsstrahlung radiation as the electron decelerates. From Figure 4.6 it can be seen that for electron interaction in Tungsten, for instance, the fractional component of the total stopping power corresponding to radiative energy loss is about 36 % for 6 MeV electrons.

![Figure 4.6](image)

**Figure 4.6** The relative (%) contributions of radiative and collisional interactions on the total stopping power of electrons in Tungsten.

The design of the target has a pronounced effect on the photon beam and thus dose distribution, as highlighted by an early paper by Rawlinson and Johns (1973). They found that the 25 MeV Varian Clinac-35 produced a beam of photons noticeably softer to those produced by the 25 MeV Allis Chalmers Betatron. The depth dose curve produced by the former was in fact more similar to the betatron operated at 16 MeV. The significant discrepancy between the two was attributed to the different designs of the target and flattening filter.
Determining angular and spectral information about the bremsstrahlung radiation from targets has been the subject of much research. Approaches to this include experimental measurement, analytical and Monte Carlo calculation. A brief overview of some studies is given heretofore, though it is difficult to separate them by the methodology employed because, as one would expect, most involve cross-comparison between the aforementioned techniques.

Analytical attempts at determination of the spectral and angular bremsstrahlung distributions from electrons incident on targets may be found as early as the 1930s. Sommerfeld (1939) integrated the Bethe-Heitler formula over the angular coordinates of fast electrons exiting a thin target in order to find an approximate solution for the bremsstrahlung produced. This is not appropriate for thick targets where multiple scattering occurs. Schiff (1946) showed that applying Williams’ (1940) theory for the angular distribution of electrons per unit solid angle with Sommerfeld’s (1939) gives an approximation for the energy-angle distribution of the resultant photons, provided that straggling is not significant. Agreement with experiment was shown for high energy electrons (> 20 MeV) incident on tungsten of thicknesses less than about half a millimetre. In a later body of work restricted to thin targets, Schiff (1951) incorporated screening effects. Studies of Schiff’s method for small angles (Sirlin 1957) and multiple scattering (Hisdal 1957) have also been undertaken. Koch and Motz (1959) provide a detailed review of analytical bremsstrahlung calculations up to 1959. Several decades later Desobry and Boyer (1991) presented an overview of Schiff’s method and a comparison with Monte Carlo calculations undertaken with EGS4 (1985). Levy et al. (1974) used the method of Hansen and Fultz (1960) to calculate the thick-target spectrum, employing an approximation for bremsstrahlung radiated when an electron is stopped in a thick target. This was compared with measurements taken using an NaI(Tl) spectrometer with pin-hole collimation of the photons from a 25 MeV accelerator (Tungsten target) and 19 MeV betatron (Platinum target). The same methodology was applied later to an 8 MeV linear accelerator (Levy et al. 1976).

Other researchers have also employed experimental methods to try and evaluate photon fluence information from targets. The yield of photons in the forward direction at the central axis has been shown to be independent of the Z number of the target (Podgorsak et al. 1974), but the total yield of electrons does increase with Z, in agreement with theoretical predictions (Koch and Motz 1959). While the photon fluences for high- and low-Z targets are similar in the forward direction, for high-Z targets there is comparatively greater fluence at large angles (Podgorsak et al. 1974; Faddegon et al. 1991). This is because the impinging electrons undergo greater deviations than in a low-Z material, which correspondingly produce x-rays at greater angles. The electrons undergo fewer collisions after being scattered at a large angle, relative to that in a low-Z target, producing more energetic x-rays at these angles. This means
that, where a low-Z target is employed, it is likely to be more difficult to flatten the beam for an extended field without compromising useful output.

The significant approximations employed in analytical evaluation, and the complexity of experimental measurement of the bremsstrahlung fluence from linac targets means that Monte Carlo radiation transport is a highly suitable alternative. Patau et al seem (1978) to be the first to simulate components of a medical linac (CGR-MeV Neptune) to determine the photon fluence emanating from a target / flattening filter combination. Details of their simulation technique may be found in earlier work (Patau 1971), the most notable improvement upon which was implementation of Koch and Motz (1959) cross sections. Their model consisted of a 5.7 MeV beam of electrons incident on a bilayer target composed of 1 mm thick tungsten brazed onto 2 mm of Copper, downstream of which was a lead flattening filter followed by a collimator. McCall et al (1978) employed the EGS3 code to calculate bremsstrahlung spectra, examining a range of materials for target and flattening filter combinations. EGS4 used bremsstrahlung angular sampling from the Koch and Motz (1959) distribution, superseding a less accurate method in an earlier iteration of EGS4 that generated photons at a fixed angle dependent upon the incident electron direction. EGS4 was employed by Faddegon et al in addition to their experimental measurements mentioned earlier (1991). DeMarco et al (1995) also compared Monte Carlo calculations to the experimental results of Faddegon et al, using the MCNP4A transport code.

The photon target in the Varian 600C is composed of a metal bilayer. There is a block of high-Z material upstream (in which most of the primary electrons are absorbed), brazed onto a relatively thicker block of medium-Z material. The exact dimensions and composition of the target employed in the model are those specified in schematics provided by Varian under a confidentiality agreement, and may not be disclosed here.

To investigate the effect on the photon fluence of using a metal bilayer as opposed to a single-Z material, fluence calculations have been performed using the Monte Carlo code FLURZnrc, which is part of the EGSnrc (2006) distribution. The simulation geometry is illustrated in Figure 4.7 (a). A 6 MeV pencil beam (radius 1.3 mm) of electrons is incident upon the high-Z layer and the fluence is measured in a plane immediately below the medium-Z layer. Two other simulations were performed with same the geometry as the true target: one simulation was performed with the high-Z material only and another with the medium-Z material only. Figure 4.7 (b) shows the fluence (per incident electron fluence) distribution radially outward from the central axis for each of the three target designs. Figure 4.7 (c) shows the fluence resulting from the high-Z target and medium-Z target relative to the fluence from the true
target, expressed as a percentage. For a target composed entirely of the medium-Z material, the photon fluence after the target is much more forward directed. On axis the fluence is roughly equal to that of the bilayer design, but at 1 cm away from the central axis the photon fluence it is about 50 % less. For a target composed entirely of the high-Z material, from a point on axis to a point about 5 cm off axis the fluence drops from being 20 % less than the bilayer design to about 50 % less. The ratio of the total mass radiative stopping power to mass collision stopping power is proportional to TZ (where T is the kinetic energy of the electron). As such, high-Z targets convert a larger proportion of the electron’s energy into bremsstrahlung compared with lower-Z targets. These findings agree with the experimental results discussed earlier. The bilayer design results in a photon fluence that is higher than both of the single-Z targets simulated here and is less forward directed, distributing the fluence more broadly. This is useful because ultimately a flat fluence profile is desired.

The flattening filter, the next component in the linac beneath the target, functions to achieve a flat profile by preferentially attenuating photons on the central axis where the fluence is higher. Clearly a flattening filter could be designed to accomplish this regardless of the target design, however, if the photon fluence from the target is too forward directed then greater attenuation will be required and ultimately will result in an efficiency loss.
Figure 4.7 (a) Diagram illustrating the geometry of the target and electron source as modelled using FLURZnrc. The simulation assumes radial symmetry. (b) shows the photon fluence at the exit of the target. Three simulations have been performed using FLURZnrc. The first models the target with dimensions and composition as specified by Varian; the corresponding curve is the solid line labelled as “High-Z brazed on medium-Z target”. Two other targets were modelled, both using the same dimensions as the true target, but being composed fully of the high-Z material in one case and the medium-Z material in the other. (c) shows the fluence at the exit of the two latter target designs, relative to the fluence from the true bilayer target (expressed as a percentage).
Primary collimator and flattening filter

The primary collimator is a diverging conical structure made of a high-Z material with a small opening at the top, above which is the target. The primary collimator is designed to allow only forward scattered photons to escape the linac. The large opening at the bottom of the cone is typically of dimensions such that a circular beam of approximately 50 cm would be incident at 100 cm source-surface distance (SSD) in the absence of secondary collimators (Metcalf et al. 1997). The primary collimator also helps prevent head leakage. The influence of the primary collimator on the absorbed dose beneath the linac is relatively small. An early study by Nilsson and Brahme (1981) found that for a 6 MV beam, 1.5% of the integral dose was due to collimator scattered photons. Faddegon et al (1999) found that scatter from the primary collimator contributes about 3% of the dose at $D_{max}$ on the central axis. Similarly, Mohan et al (1985) found that 2.8% of the photons reaching a point at 100 cm SSD had been scattered from the primary collimator.

In the Varian 600C, the flattening filter sits within the primary collimator. The former is also composed of a high-Z material, though different to that of the collimator. As has been discussed in the previous section, the design of the flattening filter has a pronounced effect on the photon fluence.

Levy et al (1974) measured the bremsstrahlung spectra from a 25 MeV linac and a 19 MeV betatron, both of which have lead flattening filters, and compared the results to analytical calculations. They felt that the use of low-Z materials for flattening filters was preferential. Podgoršak et al (1974) had earlier performed a comparison of Al and Pb flattening filters, and found that a photon beam may be flattened as readily with an Aluminium target/flattening filter combination as with a Lead target/flattening filter combination. However, it is Monte Carlo simulations that have really provided the insights into the influence of flattening filter design on the photon fluence.

McCall et al (1978) investigated a range of flattening filter materials with the Monte Carlo technique, and found that while low-Z flattening filters are able to produce a flat field, there are practical difficulties with their implementation because of their relatively large size and they exhibit a significant energy spread in large fields. They felt that a medium-Z material was far more preferable. Mohan et al (1985) investigated a range of Varian linear accelerators with EGS3 (Clinac-4, Clinac-6, Clinac-18 and Clinac-2500) and modelled the flattening filters therein with greater accuracy than had been previously performed. The cross sectional variation of the flattening filter thickness results in spectral variation arising from selective hardening of the beam. The average energy of the beam is typically lower for peripheral
regions (Kahn 2003). This softening is observed in the results of Mohan et al (1985), and in the results of Lovelock et al (1995), who found that at a distance of 20 cm away from the central axis, the beam was about 25% softer with the flattening filter in place, and only 10% softer without it. Lee (1997) employed EGS4 to investigate the effects of the flattening filter on the properties of the photon beam from a Varian 2100C operated at 6 MV, and similarly showed that beam hardening decreases with off-axis distance (softening by about 27% at 20 cm). Faddegon et al found that at the central axis, scatter from the flattener contributes about 4% of the dose. This agrees with the study by Mohan et al, wherein 3.5% of photons reaching a point at 100 cm SSD had undergone scattering interactions in the flattening filter.

They also found that they could reproduce the flatness of a field from a steel flattening filter with one made from brass (which was chosen because of the relative ease of machining) to within 2%, however the useful output was reduced by over 20% (Faddegon et al. 1999).

The flattening filter in the Varian 600C has a complex shape, and the corresponding component module in the BEAMnrc model of the linac is the most detailed of all the modules (excluding the mini-multileaf collimator). The dimensions and composition of the primary collimator and flattening filter in the model are based on the specifications provided by Varian under a confidentiality agreement. The next component downstream from the flattening filter is the monitor chamber.

4.7.2.5 Monitor chamber

After the flattening filter, the beam passes through twin parallel plate multichannel ionisation chambers. These consist of layers of typically either mica or kapton with gold plated electrodes. The function of the ionisation chamber is to integrate charge and thereby monitor the dose output in real-time during delivery, and may also be used to monitor beam flatness and symmetry (by being divided in half and mounted such that one chamber plate is rotated at 90° to the other).

One key issue with monitor chambers is the potential for backscatter from downstream collimation devices to influence the signal. Clearly, for small fields, this effect will be more pronounced because of the increased backscatter. If this occurs, the ultimate effective output of the linac will be lower than the desired number of monitor units. This effect is dealt with automatically in measured output factors in a clinical context, or minimised by improved design of monitor chambers (with use of a backscatter plate). In Monte Carlo simulations of dynamic delivery, the situation may be more complex because the number of particle histories to be simulated may need to decrease with increasing backscatter (i.e. decreasing field size).
This is only relevant for absolute dosimetry and explicit modelling of charge in monitor chamber.

This problem has been investigated experimentally in a number of studies. These include photoactivation of a foil placed downstream from the target (Patterson and Shragge 1981), beam current measurements from the target (Huang et al. 1987) and water tank measurements with an ionisation chamber with and without a sheet of Lucite downstream of the monitor chamber (Luxton and Astrahan 1988). Pulse counting (Sharpe et al. 1995; Yu et al. 1996) and charge integration (Lam et al. 1998) from the target have also been applied. Monte Carlo simulations have also been performed to investigate backscatter to monitor chambers. Liu et al (1997a) compared Monte Carlo calculations (Liu et al. 1997b) to a pulse counting method (Sharpe et al. 1995) for a Varian 2100C, and later investigated backscatter more explicitly via Monte Carlo (BEAM) (Liu et al. 2000). A Monte Carlo model of a Siemens unit found that backscatter to the monitor chamber was < 1 % for all jaw positions (Verhaegen and Das 1999). A study by Verhaegen et al (2000) of the Varian 2100C showed that a correction of 2-3 % was required for small fields when Monte Carlo is used to determine output factors or model dynamic fields.

The monitor chamber in the Varian 600C is composed of numerous layers of different materials. Some simplification has been employed in implementation of the model used in the present study. Ionisation chambers are typically filled with gas (nitrogen in the case of mica chambers and oxygen-enriched air in the case of kapton) and then sealed to avoid the complications of gas density correction et cetera (Metcalfe et al. 1997). In this model, it is assumed that the influence of the gas composition is negligible, and normal air has been used with the definition provided by the ICRU (1989) (C, O, N and Ar with a density of 1.2048 mg/cm$^3$). Furthermore, the many layers in the monitor chamber have been simplified in the model into a more simplistic set of a total of fourteen layers of material. The total thickness of each of the materials traversed by the beam is still the same (i.e. several thin layers of each material are simplified into single thick layers of equivalent thickness for geometric simplicity). Ultimately, the influence of the monitor chamber on the photon fluence is not significant.

4.7.2.6 Jaws

Downstream from the monitor chamber is a mirror that reflects the field light, the latter thus kept out of the primary beam. The field light mirror is a very thin non-retracting polyester sheet, the influence of which on the beam is not significant, but is nonetheless incorporated in
the model. Further downstream is a secondary collimation system consisting of two pairs of high-Z metal blocks called jaws. In the Varian 600C, these function to produce field sizes between 0 x 0 cm² and 40 x 40 cm² (at the patient plane). The jaws are thick and, as a result, one pair is mounted above the other, which does not seem to influence dose profiles. The upper (Y) jaws are mounted such that they travel in an arc-like motion about a point of rotation defined by the source. This design means that the angle closely matches the angle of beam divergence at different field sizes. Unlike the upper jaws, the lower (X) jaws tilt to match this angle and slide back and forth in a plane perpendicular to the beam axis.

Some approximation has been employed in the jaw design in the model. The arc motion of the Y-jaws is not explicitly modelled, nor is the tilting of the X-jaws, but the faces of the jaws are altered to reflect angular changes at different field sizes. The jaws are modelled with a trapezoidal shape whose face angle is chosen to match the divergent beam. This has a minimal effect on the resulting dose distributions. The discrepancy between the thicknesses of material traversed by the beam through the real and modelled jaws can be estimated from geometrical considerations. The jaws in the model will present a greater thickness to an incoming ray compared to the true jaws, increasing with the angle (i.e. field size) up to a maximum possible discrepancy of approximately 10 mm thickness at the far edge defined by the angle of the primary collimator. An estimate of the discrepancy in fluence is obtained by modelling a 6 MeV photon spectrum (defined by Mohan et al (1985)) with FLURZnrc through slabs of the high-Z material corresponding to the two thicknesses. In a region immediately below the jaws, the fluence from transmitted photons is about 0.25 % of the unshielded fluence. The maximum discrepancy possible will occur for a point about 10 cm beyond the edge of a 40 x 40 cm² field and corresponds to approximately 0.13 % of the unshielded fluence. For smaller field sizes this discrepancy will be significantly less; a maximum of < 3 mm along the line defining a point 50 cm off-axis, for instance, for the 9.8 x 9.8 cm² jaw field typically implemented when the mini-multileaf collimator is employed.

4.7.2.7 The BrainLAB m³ MMLC

At the William Buckland Radiotherapy Centre, a BrainLAB m³™ mini-multileaf collimator (MMLC) is mounted on the Varian 600C as a tertiary collimation device. The maximum effective field size is 9.8 x 9.8 cm² at isocentre, shaped by 26 leaf pairs: 14 of width 3 mm, six of width 4.5 mm and an outer set of six with 5.5 mm width (nominal widths are at isocentre). The leaves move orthogonally to the beam axis, and have a complex tongue and groove cross-section. This cross section is also shaped to match the beam divergence across the field. The leaf edges are not curved, but rather have three angled straight edges. Cosgrove
et al (1999) reported that each section corresponds to one third of the total length of the leave edge (totalling 6 cm), but this was contradicted by Belec et al (2005)\(^\dagger\) who stated the upper, middle and lower sections were 2.3, 1.4 and 2.3 cm respectively. The middle section is milled parallel to the beam axis to match the (non-) divergence of the beam when centred. The upper section is at an angle corresponding to the beam divergence when the leaf is fully extended (5 cm beyond the centre), and the angle of the lower section corresponds to full retraction (5 cm back from the centre). The true geometry of the BrainLAB m\(_3\) was obtained from BrainLAB directly under a non-disclosure agreement. For that reason, the level of detail that may be revealed within this work is restricted. The end of the leaf is illustrated in Figure 4.8, the leaf side is shown in Figure 4.9, a three-dimensional representation is provided in Figure 4.10 and Figure 4.11 illustrates the complexities of the leaf bank as a whole.

\[\theta = 2.862°\]

**Figure 4.8** A sketch showing an example of the end shape of one of the 26 leaves in the BrainLAB m\(_3\). There are 30 nodes defining each side of the contour of the leaf end. The circle corresponds to the screw.

**Figure 4.9** A sketch showing example of the side shape of one of the 26 leaves in the BrainLAB m\(_3\).

\(^\dagger\) *Nota bene* there is a small error in Figure 2 (c) of Belec et al (2005): the lower section of the leaf is erroneously shown to be 1.3 cm thick. This error did not feature in their code.
**Figure 4.10** A three-dimensional rendering of a single leaf of the BrainLAB MMLC.

**Figure 4.11** A schematic of the leaf bank indicating dimensions and the complexity and divergence of the leaves. A 0.1 mm leaf-gap is assumed.
Xia et al (1999) provide an early evaluation of the BrainLAB MMLC attached to a Varian 2100C operated at 4 MV. They found that, particularly for large circular fields, MMLC step artefacts are clearly evident for the 80 % isodose curve, but are less pronounced for the 20 % isodose curves. The penumbras of the circular fields were comparable to square fields, but somewhat broader than the standard conical collimators employed in stereotactic radiosurgery. The penumbras were sufficiently narrow (1.8 – 2.6 mm) to facilitate collimation for small target volumes with varying field shapes. The interleaf leakage was shown to be about 2 %, while intraleaf leakage was 1.3 % (based on film measurements). The leaf position precision was found to be sub-millimetre. In the same year, Cosgrove et al (1999) published commissioning information for the BrainLAB MMLC, mounted to a Varian 2100C operated at 6 MV. The beam penumbras were found to be invariant with increasing square field sizes and asymmetric fields, and varied non-linearly with diagonal straight edges. They found the average intraleaf transmission to be 1.9 % and interleaf leakage to be 2.8 %. The average transmission through abutted leaves positioned at 4.5 cm off-axis (it is standard practice to close leaves off-axis) was found to be 4.5 %. With the leaves closed centrally, this increased to 15 %. Cheung et al investigated the potential for multileaf collimators (MLC) to replace beam blocks in the treatment of nasopharyngeal carcinoma, comparing the BrainLAB MMLC to a Varian MLC with 40 leaves of 1 cm projected width at isocenter. To this end, they found both were acceptable alternatives to blocks. They found that the MMLC, with its smaller effective penumbra, was more appropriate for the treatment of tumours close to critical structures, being limited only by its maximum field size (Cheung et al. 1999). Monk et al (2003) compared the BrainLAB m3 to the 120 leaf multileaf collimator of the Varian 2100EX for stereotactic conformal radiotherapy fields, the latter possessing 5 mm leaves. Results showed that the MMLC provided improved planning target volume (PTV) conformity and normal tissue sparing than the MLC, however, the improvements were small. Chern et al (2006) performed a similar study, comparing a BrainLAB MMLC to the Varian Millennium MLC. Again, the MMLC consistently provided better target conformity and normal tissue sparing than the MLC for stereotactic radiosurgery, using dynamic conformal arcs. Jin et al (2005) studied the BrainLAB MMLC for dynamic conformal arcs and intensity-modulated radiosurgery, comparing it to 5 mm and 10 mm MLCs. They found significant dosimetric differences between the conformity indices and target coverage of the three MLCs, increasing with field size, for dynamic conformal arcs. For intensity modulated radio- surgery/therapy, the difference was less significant between the 3 mm and 5 mm MLCs, but more significant between the 3 mm and 10 mm MLCs.
A number of BEAMnrc component modules have been made available for modelling multileaf collimators (Rogers et al. 2007), including VARMLC, MLCP, MLCQ, MLCE and DYNVMLC. Belec et al (2005) developed a component module based on VARMLC that is suitable for modelling the BrainLAB m₃. For a comprehensive description, the reader is asked to refer to Belec et al (2005). The leaf shape was simplified from the true leaf shape. The interleaf air gap was chosen to be 0.14 mm. The angle of the top and bottom edges of the leaf end was 1.8º. The m₃ is modelled by Belec et al (2005) as three component modules on top of each other, corresponding to the upper, central and lower sections of the leaves. The true leaves have three tongues and three grooves on each side of the leaf. In the model, there are one tongue and four grooves on the left side, and four tongues and one groove on the right side, with a combined thickness equal to the true leaf so as to result in the same beam attenuation. The MMLC leaves were modelled as a tungsten alloy, W:Ni:Fe (95:3.4:1.6), with a density of 18 gcm⁻³ (Boyer et al. 2001).

Implementation of Belec’s code in this work would have necessitated re-writing the model. Referring back to the earlier description of the true geometry of the MMLC, one must note that the Belec model corresponds only to the model of m₃ that is fitted to linacs that already have an in-built MLC. The linac used in this work does not have an MLC, and consequently the geometry of the m₃ used here differs slightly from that modelled by Belec et al (2005). This aside, unfortunately, the portability of the Belec et al (2005) code is evidently limited and, after several months of attempts, there was ultimately no success in running the code error-free. Numerous FORTRAN compilers were tested, and much of the code was re-written to remove the numerous tests for equality – which are prone to errors resulting from limited numerical precision – and replace them with more robust tests.

As a corollary of the present work, an in-house model of the BrainLAB m₃ is currently being developed, which models the MMLC in full geometric detail. The code elegantly breaks the structure up into trapezoidal ingots, allowing the MMLC to be simulated in full detail with fewer numbers of regions than the (relatively simplistic) model of Belec et al (2005). This results in greater computational efficiency. Furthermore, the trapezoidal regions allow for more elegant spatial orientation checking algorithms, with a factor of four fewer computations per region than the Belec model, again increasing the computational efficiency. This model is still a work in progress. As such, the present approach is to employ the standard VARMLC code and vary the geometrical definition to best match the BrainLAB m₃. This has been shown by collaborators at the Queensland University of Technology to produce dose distributions that match measured doses to a high degree of accuracy (Kairn et al. 2010b).
The geometric parameters of the MMLC model chosen to best match experimentally measured data are listed in Table 4.6. An indication of the modelled leaf shape is given in Figure 4.12. Different options and simplifications concerning the transport physics are facilitated by BEAMnrc, and these are discussed in the following section.

**Table 4.6** Description of variables and their attributed values as used in the VARMLC model of the BrainLAB MMLC. All units are in millimetres.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaf thickness</td>
<td>64</td>
</tr>
<tr>
<td>Radius of leaf end</td>
<td>427.3</td>
</tr>
<tr>
<td>Screw width / height</td>
<td>0</td>
</tr>
<tr>
<td>Height of tongue &amp; groove</td>
<td>2.2</td>
</tr>
<tr>
<td>Width of tongue &amp; groove</td>
<td>0.003</td>
</tr>
<tr>
<td>5.5 mm leaf (x6) width</td>
<td>2.828</td>
</tr>
<tr>
<td>4.5 mm leaf (x6) width</td>
<td>2.313</td>
</tr>
<tr>
<td>3.0 mm leaf (x14) width</td>
<td>1.538</td>
</tr>
</tbody>
</table>

**Figure 4.12** An illustration of the geometry of VARMLC leaf ends, as employed in the present model of the BrainLAB MMLC.
4.7.3 Radiation transport simulation parameters

EGSnrc and BEAMnrc allow for various radiation transport options. The key simulation parameters broadly implemented in this study are summarised here:

- The (global) maximum fractional energy loss per particle step is 25%.
- The maximum first elastic scattering moment per step is 0.5.
- The ‘EXACT’ boundary crossing algorithm (BCA) has been implemented. This means that the algorithm will enter into single-scattering mode at a distance from a boundary determined by the ‘skin depth’ for BCA.
- The aforementioned skin depth for BCA is set to three elastic mean free paths from the boundary (this yields peak efficiency without compromising accuracy).
- The electron step algorithm (used to account for lateral and longitudinal correlations in a condensed history step) is PRESTA-II.
- Spin effects for elastic electron scattering are implemented.
- Electron impact ionisation is not implemented.
- ‘Simple’ bremsstrahlung angular sampling is used – i.e. only the leading term of the Koch-Motz distribution is used to determine the emission angle of bremsstrahlung photons.
- Bethe-Heitler bremsstrahlung cross sections are used with Coulomb correction above 50 MeV.
- The differential cross sections for Compton scattering are generally determined according to the Klein-Nishina formula.
- ‘Simple’ pair angular sampling is implemented to determine the positron / electron emission angles (relative to the incident photon) – i.e. only the leading term of the angular distribution is employed.
- Photoelectron angular sampling is not employed, and as such photoelectrons are given the direction of the incident photon from which they were generated.
- Coherent Rayleigh scattering is generally not employed to avoid increasing computation time, since coherent scattering is less relevant outside very low energy applications.
- Atomic relaxation (after Compton or photoelectric events) is not implemented.
- Storm-Israel photon cross sections are used.

Various methods are available for the reduction of statistical uncertainty, and these are discussed in the following section.
4.7.4 Variance reduction

An overview of variance reduction methods employed for in-field dose calculations is given here. The need for variance reduction arises because of the nature of Monte Carlo dose computation – i.e. a numerical approach is taken to determine a convergent result, which therefore has associated with it some level of statistical noise. Variance reduction techniques function to reduce the statistical uncertainty without compromising the accuracy of the result. One means of reducing this statistical uncertainty would be to model a greater number of particle histories. The key benefit of more elegant variance reduction methods is that the uncertainty may be reduced without increasing the simulation time to the extent that would be required to achieve the same uncertainty via the aforementioned approach.

One broadly implemented variance reduction method is *range rejection*. This involves the termination of a charged particle history if its residual range is such that it cannot escape the current region. A subroutine in the transport code computes tables of residual ranges to a (user-specified) threshold energy for each medium as a function of electron energy. These residual ranges are the pathlengths travelled by electrons slowing to the cut-off energy if they do not undergo any discrete interactions. Bremsstrahlung photons that would have been generated by the electrons as they slow down are assumed not to escape from the region in which the electron is terminated. The impact of this approximation can be minimised by specifying a maximum energy for which a particle history can be terminated. This increases the potential for bremsstrahlung to escape from the region in which the particle which gave rise to it is unable to escape from.

The statistics of bremsstrahlung photons borne of electron interactions can be improved via a variance reduction technique called *bremsstrahlung splitting*. In this study, directional bremsstrahlung splitting (DBS) is employed. The broad principle is that bremsstrahlung photons aimed towards a field of interest (enveloping the treatment field) are split at the point of creation, and those beyond the field are not. DBS uses a combination of interaction splitting for bremsstrahlung, annihilation, Compton scattering, pair production and photo-absorption and Russian Roulette to achieve improved simulation efficiency. For a detailed description of the DBS algorithm, readers are referred to Kawrakow *et al* (2004). For each event, DBS splits the photons a user-specified number of times (NBRSPL). The resulting photons each have their weighting multiplied by $\text{NBRSPL}^{-1}$. The optimum splitting number is approximately 1000. The field of interest is defined by the treatment field size and source-surface distance (SSD). For a 10 x 10 cm$^2$ field at 100 cm SSD, a splitting field radius of 10 cm is sufficient (Kawrakow *et al*. 2004). Clearly, DBS was not implemented where the out-
of-field doses were of key interest, in which case its implementation would have had a detrimental influence.

4.7.5 Comparison of simulation results with measured data: Varian 600C

4.7.5.1 Overview

To ensure that the model is trustworthy in its prediction of complex dose distributions, the model must be commissioned against measured data. This is done by comparison to measured dose profiles and depth dose curves where the doses are relatively ‘well known’. Depth dose curves and dose profiles for modelled data have been compared to water tank measurements (0.13 cm$^3$ ionisation chamber, Wellhöfer, USA) for a number of arrangements.

To illustrate the accuracy of the model, a standard 10 x 10 cm$^2$ field is shown; also shown is a 30 x 30 cm$^2$ field so as to demonstrate good agreement at larger field sizes. Large field sizes are, however, less important to this study, since we are dealing with stereotactic fields which when using the BrainLAB MMLC are restricted to a maximum field size of 9.8 x 9.8 cm$^2$. The agreement of smaller fields is shown in the subsequent section dealing with the accuracy of the MMLC model. Also shown here is a half-blocked (i.e. off-axis) 20 x 20 cm$^2$ field and a 40 x 40 cm$^2$ field (with dose profiles measured diagonally across the field) which function to demonstrate the limitations of the model.

During commissioning of the model, parameters within the model are iteratively adjusted to optimise the match between simulation and measurement. One key parameter is the geometry and energy of the electron beam incident on the target.

4.7.5.2 Summary of electron beam parameters

Once the geometry of the linac has been accurately represented in the model, the key simulation parameters that must be adjusted to obtain the best match between experiment and the model relate mostly to the electron beam which is incident upon the target. The best match for the linear accelerator at the William Buckland Radiotherapy Centre has been achieved with the following electron beam parameters:

- A monoenergetic electron beam of energy 5.65 MeV,
- Incident perpendicular to the target surface, such that $(u,v,w) = (0,0,1)$,
- A circular beamspot and
- A Gaussian beam profile with a full-width half-maximum of 220 µm.
These parameters have been determined based on matching of depth-dose curves and dose profiles for a number of different fields. Typically, $5.1 \times 10^9$ histories were modelled on 10 processors (AMD Barcelona 2.3 GHz quad core) requiring a total of approx. 45 hours. This is sufficient to achieve statistical uncertainties in (subsequently scored) doses of a fraction of a percent in 2 mm voxels.

### 4.7.5.3 Comparison of measured and modelled fields

When commissioning a commercial treatment planning system, it is necessary to input measured dose profile data. Similarly, refining of parameters in the Monte Carlo model is necessarily based upon measured profiles. The standard reference field is $10 \times 10\text{ cm}^2$. Figure 4.13 shows a depth dose curve in water for a $10 \times 10\text{ cm}^2$ field at 100 cm source-surface distance (SSD) and dose profiles at depths of 1.5, 5 and 10 cm. The simulated depth dose curves at profiles at multiple depths all match experimental data very closely. Large field sizes are particularly sensitive to the shape of the electron beam incident on the target. Figure 4.14 shows a depth dose curve in water for a $30 \times 30\text{ cm}^2$ field at 100 cm source-surface distance (SSD) and dose profiles at depths of 1.5, 5 and 10 cm. Figure 4.15 corresponds to a $40 \times 40\text{ cm}^2$ field at 95 cm SSD, where the dose profiles have been taken diagonally across the field at depths of 1.5, 5 and 10 cm. This reflects the increased influence of the primary collimator. There is a noticeable discrepancy between the modelled and measured data mostly related to a pronounced asymmetry in the experimental data. The inherent symmetry of the modelled geometry makes this effect prohibitively difficult to match. While not ideal, this is not a critical issue because the present study is concerned with small field sizes, which exhibit very good agreement. Figure 4.16 shows crossplane profiles at depths of 1.5, 5 and 10 cm for a half-blocked $20 \times 20\text{ cm}^2$ field at 95 cm SSD; i.e. with y-jaw positions of -10 cm and +10 cm and x-jaw positions of -20 cm and 0 cm from the central axis, the latter having coordinates of (0,0). The modelled field is slightly flatter than the measured field, being noticeably different towards $x = -20\text{ cm}$, where the calculated dose has a smaller penumbral ‘horn’.

For the reference ($10 \times 10\text{ cm}^2$) case, using a cubic spline interpolation on the measured data and no convolution for finite detector size, comparison with the calculated data reveals an average agreement within 0.3% over the full range, with discrepancies of up to ~3 to 4% in the penumbral region. Considering not only statistical uncertainties in the model but also variation that occurs between experimental measurement, compounded with issues relating to the sensitive detector volume and spatial location, this may be considered an acceptable level of agreement.
The modelled depth dose curve has a finer resolution (1 mm) in the region of maximum dose ($D_{\text{max}}$). The conformality of the modelled depth dose curve to the measured curve reflects the accuracy of the electron beam energy. In the build-up region of the depth dose curve there is a small discrepancy. This observation is not specific to the work described here, but is a widely reported phenomenon. BEAM simulation of a Varian 21EX 18 MV beam with a 40 x 40 cm$^2$ field predicted doses lower than that measured by more than 10% at 1 mm depth and 5% at 1 cm depth in water (Ding 2002). In a study using the radiation transport code PEREGRINE, Hartmann-Siantar et al (2001) took the somewhat dubious step of increasing the number of electrons incident on the surface by 50% so as to achieve a better match with experiment, without actually postulating the source of the additional electrons. Ding (2002) investigated the influence of a 2 mm Pb foil on contaminant electrons and reached the conclusion that such a source of additional contaminant electrons could not explain the dose discrepancy. A further study by Ding et al (2002) found that photoneutron dose did not explain the discrepancy in the build-up region. A study by Abdel-Rahman et al (2005) concluded that inaccurate modelling of triplet production was also not the source of the discrepancy in surface dose.

Ultimately, the broad consensus is that the discrepancy is not a modelling artefact, but is due rather to the limitations on measurement accuracy in the build-up region, and is typically explained by the steep dose gradient and the uncertainty in the position of the ionisation chamber. Studies by Kawrakow (2006) and McEwen et al (2008) have shown that the standard shift for cylindrical ionisation chambers (-0.6r, where r is the internal cavity radius) recommended in dosimetry protocols is incorrect, which can result in errors of around 0.5 mm and up to 1.4 mm depending on chamber design. These studies have shown that, once the accelerator geometry and electron beam parameters have been accurately modelled, use of the correct effective point of measurement results in a match with experimental data of 0.2 mm or better. Parallel-plate ionisation chambers, rather than cylindrical chambers, are recommended for measurement in the build-up region.

The high level of agreement between modelled and measured data indicates that the geometry and electron beam parameters have been simulated correctly, and that subsequent simulations are likely to truthfully predict what would be observed experimentally.
Figure 4.13 A comparison of doses measured at the William Buckland Radiotherapy Centre (WBRC, solid line) and doses calculated via BEAMnrc (dashed line) for a Varian 600C (6 MV) with a 10 x 10 cm² field, at 100 cm SSD. A cubic spline was employed to fit data. Mean agreement is sub-percent. (a) Depth dose curve in water, (b) dose profile at 1.5 cm depth, (c) dose profile at 5 cm depth, and (d) dose profile at 10 cm depth. The 10 x 10 cm² field is the ‘standard’ field in radiotherapy, being used as a reference cases in multiple contexts; it is thus important that the model reproduces this field accurately. The 10 x 10 cm² is the maximum field size of interest in this study.
Figure 4.14 A comparison of doses measured at the William Buckland Radiotherapy Centre (WBRC, solid line) and doses calculated via BEAMnrc (dashed line) for a Varian 600C (6 MV) with a 30 x 30 cm$^2$ field at 100 cm SSD. A cubic spline was employed to fit data. Mean agreement is within ~2 %. (a) Depth dose curve in water, (b) dose profile at 1.5 cm depth, (c) dose profile at 5 cm depth, and (d) dose profile at 10 cm depth. Although not strictly relevant to this study, it is nonetheless reassuring that the model is able to accurately reproduce experimentally measured dose distributions with such a broad field size.
Figure 4.15 A comparison of doses measured at the William Buckland Radiotherapy Centre (WBRC, solid line) and doses calculated via BEAMnrc (dashed line) for a Varian 600C (6 MV) with a 40 x 40 cm\(^2\) field at 95 cm SSD: (a) Depth dose curve in water, (b) diagonal dose profile at 1.5 cm depth, (c) diagonal dose profile at 5 cm depth, and (d) diagonal dose profile at 10 cm depth. This figure demonstrates the limited accuracy of the model for very large field sizes, particularly where the primary collimator begins to significantly influence the final treatment field. Although such large fields are irrelevant for the purposes of this study, it is nonetheless of interest to illustrate the extent to which the model is able to accurately predict doses.
Figure 4.16 A comparison of doses measured at the William Buckland Radiotherapy Centre (WBRC, solid line) and doses calculated via BEAMnrc (dashed line) for a Varian 600C (6 MV) with a half-blocked 20 x 20 cm$^2$ field at 95 cm SSD: (a) A scatterplot showing the spatial location of 10,000 particles scored at an SSD of 95 cm, (b) dose profile at 1.5 cm depth, (c) dose profile at 5 cm depth, and (d) dose profile at 10 cm depth. This figure also illustrates the limitations of the model at very large field sizes, which while not of interest in this study (which deals with stereotactic fields $< 10 \times 10$ cm$^2$ that are predicted very accurately by the model) are nonetheless interesting.
4.7.6 Comparison of calculations with measured data: Varian 600C with MMLC

4.7.6.1 Overview

As stated earlier, since the geometrically-accurate high-efficiency model of the BrainLAB MMLC being developed in-house is not yet commissioned, a different approach using the ‘VARMLC’ component module available with the standard BEAMnrc package was tailored to suit the mini-multileaf collimator. Despite the more ‘generic’ geometry, this has been shown to reproduce experimental dose distributions to a high degree of accuracy in the case of the BrainLAB MMLC (Kairn et al. 2010a; Kairn et al. 2010b). In this section of the chapter, an accurate match between measured and modelled dose distributions is demonstrated. This chapter deals with development and commissioning of the model, whilst the subsequent chapter involves application of the model for characterisation of the stereotactic fields in terms of spectral qualities, scatter and so forth.

4.7.6.2 Comparison of measured and modelled MMLC-defined fields

Figure 4.17 through to Figure 4.22 show dose profiles in the inplane and crossplane directions at 5 cm depth in water at 95 cm source-surface distance (SSD), obtained using a Scanditronix IC6 (0.06 cm³) ionisation chamber. Modelled and measured dose distributions are compared for:

- 6 x 6 mm²,
- 24 x 24 mm²,
- 42 x 42 mm²,
- 60 x 60 mm²,
- 80 x 80 mm² and
- 98 x 98 mm² fields.

Figure 4.23 shows percentage depth dose (PDD) curves at 95 cm SSD. Modelled and measured dose distributions are compared for:

- 6 x 6 mm²,
- 18 x 18 mm²,
- 24 x 24 mm²,
- 30 x 30 mm²,
- 42 x 42 mm²,
- 60 x 60 mm² and
- 80 x 80 mm².

The agreement is very good, with only small discrepancies far from the primary field.
Figure 4.17 Measured (diode) and Monte Carlo modelled profiles for a 6 x 6 mm$^2$ field at 95 cm source-surface distance and 5 cm depth: (a) cross-plane and (b) in-plane.

Figure 4.18 Measured (diode) and Monte Carlo modelled profiles for a 24 x 24 mm$^2$ field at 95 cm source-surface distance and 5 cm depth: (a) cross-plane and (b) in-plane.

Figure 4.19 Measured (diode) and Monte Carlo modelled profiles for a 42 x 42 mm$^2$ field at 95 cm source-surface distance and 5 cm depth: (a) cross-plane and (b) in-plane.
Figure 4.20 Measured (diode) and Monte Carlo modelled profiles for a 60 x 60 mm$^2$ field at 95 cm source-surface distance and 5 cm depth: (a) cross-plane and (b) in-plane.

Figure 4.21 Measured (diode) and Monte Carlo modelled profiles for a 80 x 80 mm$^2$ field at 95 cm source-surface distance and 5 cm depth: (a) cross-plane and (b) in-plane.

Figure 4.22 Measured (diode) and Monte Carlo modelled profiles for a 98 x 98 mm$^2$ field at 95 cm source-surface distance and 5 cm depth: (a) cross-plane and (b) in-plane.
Figure 4.23 Percentage depth dose curves obtained via measurement (95 cm SSD with a diode) in a water phantom, compared to those obtained using the Monte Carlo model, shown for various field sizes: (a) 6 x 6 mm\(^2\), (b) 12 x 12 mm\(^2\), (c) 18 x 18 mm\(^2\), (d) 24 x 24 mm\(^2\), (e) 30 x 30 mm\(^2\), (f) 42 x 42 mm\(^2\), (g) 60 x 60 mm\(^2\) and (h) 80 x 80 mm\(^2\).
4.7.7 Conclusions
A Monte Carlo model of a Varian 600C with mounted BrainLAB mini-multileaf collimator has been constructed and commissioned against measured data. An acceptable level of agreement has been achieved, particularly for small fields which are the focus of the present body of work. The geometry was based on specifications provided by Varian and BrainLAB under confidentiality agreements. Model parameters were iteratively adjusted to optimise the match with experimental data. Confidence in the accuracy of the model allows calculations of fluence and spectral data to be undertaken – something which is prohibitively difficult to measure experimentally – so as to fully characterise the stereotactic fields. Furthermore, the commissioned model facilitates calculation of dose distributions in complex geometries where the standard treatment planning system may be of limited accuracy. It is also possible to interrogate contributions to the primary dose field resulting from scatter and other influences. Such investigations are described in Chapter 5.

4.8 Chapter summary
Accurate calculation of the dose distributions delivered in stereotactic radiotherapy is of critical importance, for the confident delivery and assessment of clinical treatments. The dose calculation algorithms employed by treatment planning systems often incorporate approximations that potentially reduce the accuracy of calculated doses in the context of stereotactic radiotherapy, which involves small fields and (in the context of stereotactic body radiotherapy) may be in close proximity to interfaces of high- and low-density media. Not only is calculation of such dose distributions difficult, but measurement of small fields is notoriously complicated. Furthermore, key beam characteristics such as fluence and spectral data are often not possible to determine via measurement in a clinical context. To overcome many of these issues, this chapter has described the development of a Monte Carlo model of a linac-based stereotactic unit. This model has been commissioned against measured data, and – in the following chapter – will be used to determine the aforementioned critical properties of stereotactic fields.
CHAPTER FIVE

Aut quid non miraculo est, cum primum in notitiam venit? Quam multa fieri non posse prius quam sunt facta iudicantur? †

_Gaius Plinius Secundus, Naturalis Historia_

† “Rather, what exists that does not seem wondrous when it first comes to our notice? How many things are judged to be impossible, until their occurrence?” A familiar observation by Pliny the Elder (Book VII of the _Naturalis Historia_), who of course wrote extensively on the topic of science and medicine. My own translation.
CHAPTER 5

Characterisation of stereotactic fields:
In-field

Spectral qualities, dose evaluation for intracranial treatments and the influence of heterogeneities in extracranial treatments
5.4 Validation of stereotactic treatments for small intracranial tumours via normoxic polymer gel dosimetry (PAGAT) with optical CT readout

5.4.1 Introduction

5.4.2 Experimental method

5.4.2.1 Clinically-relevant stereotactic treatment delivered to phantom

5.4.2.4 Optical readout of the gel dosimeter

5.4.3 Results and discussion

5.4.4 Conclusions

5.5 Small-field radiotherapy of lung tumours: A systematic investigation of under-dosage due to electronic disequilibrium

5.5.1 Introduction

5.5.2 Method

5.5.3 Result

5.5.3.1 EGSnrc determination of under-dosage

5.5.3.2 The ‘dose reduction factor’ (DRF)

5.5.3.3 Agreement between the two Monte Carlo transport codes

5.5.3.4 Comparison with TPS prediction

5.5.4 Discussion

5.5.4.1 Clinical relevance

5.5.4.2 Influences on dose inhomogeneity

5.5.4.3 Effect on typical treatment

5.5.4.4 The influence of linac energy

5.5.4.5 Application of the DRF

5.5.5 Conclusions

5.6 Chapter summary
5.1 Chapter overview

In this chapter, a dosimetrically-matched Monte Carlo model of a linac equipped with a mini-multileaf collimator (the development of which is discussed in Chapter 4) is used to calculate a systematic dataset of stereotactic field characteristics.

Stereotactic fields were characterised in air, both in and beyond the primary field. The data presented include photon spectra, contaminant electron spectra, the spatial variation of mean photon energy, the spatial variation of mean electron energy and the angular distribution of photons. Spectral data in water is also of significant importance, thus photon energy fluences, electron energy fluences and mean energy distributions were all scored at depths of 5, 10 and 15 cm in water.

In this chapter, observations are made about the significant differences in spectra in- and out-of-field, for both photons and contaminant electrons. There are strong trends with spatial location and field size. Notable differences are also exhibited in terms of mean energy and ‘structure’ in fluence outside the primary field when comparing fields that have a static 98 x 98 mm$^2$ jaw opening to those fields that are backed-up completely by the jaws.

There are a number of observations to be made about spectra in water. For instance, photon spectra harden with depth, and the mean energy of the primary photon beam decreases significantly with increasing field size. Out-of-field mean photon energies decrease with increasing field size. The fraction of total photons in the low-energy regime is much higher for larger fields (for example, the 98 x 98 mm$^2$ field has $\sim$1000 % more photons of energy < 250 keV than the 6 x 6 mm$^2$ field).

The relevance of varying spectra is illustrated using three examples. Firstly, the typical assumption of unchanging secondary electron spectra when calibrating an ionisation chamber with a broad-beam reference field was investigated. The results in this chapter demonstrate both field-size and depth dependence of mean restricted stopping power ratios; the discrepancy when compared to the reference field increases with decreasing field size and increasing depth. Although there is a difference, within the primary field the systematic error introduced is less than 1 % and may be safely ignored. However, outside the primary field the error is larger (> 1 %) and increases with increasing field size. This is a direct result of the spatially-varying spectra as shown in this chapter, and would be impossible to determine experimentally. The second example presented in this chapter is an investigation of the over-response of radiographic film. The film was modelled at a depth of 5 cm in water and was
irradiated with an 18 x 18 mm² field. A further simulation was undertaken, scoring dose to water at an equivalent location. The radiographic film is shown to exhibit an over-response to the incident field (> 1 %), which varies spatially. This is a result of the spatial variation in the spectrum, and has consequences for the experimental characterisation of dosimetric properties in and slightly beyond the penumbral region when measuring with film. The third study undertaken was an investigation of the radiological properties of LiF TLD-100 thermoluminescent dosimeters relative to water and tissue. Specifically, the difference between TLD-100 and water are highlighted using the energy-dependent effective atomic number ($Z_{\text{eff}}$, see Chapter 3). Of particular note is the fact that the peak photon fluence coincides with the maximum discrepancy in $Z_{\text{eff}}$.

The suitability of gel dosimeters for the measurement of small stereotactic dose distributions is demonstrated in a novel study presented in this chapter. The potential for stereotactic treatment validation using normoxic polymer gel dosimetry (with optical-CT readout) in an anthropomorphic head phantom was assessed. A 12-field stereotactic treatment plan for meningioma was recalculated onto a computed tomography scan of the head phantom with gel insert and was delivered using a Varian 2100 linear accelerator with mounted BrainLAB m₃ mini-multileaf collimator.

An additional study was undertaken in the context of stereotactic body radiotherapy. Lung tumours present challenges in terms of treatment planning dose calculations, because of the juxtaposition of high and low density media. This may affect the minimum dose received by lesions and is particularly important when prescribing dose to covering isodoses. The study presented in this chapter quantifies under-dosage in key regions around a hypothetical target using Monte Carlo dose calculation methods. A systematic set of calculations are undertaken using two Monte Carlo radiation transport codes (EGSnrc and GEANT4). A factor for clinical estimation of such under-dosage is also presented; this allows informed interpretation of patient treatment plans and retrospective analysis of clinical trial data.
5.2 Spectral qualities of stereotactic fields

Critical to the thorough characterisation of small fields is the investigation of spectral properties. In fact, Attix (2004) states that “specification of a spectrum is still the most rigorous means of beam characterisation”. Direct measurement of MeV linac spectra is often prohibitively difficult because of the high beam flux. It is possible to employ techniques such as the use of scattering foils with a detector at an angle to the central axis, in order to derive some spectral information based on knowledge of Compton scattering under that particular arrangement etc. However, such approaches are very difficult, especially for small fields, and do not readily yield information on spatial variation of spectral qualities. Ultimately, the most effective means of doing this is to employ a dosimetrically-matched Monte Carlo model. This is the approach undertaken in the present work. A model of the BrainLAB m3 mini-multileaf collimator (MMLC) has been commissioned, as described in Chapter 4. In this section, the Monte Carlo model is used to assess the fluence and spectral characteristics of a range of small fields. Also of particular interest is the spectrum within and just beyond the penumbra of small fields, which is likely to be different to the primary beam, raising questions of dose response in detectors that exhibit energy dependence.

5.2.1 Background

For improved accuracy of dose calculation models and measurements with energy-dependent detectors, it is valuable to have knowledge of the fluence distributions and energy spectra from medical linear accelerators (linacs). For stereotactic radiosurgery and stereotactic radiotherapy, the necessity for accurate dose delivery is self-evident, given the potential for detriment if the target is under-dosed or if adjacent critical structures are subjected to excessive dose. The general complexities of dose calculation and measurement are compounded with the use of small fields because of issues of lateral electronic equilibrium. Clinical treatment planning systems have been shown to significantly miscalculate dose for small fields (Lydon 2005), particularly outside the primary field (Taylor et al. 2010c). Experimentally, ionisation chambers are often not appropriate for use with stereotactic fields because of their (relatively large) magnitude, and many of the alternative dosimeters (such as film, diodes and thermoluminescent dosimeters) are known to exhibit energy-dependence. For dosimeters that are not entirely media-matched (i.e. ‘tissue equivalent’), any change in the photon (or electron) spectrum causes a change in response relative to a tissue equivalent detector.
The importance of spectral characterisation is evidenced by the high number of citations (366 as of July 2010, according to ISI Web of Knowledge) of the work of Mohan et al (1985). This work also highlights the usefulness of Monte Carlo radiation transport methods in the determination of such spectra. In this way, the difficulties of direct spectral measurement (such as high beam flux) are circumvented. For small fields (such as those employed in stereotactic radiosurgery/radiotherapy) there have been explicit investigations of spectral qualities, because beam collimation affects the energy of the primary beam.

One of the earliest studies employing Monte Carlo calculations to determine the spectral changes due to collimation was that of Amols et al (1984), who modelled monoenergetic photon beams incident on a lead collimator. They found that for a 10 MeV beam the average energy transmitted through a 1 cm aperture was 9.7 ± 0.3 MeV compared to 7.0 ± 0.8 MeV for a 0.1 cm aperture. A further interesting finding was that a significant increase in collimator thickness results in far less degradation of the transmitted photon beam energy. One would expect that such energy reduction will result in secondary electrons of reduced range and consequently a shallower depth of maximum dose (dmax), and indeed this has been demonstrated. Serago et al (1992) showed this result for field diameters ranging from 10 to 40 mm and energies from 4 to 24 MV (Clinac 6/100). Sixel and Podgorsak (1993) also demonstrated this for apertures ranging from 10 to 30 mm and energies from 6 to 18 MV (Clinac 18 and Clinac 2100C). Verhaegen et al (1998) also noted the shallower dmax and lower energies with decreasing field size, for field diameters of 0.5 to 5.0 cm for a 6 MV beam (Clinac-600SR). These energies were observed at the collimator exit, and it is worth noting spectral trends in water. Beam hardening with depth is typically observed, and with larger fields there is often a decrease in beam energy resulting from the increased number of low energy photons arising from phantom scatter (Cunningham et al. 1986). This has been investigated in the context of radiographic film response, with different reports on the magnitude of the response variation (Sykes et al. 1999; Danciu et al. 2001; Chetty and Charland 2002; Palm et al. 2004).

There have been numerous studies concerned with the commissioning and implementation of stereotactic radiosurgery beams with micro-multileaf collimators; for instance (Cosgrove et al. 1999; Benedict et al. 2001; Deng et al. 2004). Belec et al (2005) and Ding et al (2006) have investigated the characteristics of stereotactic fields shaped with the BrainLAB (Feldkirchen) m3 mini-multileaf collimator (MMLC), however, a comprehensive investigation of spectral properties with varying field sizes has not been undertaken. In this thesis, Monte Carlo methods are employed to undertake systematic characterisation of the
spectra of small stereotactic fields shaped by a dosimetrically-matched model of the BrainLAB MMLC.

5.2.2 Using a dosimetrically-matched Monte Carlo model to determine beam spectra

A wide variety of Monte Carlo radiation transport codes are now available. One such code, EGSnrc (Kawrakow 2000), is interfaced with BEAMnrc (Rogers et al. 2007), allowing straightforward modelling of, in particular, radiotherapy linear accelerators. In this work we have constructed a model of the Varian 600C Clinac with a mounted BrainLAB mini-multileaf collimator using BEAMnrc. The detail of this is presented in Chapter 4, and the key transport parameters are summarised here for completeness. The model was constructed based on schematics provided by Varian Medical Systems under a non-disclosure agreement and on direct measurements of the MMLC. In this work a simplified model of the MMLC is employed, dosimetrically-matched to measured data using percent depth-dose curves, profiles and scatter factors (see Chapter 4 for this detail). A step size of 0.25 (maximum fractional energy loss, ESTEPE) was employed. EGSnrc has been shown to produce step-size independent results at a sub 0.1% level even at interfaces of high Z media in fine geometries (Kawrakow 2000; Verhaegen 2002). Here we have employed the PRESTA-ii electron-step algorithm with the exact boundary crossing algorithm such that the electron transport will go into single-scattering mode within three elastic mean free paths of the boundary, giving the necessary accuracy at peak efficiency. Calculations were performed on the VPAC Tango AMD Opteron system, which consists of 95 nodes, each with two AMD Barcelona 2.3 GHz quad core processors (totalling 760 cores). Typically, fifteen processors were employed per simulation, each simulation thus requiring approximately 24 hours for $10^{10}$ incident particle histories. In-field, uncertainties are negligible; out-of-field, uncertainties in photon fluences in air are of the order of 0.1% and for spectra uncertainties range up to (in the worst case) the order of several percent.

In this work, the energy spectrum is characterised as it varies with field sizes for fields including: 6 x 6 mm$^2$, 12 x 12 mm$^2$, 18 x 18 mm$^2$, 24 x 24 mm$^2$, 30 x 30 mm$^2$, 42 x 42 mm$^2$, 60 x 60 mm$^2$, 80 x 80 mm$^2$ and 98 x 98 mm$^2$. Characteristics are investigated within and just beyond the primary field. Far from the nominal field where leakage begins to dominate over scatter, it is likely that the Monte Carlo model would be limited in accuracy (since linac shielding was not incorporated). However, for the intermediate fields explored here, the model is expected to accurately represent the true beam.
5.2.3 Results and discussion

5.2.3.1 Spectral data in air

Spectral information has been scored in air at a source-surface distance (SSD) of 100 cm. Figure 5. to Figure 5.9 show spectral information for a range of field sizes between 6 x 6 mm\(^2\) and 98 x 98 mm\(^2\). Each figure illustrates:

- The contaminant electron fluence (scored both in a region equivalent to twice the nominal field size and in a plane extending out to 15 cm off-axis distance).
- The photon fluence (scored both in a region equivalent to twice the nominal field size and in a plane extending out to 15 cm off-axis distance).
- The mean photon energy (scored both in a region equivalent to twice the nominal field size and in a plane extending out to 15 cm off-axis distance).

Figure 5.10 summarises some of the notable trends that may be observed as a function of field size, within the primary beam, beyond the penumbra and far from the primary field.

Figure 5.11 demonstrates the variation of spectral distributions with field size, relative to the (maximum) field size of 98 x 98 mm\(^2\).

Figure 5.12 to Figure 5.14 show the angular distribution of photons at 100 cm SSD for various field sizes, scored both in a region equivalent to the nominal field size and a large scoring plane of 30 x 30 cm\(^2\) centred at the central axis.

Where normalised data is presented, the normalisation is with respect to the maximum (not the central-axis value), unless otherwise stated.
Figure 5.1 Spectral characteristics of a 0.6 x 0.6 cm$^2$ field. The information of interest is scored in air at a distance of 100 cm from the target. (a) Electron fluence distribution from central axis (CAX) out to double the primary field width. (b) Electron fluence distribution from central axis (CAX) out to a distance of 15 cm. (c) Photon fluence distribution from central axis (CAX) out to double the primary field width. (d) Photon fluence distribution from central axis (CAX) out to a distance of 15 cm. (e) Mean photon energy distribution from central axis (CAX) out to double the primary field width. (f) Mean photon energy distribution from central axis (CAX) out to a distance of 15 cm.
Figure 5.2 Spectral characteristics of a 1.2 x 1.2 cm$^2$ field. The information of interest is scored in air at a distance of 100 cm from the target. (a) Electron fluence distribution from central axis (CAX) out to double the primary field width. (b) Electron fluence distribution from central axis (CAX) out to a distance of 15 cm. (c) Photon fluence distribution from central axis (CAX) out to double the primary field width. (d) Photon fluence distribution from central axis (CAX) out to a distance of 15 cm. (e) Mean photon energy distribution from central axis (CAX) out to double the primary field width. (f) Mean photon energy distribution from central axis (CAX) out to a distance of 15 cm.
Figure 5.3 Spectral characteristics of a 1.8 x 1.8 cm² field. The information of interest is scored in air at a distance of 100 cm from the target. (a) Electron fluence distribution from central axis (CAX) out to double the primary field width. (b) Electron fluence distribution from central axis (CAX) out to a distance of 15 cm. (c) Photon fluence distribution from central axis (CAX) out to double the primary field width. (d) Photon fluence distribution from central axis (CAX) out to a distance of 15 cm. (e) Mean photon energy distribution from central axis (CAX) out to double the primary field width. (f) Mean photon energy distribution from central axis (CAX) out to a distance of 15 cm.
Figure 5.4 Spectral characteristics of a 2.4 x 2.4 cm² field. The information of interest is scored in air at a distance of 100 cm from the target. (a) Electron fluence distribution from central axis (CAX) out to double the primary field width. (b) Electron fluence distribution from central axis (CAX) out to a distance of 15 cm. (c) Photon fluence distribution from central axis (CAX) out to double the primary field width. (d) Photon fluence distribution from central axis (CAX) out to a distance of 15 cm. (e) Mean photon energy distribution from central axis (CAX) out to double the primary field width. (f) Mean photon energy distribution from central axis (CAX) out to a distance of 15 cm.
Figure 5.5 Spectral characteristics of a 3.0 x 3.0 cm$^2$ field. The information of interest is scored in air at a distance of 100 cm from the target. (a) Electron fluence distribution from central axis (CAX) out to double the primary field width. (b) Electron fluence distribution from central axis (CAX) out to a distance of 15 cm. (c) Photon fluence distribution from central axis (CAX) out to double the primary field width. (d) Photon fluence distribution from central axis (CAX) out to a distance of 15 cm. (e) Mean photon energy distribution from central axis (CAX) out to double the primary field width. (f) Mean photon energy distribution from central axis (CAX) out to a distance of 15 cm.
Figure 5.6 Spectral characteristics of a 4.2 x 4.2 cm² field. The information of interest is scored in air at a distance of 100 cm from the target. (a) Electron fluence distribution from central axis (CAX) out to double the primary field width. (b) Electron fluence distribution from central axis (CAX) out to a distance of 15 cm. (c) Photon fluence distribution from central axis (CAX) out to double the primary field width. (d) Photon fluence distribution from central axis (CAX) out to a distance of 15 cm. (e) Mean photon energy distribution from central axis (CAX) out to double the primary field width. (f) Mean photon energy distribution from central axis (CAX) out to a distance of 15 cm.
Figure 5.7 Spectral characteristics of a 60 x 60 cm$^2$ field. The information of interest is scored in air at a distance of 100 cm from the target. (a) Electron fluence distribution from central axis (CAX) out to double the primary field width. (b) Electron fluence distribution from central axis (CAX) out to a distance of 15 cm. (c) Photon fluence distribution from central axis (CAX) out to double the primary field width. (d) Photon fluence distribution from central axis (CAX) out to a distance of 15 cm. (e) Mean photon energy distribution from central axis (CAX) out to double the primary field width. (f) Mean photon energy distribution from central axis (CAX) out to a distance of 15 cm.
Figure 5.8 Spectral characteristics of a 8.0 x 8.0 cm² field. The information of interest is scored in air at a distance of 100 cm from the target. (a) Electron fluence distribution from central axis (CAX) out to double the primary field width. (b) Electron fluence distribution from central axis (CAX) out to a distance of 15 cm. (c) Photon fluence distribution from central axis (CAX) out to double the primary field width. (d) Photon fluence distribution from central axis (CAX) out to a distance of 15 cm. (e) Mean photon energy distribution from central axis (CAX) out to double the primary field width. (f) Mean photon energy distribution from central axis (CAX) out to a distance of 15 cm.
Figure 5.9 Spectral characteristics of a 98 x 98 cm$^2$ field. The information of interest is scored in air at a distance of 100 cm from the target. (a) Electron fluence distribution from central axis (CAX) out to double the primary field width. (b) Electron fluence distribution from central axis (CAX) out to a distance of 15 cm. (c) Photon fluence distribution from central axis (CAX) out to double the primary field width. (d) Photon fluence distribution from central axis (CAX) out to a distance of 15 cm. (e) Mean photon energy distribution from central axis (CAX) out to double the primary field width. (f) Mean photon energy distribution from central axis (CAX) out to a distance of 15 cm.
There are a number of observations that may be made about the fluence and spectral qualities of the stereotactic fields modelled; these are demonstrated by Figure 5.10 shows the mean energy in the primary beam, 2 cm beyond the field edge and at an out-of-field point (12 cm off-axis) for a range of field sizes. Percentage differences in mean energy are also given relative to the 9.8 x 9.8 cm\(^2\) case. The percentage differences are defined as:

\[
\overline{E}_{\text{diff}}(\%) = 100 \left( \frac{\overline{E}_{FS} - \overline{E}_{9.8x9.8}}{\overline{E}_{9.8x9.8}} \right),
\]

where the subscript \(FS\) refers to field size (variable) and 9.8x9.8 corresponds to the 9.8 x 9.8 cm\(^2\) field.

Notably, the out-of-field photon fluence is approximately 1 % of the primary beam fluence, whilst the fluence of contaminant electrons is approximately 30 % of the fluence within the primary beam. What is also demonstrated, is that the photon fluence has a sharp gradient at the field edge, whereas the fluence of contaminant electrons does not exhibit a sharp gradient. It is also clear from Figure 5. to Figure 5.9 that there is a non-uniform fluence profile just beyond the primary beam for field sizes < 9.8 x 9.8 cm\(^2\) because of the interleaf leakage through the mini-multileaf collimator. Beam hardening by the collimation device is evidenced by the fact that the mean energy of the primary beam is lower than that of the beam periphery. This pronounced for small fields, but less noticeable for larger fields that are better shielded by the jaws. In all cases, the mean energy drops again in out-of-field regions – to approximately 80 % of the primary beam energy (up to 15 cm off-axis distance). As shown by Figure 5.11, the photon energy fluence varies with field size. The variation is most pronounced at low energies (below approximately 1 MeV), where small fields are shown to have much lower fluences – the difference decreasing with increasing energy. The difference also decreases with increasing field size, as one would expect.

Figure 5.12, Figure 5.13 and Figure 5.14 show the angular distribution of photons at a source-surface distance (SSD) of 100 cm in air. These figures show that the photon beam is far more forward-directed for small fields. For instance, the distribution peaks at 0 ° for a 6 x 6 mm\(^2\) field but for a 98 x 98 mm\(^2\) field the peak is at 4 °. What is also evident, is the fact that beyond the primary field the photons are much less forward-direction, which is to be expected since these (bremsstrahlung photons borne of the target) are mostly scattered in the linac head.
Figure 5.10 Variation of mean energy with field size. (a) The mean energy in the centre of the primary beam, at 12 cm off-axis-distance ('out-of-field') and at a point 2 cm beyond the field edge in each case. (b) Ratio of the mean energy in each case to the 9.8 x 9.8 cm$^2$ field. (c) Percentage difference in mean energies in the primary beam, relative to the 9.8 x 9.8 cm$^2$ field. (d) Percentage difference in mean energies at a point 12 cm from the central axis, relative to the 9.8 x 9.8 cm$^2$ field.
Figure 5.11 The variation of spectral distribution with field size. The information of interest is scored in air at a distance of 100 cm from the target. (a) The spectral distribution for a 9.8 x 9.8 cm$^2$ field. (b) An indication of the relationship between the spectral distribution and field size, illustrated by presentation of the ratio of difference field spectra to the 9.8 x 9.8 cm$^2$ field spectrum. The most pronounced variation is in the low energy regime (below approximately 1 MeV), where small fields exhibit significantly lower fluence. The discrepancy above 1 MeV decreases with increasing field size (from 20-30 % lower for a 0.6 x 0.6 cm$^2$ field to < 10 % for the large field sizes.)
Figure 5.12 Angular distribution of particles (100 cm from the target) scored in nominal field sizes and in a large (30 x 30 cm$^2$) scoring plane for the following field sizes: (a),(b) 0.6 x 0.6 mm$^2$ (c),(d) 1.2 x 1.2 mm$^2$ (e),(f) 1.8 x 1.8 mm$^2$. 
Figure 5.13 Angular distribution of particles (100 cm from the target) scored in nominal field sizes and in a large (30 x 30 cm$^2$) scoring plane for the following field sizes: (a),(b) 2.4 x 2.4 mm$^2$ (c),(d) 3.0 x 3.0 mm$^2$ (e),(f) 4.2 x 4.2 mm$^2$. 
Figure 5.14 Angular distribution of particles (100 cm from the target) scored in nominal field sizes and in a large (30 x 30 cm$^2$) scoring plane for the following field sizes: (a),(b) 6.0 x 6.0 cm$^2$ field; (c),(d) 8.0 x 8.0 cm$^2$ field; (e),(f) 9.8 x 9.8 cm$^2$ field.
There are a number of observations one may make from the data presented. These are summarised here in point form:

- Out-of-field photon fluence ~1 % of primary beam fluence.
- Out-of-field electron fluence ~30 % of primary beam fluence.
- Photon fluence has sharp gradient at field edge.
- Electron (contaminant) fluence does not have a sharp gradient at field edge.
- ‘Structure’ evident in fluence profiles just beyond the primary beam (due to interleaf leakage through collimator).
- Mean energy of primary photon field lower than surrounding peripheral regions (due to beam hardening by collimators) for small fields; mean energy drops again in far out-of-field regions.
- Photon energy fluence varies with field size, most notably at low energies (below ~1 MeV).
- The photon beam is more forward directed for smaller fields, as evidenced by the primary field angular photon distributions (in fact, for the 9.8 x 9.8 cm2 field the distribution peaks at approx. 3º rather than 0 º).
- The photons outside the primary field are much less forward-directed.

5.2.3.2 Spectral data in water

Radiation spectra change significantly within water and, as such, spectral data has also been presented for various depths in water for various field sizes. Figure 5.15 to Figure 5.23 present this information for field sizes varying from 0.6 x 0.6 cm² to 9.8 x 9.8 cm². Each figure contains:

- The mean photon energy spatial distribution as a function of distance from the central axis (CAX). In each case spectral data is plotted from the central axis to a distance twice that of the nominal field size, and also out to a distance of 15 cm (so that out-of-field spectral qualities may be observed.
- The spectral distribution (fluence as a function of energy) for both electrons and photons.
- In each case, data for depths in water of 5, 10 and 15 cm is given.

Several trends may be observed. Figure 5.24 shows the difference in mean energy for different field sizes, for both the primary field (i.e. at the central axis) and at a distance of 12 cm off-axis (so as to illustrate mean energy trends out-of-field) at a depth of 5 cm in water with an SSD of 95 cm.
Percentage differences are also given relative to the 9.8 x 9.8 cm$^2$ case. The percentage differences are defined as:

$$E_{\text{diff}}(\%) = 100 \left( \frac{E_{FS} - E_{9.8x9.8}}{E_{9.8x9.8}} \right),$$

where the subscript $FS$ refers to field size (variable) and 9.8x9.8 corresponds to the 9.8 x 9.8 cm$^2$ field.

One notable feature of the spectral distributions is that there are greater low-energy photons contributing to the primary field with larger field sizes. Figure 5.25 illustrates this trend (varying with field size), indicating the percentage fraction (of the total) of photons with less than 250 keV and less than 500 keV. The percentage difference between the different field sizes and the 0.6 x 0.6 cm$^2$ case are also given, defined similarly to the mean energy difference, where $\Psi$ is the fluence:

$$\Psi_{\text{diff}}(\%) = 100 \left( \frac{\Psi_{FS} - \Psi_{0.6x0.6}}{\Psi_{0.6x0.6}} \right).$$

Make special note that this difference is relative to the 0.6 x 0.6 cm$^2$ case, unlike the difference in mean energy is given relative to the 9.8 x 9.8 cm$^2$ field. This is so that the difference remains a positive number.
Figure 5.15 Spectral characteristics of a 0.6 x 0.6 cm$^2$ field. Each parameter of interest is scored at multiple depths (5, 10 and 15 cm) within a water phantom. (a) Mean energy distribution from central axis (CAX) out to double the primary field width. (b) Mean energy distribution from central axis (CAX) out to a distance of 15 cm. (c) Energy fluence of electrons in a scoring plane equal to the nominal field size. (d) Energy fluence of photons in a scoring plane equal to the nominal field size.
Figure 5.16 Spectral characteristics of a 1.2 x 1.2 cm$^2$ field. Each parameter of interest is scored at multiple depths (5, 10 and 15 cm) within a water phantom. (a) Mean energy distribution from central axis (CAX) out to double the primary field width. (b) Mean energy distribution from central axis (CAX) out to a distance of 15 cm. (c) Energy fluence of electrons in a scoring plane equal to the nominal field size. (d) Energy fluence of photons in a scoring plane equal to the nominal field size.
Figure 5.17 Spectral characteristics of a 1.8 x 1.8 cm² field. Each parameter of interest is scored at multiple depths (5, 10 and 15 cm) within a water phantom. (a) Mean energy distribution from central axis (CAX) out to double the primary field width. (b) Mean energy distribution from central axis (CAX) out to a distance of 15 cm. (c) Energy fluence of electrons in a scoring plane equal to the nominal field size. (d) Energy fluence of photons in a scoring plane equal to the nominal field size.
Figure 5.18 Spectral characteristics of a 2.4 x 2.4 cm² field. Each parameter of interest is scored at multiple depths (5, 10 and 15 cm) within a water phantom. (a) Mean energy distribution from central axis (CAX) out to double the primary field width. (b) Mean energy distribution from central axis (CAX) out to a distance of 15 cm. (c) Energy fluence of electrons in a scoring plane equal to the nominal field size. (d) Energy fluence of photons in a scoring plane equal to the nominal field size.
Figure 5.19 Spectral characteristics of a 3.0 x 3.0 cm² field. Each parameter of interest is scored at multiple depths (5, 10 and 15 cm) within a water phantom. (a) Mean energy distribution from central axis (CAX) out to double the primary field width. (b) Mean energy distribution from central axis (CAX) out to a distance of 15 cm. (c) Energy fluence of electrons in a scoring plane equal to the nominal field size. (d) Energy fluence of photons in a scoring plane equal to the nominal field size.
Figure 5.20 Spectral characteristics of a 4.2 x 4.2 cm² field. Each parameter of interest is scored at multiple depths (5, 10 and 15 cm) within a water phantom. (a) Mean energy distribution from central axis (CAX) out to double the primary field width. (b) Mean energy distribution from central axis (CAX) out to a distance of 15 cm. (c) Energy fluence of electrons in a scoring plane equal to the nominal field size. (d) Energy fluence of photons in a scoring plane equal to the nominal field size.
Figure 5.21 Spectral characteristics of a 6.0 x 6.0 cm² field. Each parameter of interest is scored at multiple depths (5, 10 and 15 cm) within a water phantom. (a) Mean energy distribution from central axis (CAX) out to double the primary field width. (b) Mean energy distribution from central axis (CAX) out to a distance of 15 cm. (c) Energy fluence of electrons in a scoring plane equal to the nominal field size. (d) Energy fluence of photons in a scoring plane equal to the nominal field size.
Figure 5.22 Spectral characteristics of a 8.0 x 8.0 cm$^2$ field. Each parameter of interest is scored at multiple depths (5, 10 and 15 cm) within a water phantom. (a) Mean energy distribution from central axis (CAX) out to double the primary field width. (b) Mean energy distribution from central axis (CAX) out to a distance of 15 cm. (c) Energy fluence of electrons in a scoring plane equal to the nominal field size. (d) Energy fluence of photons in a scoring plane equal to the nominal field size.
Figure 5.23 Spectral characteristics of a 9.8 x 9.8 cm² field. Each parameter of interest is scored at multiple depths (5, 10 and 15 cm) within a water phantom. (a) Mean energy distribution from central axis (CAX) out to double the primary field width. (b) Mean energy distribution from central axis (CAX) out to a distance of 15 cm. (c) Energy fluence of electrons in a scoring plane equal to the nominal field size. (d) Energy fluence of photons in a scoring plane equal to the nominal field size.
The systematic set of in-water spectral data clearly reveals a number of trends. The photon and electron spectra harden with depth in water. As Figure 5.24 shows, the mean energy of the primary photon beam decreases with increasing field size. The largest (9.8 x 9.8 cm$^2$) field is approximately 30% softer than the 0.6 x 0.6 cm$^2$ field, as made evident in Figure 5.24(b). Out-of-field characteristics are illustrated at a distance of 12 cm off-axis. The mean photon energies decrease with increasing field size as shown in Figure 5.24(c), where the 0.6 x 0.6 cm$^2$ field is approximately 250% harder than the 9.8 x 9.8 cm$^2$ field.

The lower mean energy of the larger beams is expected (since opened collimators present more surface area to the beam and concomitantly more scatter) and may be indicated by the relative fraction of low-energy photons in the primary beam spectra. This is highlighted clearly by Figure 5.25. The fraction (of the total) of photons with energies of < 250 keV and < 500 keV is shown for various field sizes. There is strong field size dependence. For instance, the 9.8 x 9.8 cm$^2$ field has approximately 1000% more photons of energies < 250 keV than the 0.6 x 0.6 cm$^2$ beam.

The electron spectrum also changes with field size, most evidently in the sub-MeV regime. The larger fields have a larger fraction of low-energy electrons, decreasing with decreasing field size. This is illustrated in Figure 5.26.
Figure 5.24 This figure indicates the difference in mean energy for different field sizes, shown for both the primary field (at the central axis) and at a distance of 12 cm off-axis (to illustrate the mean energy trend out-of-field) at a depth of 5 cm in water (95 cm source-surface distance). (a) The mean energy of the primary field and at a point 12 cm off-axis as a function of field size. (b) The percentage difference between the mean primary beam energy for various field sizes relative to the 98 x 98 mm$^2$ field. (c) The percentage difference between the mean out-of-field (12 cm off-axis) beam energy for various field sizes relative to the 98 x 98 mm$^2$ field.
Figure 5.25 (a) The fraction of photons (as a percentage of the total from 0 – 6 MeV) with energies less than 250 keV or 500 keV, for various field sizes between 0.6 x 0.6 cm$^2$ and 9.8 x 9.8 cm$^2$. Scored at 5 cm depth in a water phantom at 95 cm source-surface distance. (b) A comparison of the low-energy photon fraction for the different field sizes, presented as the percentage difference relative to the 0.6 x 0.6 cm$^2$ case (this is so that the percentage differences remain positive; see main body text for explanation).
Figure 5.26 (a) Spectral distribution of electrons for a 9.8 x 9.8 cm\(^2\) at 5 cm depth in water. (b) Spectral distribution of electrons for various field sizes, presented as a ratio to the distribution for a 9.8 x 9.8 cm\(^2\). The ratio is only shown to 4.5 MeV because of the high uncertainty associated with the (negligible) fluence at high energies.
There are a number of observations that may be made based on the data presented pertaining to spectral qualities in water, which are summarised in point form here:

– Photon spectra harden with depth in water.
– Electron spectra harden with depth in water.
– Mean energy of primary photon beam decreases with increasing field size (6 x 6 mm$^2$ beam is 30% harder than 98 x 98 mm$^2$ beam).
– Out-of-field mean photon energies (at 12 cm off-axis distance) decrease with increasing field size (6 x 6 mm$^2$ beam is 250% harder than 98 x 98 mm$^2$ beam).
– The fraction of total photons in the low energy regime increases with field size (98 x 98 mm$^2$ beam has ~1000% more photons with energies < 250 keV than 6 x 6 mm$^2$ beam).
– Electron spectrum varies with field size, most notably in the low-energy regime (< 1 MeV), such that larger fields have a larger fluence of low-energy electrons.

5.2.3.3 Comparison with ‘backed-up’ fields
Thus far the focus has been on fields shaped entirely with the mini-multileaf collimator. The reason for this is twofold: firstly, in clinical practice, the ‘back-up’ jaw sizes are determined by the maximum MMLC field sizes only and remain static and, secondly, for the sake of brevity – it is not feasible to include all possible combinations of MMLC and jaw sizes. Nevertheless, it is of interest to compare the spectral and fluence characteristics of purely MMLC shaped field with those shaped by both the jaws and MMLC. As such, several field sizes have been chosen for comparison.

Scored in air at 100 cm source-surface distance, mean photon energy distributions, photon and electron spectral distributions and photon angular distributions are shown in Figure 5.27 to Figure 5.29. The spectral distributions of photons and electron in-field show great similarity, and are clearly not greatly affected by the presence of back-up jaws. For the smaller fields in particular, the mean energy distributions beyond the primary field differ noticeably. The mean energies typically increase closer to the field edge than the non backed-up case, are relatively low in the shadow of the MMLC, then remain higher far from the primary field (most likely because of the finite lateral width of the jaws). There is also a noticeable difference in the angular distribution of photons at the patient plane, being more forward-directed for smaller fields but less so for larger fields (relative to the non backed-up case).
Figure 5.27 Comparison of MMLC-shaped fields, with and without back-up jaws with the same field opening of 24 x 24 mm². (a) The photon mean energy distribution shown from the central axis to a distance twice that of the nominal field size. (b) The photon mean energy distribution, shown out to 15 cm from the central axis. (c) The spectral distribution for photons in the primary field. (d) The spectral distribution for (contaminant) electrons in the primary field. (e) Angular distributions of photons within the primary beam. (f) Angular distribution of photons in a large (30 x 30 cm²) scoring plane.
Figure 5.28 Comparison of MMLC-shaped fields, with and without back-up jaws with the same field opening of 30 x 30 mm². (a) The photon mean energy distribution shown from the central axis to a distance twice that of the nominal field size. (b) The photon mean energy distribution, shown out to 15 cm from the central axis. (c) The spectral distribution for photons in the primary field. (d) The spectral distribution for (contaminant) electrons in the primary field. (e) Angular distributions of photons within the primary beam. (f) Angular distribution of photons in a large (30 x 30 cm²) scoring plane.
Figure 5.29 Comparison of MMLC-shaped fields, with and without back-up jaws with the same field opening of 60 x 60 mm². (a) The photon mean energy distribution shown from the central axis to a distance twice that of the nominal field size. (b) The photon mean energy distribution, shown out to 15 cm from the central axis. (c) The spectral distribution for photons in the primary field. (d) The spectral distribution for (contaminant) electrons in the primary field. (e) Angular distributions of photons within the primary beam. (f) Angular distribution of photons in a large (30 x 30 cm²) scoring plane.
5.2.4 Clinical relevance

The results presented in this work clearly indicate that photon and electron (contaminant and secondary) spectra vary spatially, for different field sizes, different media and different depths in water phantoms. While identifying associated trends is interesting from a purely academic perspective, there are also clinical consequences. Primarily, these are concerned with dose measurement with dosimeters that exhibit energy dependence. Considering dose-effect curves, a 5% shift in dose may result in a 10 or 20% shift about a tumour control probability (TCP) of 50%. Complication rates in normal tissues may be affected by 20 or 30% with the same 5% shift in dose. A patient’s response to a 7% difference in dose may be clinically detectable by an oncologist (Papanikolaou et al. 2004). Accurate dosimetry is of critical importance.

As discussed in earlier chapters, media-matching of dosimeters is of significant importance. Where the radiological properties of the dosimeter deviate from those of the medium (such as water), then corresponding energy dependence may generate inaccurate measurements when the spectra of the radiation fields change.

To illustrate this point, several clinically-relevant cases are presented here. Firstly, the acceptability of the use of a standard 10 x 10 cm$^2$ reference field for ionisation chamber calibration with the assumption that secondary electron spectra are field-size and depth independent is investigated in the context of stereotactic radiotherapy. Secondly, the response of radiographic film for small-field measurement is investigated. Thirdly, the response of thermoluminescent dosimeters (in- and out-of-field) for stereotactic radiotherapy dosimetry is studied. The latter two approaches have both involved explicit Monte Carlo dose calculation.

Much of the work presented in this section has been submitted for publication (Taylor et al. 2011a).
5.2.4.1 Measurement of absorbed dose with an ionisation chamber

It is possible to relate the dose to the gas in an ionisation chamber to that in the medium of interest occupied by the dosimeter (Attix 2004), such that the dose in the medium is given by:

\[
D_{\text{med}} = MN_{\text{gas}} \left( \frac{L}{\rho} \right)^{\text{med}} \rho_{\text{gas}} P_{\text{ion}} P_{\text{repl}} P_{\text{wall}},
\]

where \( M \) is the electrometer reading, \( N_{\text{gas}} \) is the gas cavity calibration factor, \( \left( \frac{L}{\rho} \right)^{\text{med}} \) is the ratio of the mean restricted stopping power of the medium (phantom material) to that of the chamber gas (air). \( P_{\text{ion}} \) is a factor that accounts for ionisation recombination losses (the inverse of the ionisation collection efficiency). \( P_{\text{repl}} \) is a replacement correction depending on the type and energy of radiation, the gradient of the depth dose curve where the measurement is made and the radius of the chamber cavity. \( P_{\text{wall}} \) is unity when the chamber wall and medium are of the same composition, and otherwise is a stopping power based correction which may be found elsewhere (Schulz 1983; Attix 2004). These various factors account for the fact that the ionisation chamber perturbs the dose field.

The ratio of the mean restricted stopping powers, \( \left( \frac{L}{\rho} \right)^{\text{med}}_{\text{gas}} \), may be given by:

\[
\left( \frac{L}{\rho} \right)^{\text{med}}_{\text{gas}} = \int_{\Delta}^{E_{\text{max}}} \frac{d\Phi(E)}{dE} \left( \frac{L}{\rho} \right)^{\text{med}}_{\text{gas}} dE,
\]

where, in this case, we will assume the medium (med) refers to water and the gas is air, \( \left( \frac{d\Phi(E)}{dE} \right) \) is the energy spectrum of electrons and \( \Delta \) is the cut-off energy. This stopping power ratio is often assumed to be constant, since the variation in the energy spectrum in the case of broad-beam photon irradiation is typically slight (for instance, calibration is performed with a 10 x 10 cm\(^2\) field). However, as has been established in this study, there are changes to the spectrum in the case of small fields (as relevant to stereotactic radiotherapy). As such, it is of interest to try and quantify any dependence of field size and phantom depth on the stopping power ratio. Monte Carlo methods are employed to explicitly investigate the extent of the influence of changing spectra on the absorbed dose as measured using an ionisation chamber, and thus to identify any corresponding systematic errors that may be introduced.
The spectral distributions of electrons in the primary field calculated via Monte Carlo methods were multiplied by collisional stopping powers (ICRU 1984b) at the same electron energies (each matrix having >400 data points) and integrated between $\Delta = 10$ keV and the maximum kinetic energy 6 MeV. This was done for both water and air and the ratio calculated for field sizes between $0.6 \times 0.6 \text{ cm}^2$ and $9.8 \times 9.8 \text{ cm}^2$ at depths of 5, 10 and 15 cm. The calculated values of $\left( \frac{L}{\rho} \right)_\text{gas}^{\text{med}}$ are given in Table 5.1.

The ratios for the various cases were compared against the calibration reference condition of a $9.8 \times 9.8 \text{ cm}^2$ field – the largest possible and closest to $10 \times 10 \text{ cm}^2$ as recommended by various protocols (Schulz 1983; Almond et al. 1999; IAEA 2000) at a depth ($d$) of 5 cm. This is represented by $\left( \frac{L}{\rho} \right)_R$ in Equation 5.3 below.

$$\left( \frac{L}{\rho} \right)_R = \frac{\left( \frac{L}{\rho} \right)_{\text{gas}}^{\text{med}}_{FS,d}}{\left( \frac{L}{\rho} \right)_{\text{gas}}^{\text{med}}_{FS=9.8\times9.8,d=5}}.$$  

This is given in Table 5.2 for the various field sizes ($FS$). To illustrate the extent of the discrepancy for different field sizes and depths, the percentage difference is plotted in Figure 5.30, where the difference (for various field sizes, $FS$, and depths, $d$) is defined as:

$$\left( \frac{L}{\rho} \right)_{\text{gas}}^{\text{med}}_{FS=9.8\times9.8,d=5} - \left( \frac{L}{\rho} \right)_{\text{gas}}^{\text{med}}_{FS,d} = 100 \left( \frac{\left( \frac{L}{\rho} \right)_{\text{gas}}^{\text{med}}_{FS=9.8\times9.8,d=5} - \left( \frac{L}{\rho} \right)_{\text{gas}}^{\text{med}}_{FS,d}}{\left( \frac{L}{\rho} \right)_{\text{gas}}^{\text{med}}_{FS,d}} \right).$$  

The results clearly show that although there is a spectral change, it is not significant enough to generate discrepancies greater than half a percent relative to the reference condition (for the range of field sizes and depths studied here). It should be noted that these results correspond only to the primary field, and differences may be more pronounced for out-of-field measurements. This point is highlighted by Figure 5.31.
Table 5.1 The mean collisional stopping power ratio (where the medium *med* is water and the gas is *air*) for various field sizes at various depths (5, 10 and 15 cm).

<table>
<thead>
<tr>
<th>Field size</th>
<th>$\left( \frac{L}{\rho} \right)_{med}^{depth=5cm}$</th>
<th>$\left( \frac{L}{\rho} \right)_{med}^{depth=10cm}$</th>
<th>$\left( \frac{L}{\rho} \right)_{med}^{depth=15cm}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6 x 0.6 cm$^2$</td>
<td>1.1158</td>
<td>1.1153</td>
<td>1.1141</td>
</tr>
<tr>
<td>1.2 x 1.2 cm$^2$</td>
<td>1.1167</td>
<td>1.1160</td>
<td>1.1152</td>
</tr>
<tr>
<td>1.8 x 1.8 cm$^2$</td>
<td>1.1170</td>
<td>1.1163</td>
<td>1.1156</td>
</tr>
<tr>
<td>2.4 x 2.4 cm$^2$</td>
<td>1.1173</td>
<td>1.1167</td>
<td>1.1160</td>
</tr>
<tr>
<td>3.0 x 3.0 cm$^2$</td>
<td>1.1175</td>
<td>1.1169</td>
<td>1.1161</td>
</tr>
<tr>
<td>4.2 x 4.2 cm$^2$</td>
<td>1.1177</td>
<td>1.1172</td>
<td>1.1166</td>
</tr>
<tr>
<td>6.0 x 6.0 cm$^2$</td>
<td>1.1180</td>
<td>1.1176</td>
<td>1.1171</td>
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<tr>
<td>8.0 x 8.0 cm$^2$</td>
<td>1.1183</td>
<td>1.1180</td>
<td>1.1176</td>
</tr>
<tr>
<td>9.8 x 9.8 cm$^2$</td>
<td>1.1185</td>
<td>1.1185</td>
<td>1.1185</td>
</tr>
</tbody>
</table>

Table 5.2 The ratio of mean collisional stopping power ratios (where the medium *med* is water and the gas is *air*) for various field sizes at various depths (5, 10 and 15 cm), relative to the reference case of field size 9.8 x 9.8 cm$^2$ and depth 5 cm.

<table>
<thead>
<tr>
<th>Field size</th>
<th>$\left( \frac{L}{\rho} \right)_{R}^{depth=5cm}$</th>
<th>$\left( \frac{L}{\rho} \right)_{R}^{depth=10cm}$</th>
<th>$\left( \frac{L}{\rho} \right)_{R}^{depth=15cm}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6 x 0.6 cm$^2$</td>
<td>0.9976</td>
<td>0.9971</td>
<td>0.9961</td>
</tr>
<tr>
<td>1.2 x 1.2 cm$^2$</td>
<td>0.9984</td>
<td>0.9977</td>
<td>0.9970</td>
</tr>
<tr>
<td>1.8 x 1.8 cm$^2$</td>
<td>0.9986</td>
<td>0.9981</td>
<td>0.9974</td>
</tr>
<tr>
<td>2.4 x 2.4 cm$^2$</td>
<td>0.9990</td>
<td>0.9984</td>
<td>0.9978</td>
</tr>
<tr>
<td>3.0 x 3.0 cm$^2$</td>
<td>0.9991</td>
<td>0.9985</td>
<td>0.9979</td>
</tr>
<tr>
<td>4.2 x 4.2 cm$^2$</td>
<td>0.9993</td>
<td>0.9988</td>
<td>0.9983</td>
</tr>
<tr>
<td>6.0 x 6.0 cm$^2$</td>
<td>0.9996</td>
<td>0.9992</td>
<td>0.9988</td>
</tr>
<tr>
<td>8.0 x 8.0 cm$^2$</td>
<td>0.9998</td>
<td>0.9995</td>
<td>0.9991</td>
</tr>
<tr>
<td>9.8 x 9.8 cm$^2$</td>
<td>1.0000</td>
<td>1.0000</td>
<td>1.0000</td>
</tr>
</tbody>
</table>
Figure 5.30 The difference in mean stopping power ratios, $\left(\frac{L}{\rho}\right)_{\text{gas}}^{\text{med}}$ (defined in Equation 5.4), between various field sizes and the reference case (9.8 x 9.8 cm$^2$ at 5 cm depth). The discrepancy is clearly larger for smaller field sizes and greater depths, but is nonetheless less than 1%.

Figure 5.31 The objective of this figure is to demonstrate that although the mean energy of the secondary electron spectrum within the primary field is similar for (significantly) different field sizes, beyond the primary beam discrepancies of almost a factor of two may exist. (a) The mean energy as a function of distance from the central axis (CAX) for a 6 x 6 mm$^2$ field (solid line) and a 98 x 98 mm$^2$ field (broken line). (b) The ratio of the mean energy of the small field to the large field as a function of distance from the central axis.
In the case of out-of-field doses, an example is demonstrated for the $6 \times 6$ mm$^2$ field. The difference in electron spectra in- and out-of-field is illustrated by Figure 5.31, which shows the mean energy as a function of distance from the central axis, as well as the ratio of mean energy for the $6 \times 6$ mm$^2$ relative to the $98 \times 98$ mm$^2$ field. The discrepancy in mean energy is clearly larger in the region approximately 6 to 11 cm off-axis. Calculations of \( \bar{\rho} \frac{L}{\rho} \) corresponding to the out-of-field spectrum for the $6 \times 6$ mm$^2$ and $60 \times 60$ mm$^2$ fields were undertaken. Comparing these to \( \bar{\rho} \frac{L}{\rho} \) for the $98 \times 98$ mm$^2$ primary field, the percentage differences, \( \frac{\bar{\rho} L - \bar{\rho} L_{\text{diff}}}{\bar{\rho} L} \), were determined. These are summarised in Table 5.3.

Although the difference between the two is opposite (i.e. negative) to the primary field comparison observed earlier, the difference is still nonetheless $< 1\%$ for the case of small fields. However, this is the case purely because the small-field out-of-field electron spectrum – while differing from the primary beam spectrum – happens to be close to that of the large-field primary beam spectrum.

Referring to Figure 5.31(a), it is clear that the mean out-of-field energy for the small-field case is comparable to the mean energy of the primary beam of the $98 \times 98$ mm$^2$ field. Unlike the previous cases, where small fields have exhibited the largest discrepancy, Figure 5.31(a) indicates that for out-of-field measurements, large fields might be more problematic (the mean out-of-field energy for the large field is approximately half that of the primary field). As such, the stopping power ratios have also been calculated for the out-of-field electron spectra for the $60 \times 60$ mm$^2$ and $98 \times 98$ mm$^2$ beam. This is also summarised in Table 5.3; the discrepancy is much more pronounced for out-of-field spectra for larger fields – ranging up to approximately $1.2\%$.

As such, for the vast majority of applications, it may be stated that the approximation of a constant stopping power ratio obtained with use of a broad beam (typically $10 \times 10$ cm$^2$) is acceptable, since the associated error is small ($< 1\%$).

However, for out-of-field measurements that, in particular, employ larger field sizes, there may be a systematic error $> 1\%$ attributable to the assumption of unchanging electron spectra for different field sizes and spatial locations within the phantom.
Table 5.3 The mean collisional stopping power ratios (med refers to water and gas is air) for the out-of-field spectra (6 – 12 cm off-axis) for a 6 x 6 mm$^2$, 60 x 60 mm$^2$ and 98 x 98 mm$^2$ field. Also shown is the percentage difference compared to the reference 98 x 98 mm$^2$ field. These are shown for depths of 5, 10 and 15 cm in water. Note in particular that the percentage differences are in this case negative, unlike the difference for a primary field comparison. Please see the main body text for definition of the parameters in this table.

<table>
<thead>
<tr>
<th>Primary field size:</th>
<th>0.6 x 0.6 cm$^2$</th>
<th>6.0 x 6.0 cm$^2$</th>
<th>9.8 x 9.8 cm$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\left(\frac{L}{\rho}\right)_{\text{med}}$</td>
<td>1.1234</td>
<td>1.1274</td>
<td>1.1311</td>
</tr>
<tr>
<td>$\left(\frac{L}{\rho}\right)_{\text{gas}}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\left(\frac{L}{\rho}\right)_{\text{med}}$</td>
<td>1.1234</td>
<td>1.1287</td>
<td>1.1317</td>
</tr>
<tr>
<td>$\left(\frac{L}{\rho}\right)_{\text{gas}}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\left(\frac{L}{\rho}\right)_{\text{med}}$</td>
<td>1.1240</td>
<td>1.1294</td>
<td>1.1313</td>
</tr>
<tr>
<td>$\left(\frac{L}{\rho}\right)_{\text{gas}}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\left[\frac{\left(\frac{L}{\rho}\right)<em>{\text{med}}}{\left(\frac{L}{\rho}\right)</em>{\text{gas}}}\right]_{\text{diff,depth=5cm}}$</td>
<td>-0.4345 %</td>
<td>-0.7906 %</td>
<td>-1.111 %</td>
</tr>
<tr>
<td>$\left[\frac{\left(\frac{L}{\rho}\right)<em>{\text{med}}}{\left(\frac{L}{\rho}\right)</em>{\text{gas}}}\right]_{\text{diff,depth=10cm}}$</td>
<td>-0.4770 %</td>
<td>-0.9063 %</td>
<td>-1.1662 %</td>
</tr>
<tr>
<td>$\left[\frac{\left(\frac{L}{\rho}\right)<em>{\text{med}}}{\left(\frac{L}{\rho}\right)</em>{\text{gas}}}\right]_{\text{diff,depth=15cm}}$</td>
<td>-0.4869 %</td>
<td>-0.9615 %</td>
<td>-1.1274 %</td>
</tr>
</tbody>
</table>
5.2.4.2 Dose measurement with radiographic film

Radiographic film is used for radiation dosimetry with advantages in spatial resolution, reading permanence, commercial availability, geometry (for field-mapping), linearity with dose and dose-rate independence (Attix 2004). However, radiographic film is known to exhibit energy dependence, with an over-response (factor of 10-50) to photons less than 100 keV in particular. See, for instance, early work such as that of Herz (1969) and more recent publications such as Task Group 69 on radiographic film (Pai et al. 2007). Yeo (Yeo et al. 2004) showed EDR2 overestimates by ~9% in clinically-relevant conditions. Radiographic film consists of an emulsion of microscopic grains of silver bromide (AgBr) dispersed in a gelatine layer on both sides of a supporting film base. Incident charged particles generate ion pairs in/near the grains, converting Ag⁺ ions to Ag atoms. Chemical processing removes the bromine and leaves behind an (opaque) microscopic grain of silver, the presence of which may be detected optically and related quantitatively to the dose absorbed.

Palm et al (2004) investigated the response of Kodak XV radiographic film. They assumed a uniform mix of AgBr with cellulose nitrate, describing the film as having a fractional elemental composition by weight given by H:0.023948, C:0.222374, N:0.099407, O:0.473944, Br:0.076736 and Ag:0.103592. The density is 1.731 gcm⁻³ and the total thickness is 7.8 µm (3.9 µm either side of a polyethylene terephthalate substrate). In this study, an in silico investigation of the response of radiographic film (compared to water) is undertaken using EGSnrc. The composition given by Palm et al is used to define a 187.8 µm thick radiographic film in a water phantom. For computational efficiency, a cylindrically-symmetric geometry was defined. This is illustrated in Figure 5.32.

![Figure 5.32](image)

*Figure 5.32* A representation of the modelled geometry. Monte Carlo radiation transport calculations were undertaken on a cylindrically-symmetric geometry incorporating a 3.9:180:3.9 µm emulsion-substrate-emulsion film at a depth of 5 cm in water. Equivalent simulations were undertaken with water in place of film, so as to determine the relative response of the film. A 18 x 18 mm² 6 MV beam (generated with the commissioned model of the Varian 600C with mounted MMLC) was made incident upon the cylindrical phantom. Dose was scored in radial bins of 2.5 mm width.
The film was modelled at a depth of 5 cm in water and irradiated with an 18 x 18 mm² field. The radiographic film is shown to exhibit an over-response to the incident field (Figure 5.33). The dose to the film is approximately 1.2 % higher than that to water at an equivalent spatial location irradiated with the same field. Considering only the 3.9 µm emulsion layer, the discrepancy between film and water is higher – approximately 2 %. Note also that the discrepancy varies spatially. One might hypothesise a greater concern may be the difference in spectrum between small fields and the larger reference field used for calibration.
5.2.4.3 Dose measurement with thermoluminescent dosimeters

Thermoluminescent dosimeters (TLD) are widely employed in a clinical context because of their applicability to small field measurement, *in vivo* dosimetry and out-of-field dose measurement. In clinical dosimetry, Lithium Fluoride is the most commonly employed thermoluminescent material, and for a comprehensive review the interested reader is referred to the manuscript by Kron (1994). Lithium Fluoride doped with Magnesium and Titanium (LiF:Mg,Ti), known as TLD-100, is the most widely implemented. For applications requiring greater sensitivity, LiF doped with Magnesium, Copper and Phosphorous (LiF:Mg,Cu,P) TLDs, known as TLD-100H, are often employed. This includes such applications as measurement of out-of-field organ doses in radiotherapy (Taylor et al. 2011c), where scattered and leaked radiation dominates and the radiation spectrum differs notably from the primary field. McKeever *et al.* (1995) and the references therein provide a good overview of the characteristics of TLD-100 and TLD-100H dosimeters, the radiological properties of which are of significant interest (Horowitz 1993b; Mobit *et al.* 1998; Horowitz 1999; Saez-Vergara *et al.* 1999; Schoner *et al.* 1999; Bilski 2002; Horowitz and Olko 2004).

The dose information ultimately yielded by TLDs after exposure to ionising radiation is not straightforward, with many contributing factors. One parameter of interest is the effective atomic number, $Z_{\text{eff}}$ – often used as a means of characterising the radiological properties of dosimeters. This is because, as McKeever *et al.* (1995) state, it is ‘the critical material parameter’, the value of which determines which interaction processes dominate.

There is a notable difference between the effective atomic number of thermoluminescent dosimeters compared to water and soft tissue. This is illustrated by Figure 5.34 and Figure 5.35. The maximum discrepancy between $Z_{\text{eff}}$ of TLD and of water coincides with the maximum photons fluence. See Taylor (2011) for a more comprehensive discussion of the effective atomic numbers of TLD-100 and TLD-100H and the influence of dopants and impurities.
Figure 5.34 (a) The effective atomic numbers ($Z_{eff}$) for total photon interaction processes calculated using the method of Taylor (2011), for water, soft tissue (ICRU 1989), TLD-100H and the PAGAT polymer gel dosimeter (Venning et al. 2005a). (b) The same $Z_{eff}$ data for the various media is presented as a ratio to that of water. The gel matches water very closely, more so in fact than soft tissue. The effective atomic number of the TLD is consistently higher than water, especially (and perhaps surprisingly) in the Compton regime.

Figure 5.35 Effective atomic numbers ($Z_{eff}$) for total photon interaction processes calculated using the method of Taylor (2011), for water, soft tissue (ICRU 1989), TLD-100H and the PAGAT polymer gel dosimeter (Venning et al. 2005a). Overlayed is the photon spectrum at 5 cm depth in water for a 18 x 18 mm$^2$ field. The photon fluence is greatest at energies where the discrepancy between $Z_{eff}$ of water, tissue and gel are similar, but the difference between water and TLD-100H is high.
5.2.5 Conclusions

A systematic study of stereotactic beam characteristics has been undertaken, calculated with a dosimetrically-matched Monte Carlo model of a Varian 600C with mounted BrainLAB MMLC. A large dataset has been obtained to facilitate thorough characterisation, including:

- Photon spectra,
- Contaminant electron spectra,
- Spatial variation of mean photon energy,
- Spatial variation of mean electron energy, and
- Angular distribution of photons.

Spectral data in water at several depths (5, 10 and 15 cm) has also been calculated, including:

- Photon energy fluences,
- Electron energy fluences, and
- Mean energy distributions.

Further data has been compiled for comparison using ‘backed-up’ field, i.e. jaws set at the same field opening as the MMLC. Mean energy, spectral and angular distributions were calculated for several representative cases.

Furthermore, three examples have been given to illustrate the effect of energy dependent dosimeters. In the first case, it is shown that the routine calibration of ionisation chambers performed with a reference (10 x 10 cm²) field and the assumption of unchanging secondary electron spectra does result in a systematic error that increases for decreasing field size. However, this error is less than 1 % within the primary field and may be considered negligible. Conversely, measurements taken beyond the primary field are subject to greater errors that increase with field size. The latter phenomenon is a direct result of the different spectra in- and out-of the primary field. The second example demonstrated is the over-response of radiographic film. Film is shown to over-respond by up approx. 1.2 % compared to water alone. This over-response varies in degree spatially, being high in the primary field, then low in the immediate periphery, then rising again slightly in the out-of-field region. The third example involves TLD-100 LiF thermoluminescent dosimeters. Studying the energy dependence of the effective atomic number of the TLD shows the maximum discrepancy between Z_{eff} of the TLD and of water coincides with the peak of the photon spectrum.
5.3 Dosimetric characteristics of small stereotactic fields

The dosimetric characteristics of small fields as used in stereotactic radiotherapy are difficult to measure in comparison to broad-beam fields. This issue has been discussed in greater detail in previous chapters. Issues of charged particle equilibrium raise questions about the accuracy of dose calculation using conventional treatment planning systems. Even newer, more rigorous dose calculation algorithms are nonetheless reliant upon measured dose profiles for input, and are thus still subject to the limitations of the experimentally measured doses. These limitations include effects such as detector volume averaging, which complicates the accurate measurement of penumbra and limits the field size measurable. It is common clinical practice to employ multiple dosimeter types for the measurement of small fields, and then average the measured results.

The first half of this chapter has involved thorough characterisation of spectral qualities of stereotactic fields. The subsequent half of the chapter investigates dosimetric aspects of stereotactic radiotherapy. Specifically, this is undertaken for two ‘case studies’ – one intracranial and one extracranial.

In previous chapters, the potential for three-dimensional gel dosimetry for the measurement of small-field characteristics has been described. In this chapter, polymer gel dosimetry is employed to investigate the dose distribution in an anthropomorphic phantom to demonstrate the feasibility of gel dosimetry stereotactic plan verification.

Also presented in this chapter is an investigation of lung tumour under-dosage; this study is an example where Monte Carlo calculations show great promise in complementing or even replacing measurements. As stated, electronic disequilibrium may complicate the calculation of absorbed dose at interfaces of dissimilar media. One such example is that of a lung tumour (which has a density close to that of soft tissue or water) within lung tissue (which has a density approximately one third that of soft tissue). In such a case, treatment planning system algorithms such as pencil beam convolution are expected not to accurately predict the dose to peripheral regions. Even calculation via more advanced algorithms is often limited by the dose grid size. Furthermore, clinical trials often employ algorithms such as the pencil beam. As such, it is useful to be able to estimate the extent of peripheral under-dosage in order to determine (whether prospectively or retrospectively) the dose to a lung tumour. This chapter provides a systematic investigation of lung tumour under-dosage.
Both of the following sections of this chapter constitute self-contained papers prepared for submission to scientific journals. As such, there is a separate introduction to highlight the clinical relevance and case specific conclusions. However, both sections serve to explore the complexity of the three-dimensional dose distributions encountered in small-field dosimetry. They were chosen to highlight the role of experimental and theoretical methods for this purpose. Some of the introductory material has been covered earlier in greater detail and the reader may elect to pass over some of the prefatory sections.

5.4 Validation of stereotactic treatments for small intracranial tumours via normoxic polymer gel dosimetry (PAGAT) with optical CT readout†

Stereotactic radiotherapy and radiosurgery often employ small photon fields in the treatment of intracranial targets. Complexities associated with small fields, such as an absence of charged particle equilibrium, make measurement of such fields inherently difficult and impose a level of uncertainty on the treatment. A particular focus of this thesis is the applicability of three-dimensional (3D) gel dosimetry as a potential solution to many of the problems associated with small-field dosimetry. This has been discussed in detail in Chapter 3.

Here, the potential for stereotactic treatment validation using normoxic polymer gel dosimetry (with optical-CT readout) in an anthropomorphic head phantom is assessed. A 12-field stereotactic treatment plan for meningioma was recalculated onto a computed tomography scan of the head phantom with gel insert and was delivered using a Varian 2100 linear accelerator with mounted BrainLAB m3 mini-multileaf collimator. Via quantitative comparison using indices such as percentage pixel agreement and gamma analysis, it is demonstrated that 3D gel dosimetry may be readily employed for assessment of PTV coverage. Gamma analysis showed that above the 80% isodose line, ~90% of the gamma values were less than unity (for criteria of 2%/2mm). Poorer agreement was observed at low isodoses, most likely because in these regions: (i) the gel receives only low doses and may exhibit nonlinearity, (ii) the effects of slight misregistration of the plan and gel dose distributions may be more pronounced, (iii) optical scatter and (iv) the treatment planning system may not accurately calculate dose adjacent to the container wall.

† Note for the sake of scientific integrity, this section of the chapter repeats the associated publication verbatim; ML Taylor et al, Three-dimensional dose verification for clinical treatments of small intracranial tumours, Medical Physics, in prep
5.4.1 Introduction

Cancers of the brain and central nervous system account for 1.6% of new cancers and 1.8% of cancer deaths globally. The highest rates of all developed nations are observed in Australia and New Zealand (Parkin et al. 1999). Despite being less common than some other cancers of the human body, a relatively large variety of benign and malignant brain tumours exist. These are often treated by means of intracranial radiotherapy, as are vascular disorders such as arteriovenous malformations (AVM).

The brain exhibits a high degree of sensitivity for radiation damage, both acute and delayed. Immediate side effects occur in one third of patients \((N = 78)\) treated with SRS and SRT, but are usually moderate (Werner-Wasik et al. 1999). The typical acute effect of high radiation doses to the brain is an increased intracranial pressure, arising from brain oedema (an abnormal build-up of serous fluid between tissue cells). Contemporary radiotherapy methods of dose delivery and fractionation effectively eliminate the potential for acute radiation damage, however, there can be a delayed reaction to brain irradiation that is likely to result from transient interruption of myelin (which acts as an insulator between nerve fibres) synthesis by oligodendrocytes (Rider 1963). This manifests itself in forms of neurological deterioration. This is generally nonfatal and the aforementioned effects are often temporary, however, severe late radiation damage is typically permanent and can result in effects ranging from mild neurological impairment to death. Such radiation necrosis is the gravest potential consequence of therapeutic brain irradiation. This can occur with relatively high probability when treatment plans exceed 40 Gy in 20 fractions, or 60 Gy in 30 fractions in five weeks, or when fractions exceed 3 Gy (Lee et al. 1988; Marks and Spencer 1991). Adverse radiation reactions have been reported in applications of radiosurgery, despite the small treatment volumes involved (Flickinger et al. 1995; Ianssen et al. 2004; Jensen et al. 2005). High dose focal and whole brain irradiation are often performed for intracranial lesions, though little is known about long-term neuropsychological effects. Clinical findings show children exhibit cognitive decline subsequent to radiotherapy of brain tumours; data for adults is comparatively scarce, with preliminary findings suggesting some cognitive function, such as memory, may be particularly vulnerable (Roman and Sperduto 1995).

The potential for such detriment necessitates a high degree of conformality in the delivered dose, particularly in the case of SRS which employs high-dose single-fraction treatments. In vivo measurement of dose is not feasible. The treatment planning system employs a dose computation algorithm (pencil beam) that is limited in its treatment of electronic disequilibria, such as those which occur in the vicinity of interfaces and with small fields. In this study, the efficacy of gel dosimetry for dosimetric verification of stereotactic fields is investigated using a radiosensitive polymer gel in an anthropomorphic head phantom.
5.4.2 Experimental method

5.4.2.1 Clinically-relevant stereotactic treatment delivered to phantom

A 12-field stereotactic treatment plan for a patient with meningioma was recalculated on a computed tomography (CT) scan of an anthropomorphic head phantom with an intracranial cavity (CIRS, Virginia). The cubic (63.5mm$^3$) cavity contains a block with a gel container – a cylindrical vessel (with a very slight divergence) 43 mm in diameter (at base) by 63 mm in length. Figure 5.36 shows a three-dimensional (3D) render and two-dimensional (2D) slice generated from the CT scan, as well as a photo of the head phantom. The treatment plan was calculated using the pencil beam algorithm in iPlan RT Dose (BrainLAB, Feldkirchen). The phantom was scanned and treated with a thermo-transformable fixation mask for reproducibility (this is also evident in the 3D render in Figure 5.36). A total dose of 5.19 Gy was delivered to the PTV in a single fraction with 12 conformal fields (see Table 5.4 for more detail). The planned dose distribution was exported with 0.5 mm resolution and analysed using Matlab (MathWorks Inc., Massachusetts).

<table>
<thead>
<tr>
<th>Conformal field</th>
<th>Weight (%)</th>
<th>$D_{isc}$ (Gy)</th>
<th>Gantry (°)</th>
<th>Couch (°)</th>
<th>Collimator (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.8</td>
<td>0.37</td>
<td>25</td>
<td>0</td>
<td>135</td>
</tr>
<tr>
<td>2</td>
<td>5.7</td>
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<td>300</td>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>9.8</td>
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<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>9.8</td>
<td>0.36</td>
<td>350</td>
<td>0</td>
<td>90</td>
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<tr>
<td>5</td>
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<td>225</td>
<td>0</td>
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<td>7</td>
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<td>268</td>
<td>338</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>6.2</td>
<td>0.34</td>
<td>294</td>
<td>338</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>10.0</td>
<td>0.58</td>
<td>285</td>
<td>300</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
<td>6.9</td>
<td>0.42</td>
<td>320</td>
<td>300</td>
<td>90</td>
</tr>
<tr>
<td>11</td>
<td>9.8</td>
<td>0.56</td>
<td>330</td>
<td>270</td>
<td>90</td>
</tr>
<tr>
<td>12</td>
<td>9.9</td>
<td>0.37</td>
<td>20</td>
<td>270</td>
<td>90</td>
</tr>
</tbody>
</table>
5.4.2.2 Gel dosimeter
In this work we employed a normoxic polyacrylamide gel (PAG) dosimeter containing tetrakis (hydroxymethyl phosphonium chloride (THP) as an anti-oxidant, known as PAGAT (polyacrylamide, gel and THP). This gel dosimeter contains (in order of concentration) pure water, gelatine, bis, acrylamide, hydroquinone and THPC. Readers are referred to the original work by Venning et al (2005a) for details of the gel manufacturing process. The gel exhibits good water/tissue equivalency as evidenced by Table 5.5, which shows the mean effective atomic numbers for photon and electron interactions, weighted a 6 MV photon spectrum using a method described elsewhere (Taylor et al. 2008; Taylor et al. 2009b). ‘Large tub’(Taylor et al. 2007; Taylor et al. 2009a) calibration is the most appropriate approach.

5.4.2.4 Optical readout of the gel dosimeter
The gel was read out using an Octopus-IQ laser optical computed tomography (CT) scanner (MGS Research Inc., Madison USA). Although the scan speed is slower than cone-beam optical CT scanners, the advantage of the laser scanner is significantly reduced scatter artefacts when reading out polymer gels as compared with broad beam techniques. The scan employed a slice thickness of 0.5 mm and 720 angular projections for 0.5 mm pixels. The refractive index matching fluid was approximately 70 % water to 30 % glycerol, with food dye and trace amounts of sulphuric acid and sodium benzoate (< 0.1 %) to prevent algae growth.
Figure 5.36 A (a) render and (b) midsagittal slice generated from a CT scan of the anthropomorphic head phantom. The fixation mask is readily noticeable in the render. In the sagittal slice one can clearly see the large intracranial cavity, filled with two solid spacers on the left and the gel container on the right. (c) A photo of the head phantom (MGS Research Inc., Madison USA), in this case with a film stack in the intracranial cavity rather than the gel insert.

Table 5.5 Data indicating the water / tissue equivalence of PAGAT gel. Compositional details of soft tissue sourced from ICRU data. The mass densities of PAGAT, water and soft tissue are given. The effective atomic number of a material varies significantly with the energy of the incident radiation. Calculated here are mean effective atomic numbers corresponding to the total interaction cross section for photons and electrons, weighted by a 6 MV photon spectrum (Mohan et al. 1985), as described elsewhere (Taylor et al. 2008; Taylor et al. 2009b).

<table>
<thead>
<tr>
<th>Material</th>
<th>( \rho, \text{kg.m}^{-3} )</th>
<th>( \overline{Z_{\text{eff}}}(\text{Photons}) )</th>
<th>( \overline{Z_{\text{eff}}}(\text{Electrons}) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAGAT</td>
<td>1026</td>
<td>3.40</td>
<td>3.37</td>
</tr>
<tr>
<td>Water</td>
<td>1000</td>
<td>3.36</td>
<td>3.40</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>1060</td>
<td>3.36</td>
<td>3.35</td>
</tr>
</tbody>
</table>
5.4.3 Results and discussion

Figure 5.37 illustrates the 3D dose distribution as measured with the gel dosimeter. A number of methods have been employed to compare the measured dose distribution with that calculated by the treatment planning software. The treatment was delivered such that the isocentre was located at the centre of the gel container, so as to maximize the distance from interfaces. Figure 5.38 shows 2D dose maps and profiles to illustrate the agreement between the gel measurements and treatment planning predictions. The good agreement in high-dose regions is also reflected in Figure 5.40, which graphically indicates the level of agreement via histograms of pixel agreement. The high dose regions clearly match well, indicating good agreement in the PTV dose and its immediate periphery. Poorer agreement exists at lower isodoses. This is also made clear from Table 5.6 which quantifies the percentage of pixels that match within 2%. The dose to the PTV matches well, with >96% of pixels matching better than 2% above the 90% isodose curve. Figure 5.39 shows line profiles illustrating the level of agreement between the measured and calculated doses.

**Figure 5.37** Illustration of the 3D dose distribution measured with the gel dosimeter (dark = 90% isodose, medium = 80% isodose and light = 75% isodose). The scale is in pixel numbers (where the pixel size is 0.5 mm).
Figure 5.38 Surface plots corresponding to 2D slices through the isocentre for the (a) gel and (b) iPlan dose distributions. The most pronounced difference is the scatter artefacts caused by the gel container. The colour-bar and vertical axis correspond to relative dose, ranging from 0 to 100 %. The x- and y-axes correspond to distance, with 10 mm increments.
One may observe that in Figure 5.39 there is a notable discrepancy between measured and predicted (treatment planning system) doses. There are likely to be a range of reasons for such differences, but it is important to note that more recent work involving replication of this experiment using Monte Carlo methods indicates much better agreement with the gel dose than the treatment planning system (Kairn et al. 2011). Not only other there many physics approximations in the pencil beam algorithm employed, but the commissioning data is limited for such small fields (uncertainties in scatter factors may range beyond 10 %) and the cumulative effect for such a complex treatment as this one may be significant. Indeed, this may be seen as an important result, highlighting again the complexities of small fields which are the focus of this thesis.

Gamma ($\gamma$) analysis was also undertaken to quantify the level of agreement. The $\gamma$ evaluation method involves the combination of a dose-difference criterion and a distance-to-agreement (DTA) criterion to assess the discrepancies between two dose distributions (Low et al. 1998a). In brief, the measured dose distribution, $D_{\text{gel}}(\vec{r}_{\text{gel}})$, is compared to the calculated dose distribution, $D_{\text{calc}}(\vec{r}_{\text{calc}})$, at points $\vec{r}_{\text{gel}}$ and $\vec{r}_{\text{calc}}$ such that the dose difference may be specified as:

$$\delta(\vec{r}_{\text{gel}}, \vec{r}_{\text{calc}}) = D_{\text{gel}}(\vec{r}_{\text{gel}}) - D_{\text{calc}}(\vec{r}_{\text{calc}}),$$

5.5
and the spatial difference may then be given by:

\[ r \left( \mathbf{r}_{\text{gel}}, \mathbf{r}_{\text{calc}} \right) = \left\| \mathbf{r}_{\text{gel}} - \mathbf{r}_{\text{calc}} \right\|. \tag{5.6} \]

Specifying acceptance criteria for dose and distance-to-agreement of \( \Delta D \) and \( \Delta d \) respectively, one may then define the \( \gamma \)-function as:

\[ \gamma \left( \mathbf{r}_{\text{gel}}, \mathbf{r}_{\text{calc}} \right) = \sqrt{\frac{\delta^2 \left( \mathbf{r}_{\text{gel}}, \mathbf{r}_{\text{calc}} \right)}{\Delta D^2} + \frac{r^2 \left( \mathbf{r}_{\text{gel}}, \mathbf{r}_{\text{calc}} \right)}{\Delta d^2}}. \tag{5.7} \]

A \( \gamma \) value less than unity is considered as accepted. One must be careful in the interpretation of the \( \gamma \) evaluation; for instance, for criteria of \( \Delta D = 3\% \) and \( \Delta d = 3\,\text{mm} \), a dose difference of 2.9\% and distance disagreement of 2.9 mm would result in \( \gamma > 1 \) and fail the \( \gamma \) test.

The results of the \( \gamma \) analysis (with criteria of \( \Delta D = 2\% \) and \( \Delta d = 2\,\text{mm} \), and \( \Delta D = 5\% \) and \( \Delta d = 5\,\text{mm} \)) are given in Table 5.7. For the PTV, above the 90\% isodose, \( \gamma \) agreement of 86\% was exhibited for 2\%/2\,mm criteria. Above the 60\% isodose \( \gamma \) agreement is \sim 80\%, dropping to 20\% at the 20\% isodose for the same criteria.
Figure 5.40 A set of relative-frequency histograms (normalised to unity) illustrating the level of agreement between doses measured in the radiosensitive gel and those predicted with iPlan, highlighting the good PTV coverage (as evidenced by (b), which shows good agreement above the 90% isodose) and the difficulties in obtaining accurate measured data in the low-dose regions in close proximity to the walls of the gel container, such as in (e) and (f). Subfigures (a) through (f) show the percentage differences between the measured and planned dose distributions (from the maximum dose out to the isodoses indicated in each case).
Table 5.6 An indication of the agreement between the planned and measured dose distributions. Here, ‘Agreement’ refers to the number of pixels values that agree within 2%. The mean difference and standard deviation are also given. There is clearly poorer agreement at lower isodoses.

<table>
<thead>
<tr>
<th>Isodose (%)</th>
<th>Agreement (%)</th>
<th>Mean difference (%)</th>
<th>σ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>96.2</td>
<td>-0.844</td>
<td>10.2</td>
</tr>
<tr>
<td>80</td>
<td>89.2</td>
<td>-0.37</td>
<td>11.1</td>
</tr>
<tr>
<td>70</td>
<td>87.8</td>
<td>-0.396</td>
<td>8.85</td>
</tr>
<tr>
<td>60</td>
<td>83.7</td>
<td>0.006</td>
<td>10.5</td>
</tr>
<tr>
<td>50</td>
<td>77.0</td>
<td>-1.50</td>
<td>11.2</td>
</tr>
<tr>
<td>40</td>
<td>74.4</td>
<td>-1.22</td>
<td>8.42</td>
</tr>
<tr>
<td>30</td>
<td>63.4</td>
<td>3.74</td>
<td>8.49</td>
</tr>
<tr>
<td>20</td>
<td>35.6</td>
<td>-0.238</td>
<td>8.75</td>
</tr>
<tr>
<td>10</td>
<td>29.5</td>
<td>5.86</td>
<td>10.5</td>
</tr>
<tr>
<td>Mean</td>
<td>70.7</td>
<td>0.56</td>
<td>9.78</td>
</tr>
</tbody>
</table>

Table 5.7 This table indicates the agreement between the planned and measured dose distributions via 2D gamma map analysis (through the isocentre). Gamma criteria of 2%/2mm and 5%/5mm are shown.

<table>
<thead>
<tr>
<th>Isodose (%)</th>
<th>γ (2% / 2mm)</th>
<th>γ (5% / 5mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>86.3</td>
<td>94.4</td>
</tr>
<tr>
<td>80</td>
<td>84.6</td>
<td>94.2</td>
</tr>
<tr>
<td>70</td>
<td>81.5</td>
<td>92.7</td>
</tr>
<tr>
<td>60</td>
<td>79.8</td>
<td>88.4</td>
</tr>
<tr>
<td>50</td>
<td>74.6</td>
<td>81.7</td>
</tr>
<tr>
<td>40</td>
<td>66.4</td>
<td>78.5</td>
</tr>
<tr>
<td>30</td>
<td>56.7</td>
<td>64.8</td>
</tr>
<tr>
<td>20</td>
<td>19.7</td>
<td>38.6</td>
</tr>
<tr>
<td>10</td>
<td>17.9</td>
<td>27.0</td>
</tr>
<tr>
<td>Mean</td>
<td>63.1</td>
<td>73.2</td>
</tr>
</tbody>
</table>
There are a range of issues that may potentially influence the agreement between the plan and the measured dose:

(i) **Registration accuracy.** The CT (and therefore the dose distribution calculated by the treatment planning system) was not aligned with the Cartesian axes, which, combined with the limited resolution of the plan, made alignment of the measured and calculated dose distributions difficult. The registration was optimized, but is unlikely to be ideal.

(ii) **Dose response.** The maximum dose delivered to the gel was 5.19 Gy. Although the dose response of PAGAT when readout optically (or with MRI) is fairly linear out to about 10 or 15 Gy, at low doses (particularly <1 Gy) the response of PAGAT is poorly known (Senden et al. 2006a; Bosi et al. 2007).

(iii) **Optical scatter.** Despite subtraction of a ‘background’ matrix (an optical scan of a gel in the same arrangement with zero dose), there were issues of optical scatter around the interface of the container and gel; this is indicated in Figure 5.41. Stray light due to scattering from the dose distribution itself is also expected, since the polymer gel scatters (rather than absorbs) light.

(iv) **Normalisation/calibration.** The TPS-calculated and gel doses are compared by normalising to maximum dose. If the gel exhibits a non-linear dose response at higher doses then the agreement at low doses will be poorer. Furthermore, optical scatter is greater at higher doses, which again will affect the agreement (the total signal is a combination of light transmitted through the gel and scatter; thus, for high dose regions there is low transmittance and a greater fraction of scattered light).

(v) **Accuracy of pencil beam at interfaces.** The poor match of experimental data and that calculated using the iPlan pencil beam algorithm occurs within the vicinity of the interface with the container. One would not expect the error in dose prediction to be significant in this region since the radiological properties of the two juxtaposed media are not dissimilar; however, the influence of a possible miscalculation in this region may not be discounted. Also relevant is the accuracy of the commissioning of small-field data. Scatter factors for very small fields exhibit relatively high uncertainty; the integral dose result for this 12 beam case may also result in significant discrepancies. This notion is supported by high agreement between Monte Carlo and the gel results presented here (Kairn et al. 2011).
5.4.4 Conclusions

There is a demonstrated requirement for accurate dosimetry of stereotactic fields, such as the 12-field treatment for a small meningioma as investigated here. Gel dosimetry is not subject to limitations such as volume averaging, yielding a fully three-dimensional dose distribution for verification of a planned clinical treatment. Agreement close to the PTV is generally good; above the 90% isodose, $\gamma$ evaluation indicated 86% agreement for criteria of 2%/2mm. Limitations in low-dose regions may be attributable to nonlinearity of dose response when read out optically, optical scatter at interfaces, poor registration and potentially the limited accuracy of the pencil beam algorithm for dose calculation (the container is 63 mm in diameter and the electron range is ~16 mm). Though it is tempting to attribute discrepancies to the limitations of gel dosimetry, it is important to remember that the accuracy of the dose calculation (to which the gel measurements are compared) is questionable. This is due not only to the inherent limitations of the pencil beam algorithm, but the scatter factors for such small fields are not well known. Spatially, the PTV occupies a region only 10-17 mm across. Clinically, scatter factors are typically known down to about $1 \times 1$ cm$^2$ or $2 \times 2$ cm$^2$, and interpolation to smaller field sizes may be dubious (particularly since measured output factors employed clinically typically exhibit standard deviations up to the order of 15% at 99% CI). Evidence for the clinical feasibility of gels for plan verification has been provided, making special note of the fact that agreement is much stronger between gel and Monte Carlo than gel and TPS (Kairn et al. 2011).
5.5 Small-field radiotherapy of lung tumours: A systematic investigation of under-dosage due to electronic disequilibrium

Prediction of dose distributions in close proximity to interfaces is difficult. In the context of radiotherapy of lung tumours, this may affect the minimum dose received by lesions and is particularly important when prescribing dose to covering isodoses. The objective of this work is to quantify under-dosage in key regions around a hypothetical target using Monte Carlo dose calculation methods, and to develop a factor for clinical estimation of such under-dosage. A systematic set of calculations are undertaken using two Monte Carlo radiation transport codes (EGSnrc and GEANT4). Discrepancies in dose are determined for a number of parameters, including beam energy, tumour size, field size and distance from chest wall. Calculations were performed for 1 mm³ regions at proximal, distal and lateral aspects of a spherical tumour, determined for a 6 MV and a 15 MV photon beam. The simulations indicate regions of tumour under-dose at the tumour-lung interface. Results are presented as ratios of the dose at key peripheral regions to the dose at the centre of the tumour, a point at which the TPS predicts the dose more reliably. Comparison with TPS data (pencil beam convolution) indicates such under-dosage would not have been predicted accurately in the clinic. We define a Dose Reduction Factor (DRF) as the average of the dose in the periphery in the six cardinal directions divided by the central dose in the target, the mean of which is 0.97 and 0.95 for a 6 MV and 15 MV beam respectively. The DRF can assist clinicians in the estimation of the magnitude of potential discrepancies between prescribed and delivered dose distributions as a function of tumour size and location. Calculation for a systematic set of ‘generic’ tumours allows application to many classes of patient case, and is particularly useful for interpreting clinical trial data.

For the sake of scientific integrity, this section of the chapter repeats the associated publication verbatim (Taylor et al. 2011b).
5.5.1 Introduction

It is known that the periphery of lung tumours is under-dosed in radiotherapy due to electronic disequilibrium at the interfaces of tumour and lung tissue (Metcalfe et al. 2007). Knowledge or estimation of the degree of dose inhomogeneity is required so as to interpret outcomes from clinical trials or for the design of new treatment protocols. While the best of contemporary treatment planning systems may be able to calculate these effects adequately, those clinics using more simplistic algorithms (such as pencil beam convolution) and clinical trial data from treatments planned using earlier algorithms require further information for accurate assessment (Timmerman et al. 2006). The aim of this work was to develop a generalised method with a simple geometry involving several variables to allow a straightforward estimation of the magnitude of peripheral under-dosage. This is facilitated by tabulation of minimum doses at key points and the introduction of a ‘dose reduction factor’ – a mean value representing the under-dosage to the peripheral ‘shell’ of a lung tumour relevant for multiple-field or arc therapy. Assessment of incorrect dose prediction in the periphery of the tumour would be particularly important if the prescription is based on a covering isodose. A generic model can be used to inform protocols and used to interpret clinical data retrospectively. It can also be useful when evaluating new plans if accurate dose calculation on a millimetre scale are not available.

The extent of under-dosage was evaluated using Monte Carlo radiation transport methods. Monte Carlo simulation is accepted as an accurate means of modelling dose distributions, particularly in regions of electronic disequilibrium such as interfaces of high and low density media. In the field of radiotherapy, EGSnrc is extensively used for Monte Carlo calculations, and has found to be accurate at the sub-percent level in the context of external beam radiotherapy (Chibani and Li 2002; Doucet et al. 2003). Moreover, a literature survey of papers involving Monte Carlo methods in the context of stereotactic (body) radiotherapy indicates EGSnrc is employed with far greater frequency than other Monte Carlo transport codes. For this reason, the results shown in this work were derived using EGSnrc. Nevertheless, to strengthen the results, agreement with an alternative transport code (GEANT4) was assessed. GEANT4 (GEometry ANd Tracking) is a detector simulation toolkit for the simulation of the passage of particles through matter using Monte Carlo methods and an Object Oriented (C++) basis. GEANT4 simulations have been compared with established and authoritative reference data taken from open and recognised databases (NIST, ICRU, etc.). Poon and Verhaegen (2005) validated the photon and electron transport of the GEANT4 toolkit by examining cross sections and sampling algorithms, and showed an agreement with EGSnrc to within 2% except in the buildup region for depth-dose distributions in water. Perturbation
effects near high-Z and low-Z interfaces can be overcome by careful selection of physics processes and transport parameters. In particular, use of step-size restrictions can yield accurate results at interfacial regions (Poon et al. 2005). The use of two transport codes based on different physical models improves the confidence in results presented in this study.

5.5.2 Method
In this study, Monte Carlo methods are employed to develop a systematic set of data that may be used by clinicians to estimate the magnitude of dose prediction error that may occur as a result of the complex nature of the treatment and limitations of clinical planning tools. The accurate modelling of radiation interactions, particularly in the vicinity of heterogeneities, by Monte Carlo techniques facilitates assessment of tumour under-dosage. The modelled geometry is shown in Figure 5.42. The EGSnrc model used rectilinear 1 mm$^3$ voxels, while the geant4 model employed spherical 1 mm$^3$ voxels at the dose calculation points. A virtual tumour within lung tissue that lies beyond a soft tissue layer (such as the chest wall) was irradiated with an external photon beam. Several factors were varied to determine influences on dose distributions. These parameters include beam energy, field size, tumour size and distance of the tumour from the internal chest wall, as summarised in Table 5.8. A parallel beam of flat profile was chosen to remove inverse-square law contributions and relate to an isocentric arrangement, with field sizes chosen to extend 10 mm beyond the tumour boundary. For reproducibility the photon spectra employed are those given by Mohan et al (1985). Photon beams of 6 and 15 MV were chosen because 6 MV is commonly employed clinically and 15 MV is at the high end of the possible treatment energy choices, and serves to illustrate the energy dependence of the results. Thus, readers may be able to estimate intermediate values relevant to their own clinic. The tissue compositions, outlined in Table 5.9, are those defined by the International Commission on Radiological Units (ICRU 1989) except for that of the lung tumour, which was determined by Maughan et al (1997) using combustion analysis of excised squamous cell lung carcinoma.
Figure 5.42 Schematic of simulated geometry. A photon beam (the energy spectrum, $E$, and field size, $FS$, of which are varied) is made incident upon a voxelated phantom consisting of a wall of soft tissue followed by lung tissue, in which exists a spherical tumour. The thickness of soft tissue is set to 20 mm. The distance, $d$, from the soft-lung tissue interface to the tumour is varied. The diameter of the tumour, $\Theta_t$, is also varied, and determines the field size. The uniform voxel size is 1 mm$^3$.

Table 5.8 Systematic set of simulation parameters varied to indicate the influence on dose. Multiple photon spectra were modelled using the well known definitions provided by Mohan et al (1985).

<table>
<thead>
<tr>
<th>Varied parameters</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Photon beam spectrum, $E$ (MV)</td>
<td>6 and 15</td>
</tr>
<tr>
<td>Tumour diameter, $\Theta_t$ (mm)</td>
<td>10, 16, 20, 30 and 50</td>
</tr>
<tr>
<td>Field size, $FS$ (mm$^2$)</td>
<td>30 x 30, 35 x 35, 40 x 40, 50 x 50 and 70 x 70</td>
</tr>
<tr>
<td>Distance from chest wall, $d$ (mm)</td>
<td>5, 10, 20 and 40</td>
</tr>
</tbody>
</table>
Physics processes in EGSnrc include: bremsstrahlung production, positron annihilation (in flight and at rest), multiple scattering by coulomb scattering from nuclei, Möller scattering, Bhabha scattering, continuous energy loss between discrete events, pair/triplet production, Compton scattering, Rayleigh scattering, the photoelectric effect, atomic relaxation and electron impact ionisation. The work undertaken with EGSnrc employs the PRESTA-II electron-step algorithm with the EXACT boundary crossing algorithm such that the electron transport will go into single-scattering mode within three elastic mean free paths of the boundary, giving the necessary accuracy at peak efficiency. In the Monte Carlo investigations carried out here, a step size of 0.25 (maximum fractional energy loss, ESTEPE) was employed. EGSnrc has been shown to produce step-size independent results at a sub 0.1 % level even at interfaces of high Z media in fine geometries (Kawrakow 2000; Verhaegen 2002). Calculations were performed on the VPAC Tango AMD Opteron system. Typically, four processors (AMD Barcelona 2.3 GHz quad core) were employed per simulation, each simulation thus requiring approximately 9 hours for $10^{10}$ initial particle histories.

The GEANT4 package allows construction of complex scoring and transport geometries of any element, mixture, or compound, as well as transportation and tracking of a variety of particles which fall under the classes leptons, mesons, baryons, bosons, short-lived particles and ions. For the purposes of this study however, only photons, electrons and positrons are considered. Physics processes include those listed for EGSnrc above as well as photonuclear interactions and high-energy processes. GEANT 4.9.4 beta was used in this study and is currently the latest release. For the GEANT4 simulations, energy cut-offs for photons were set to 990 eV and electron energy cut-offs to 40 keV. These energies correspond to range cut-offs of 0.1 mm. Processing time is on the order of ten to twenty times that of EGSnrc for the same number of histories. Hence, in most cases, a factor of 10 fewer particle histories were simulated with GEANT4, the output of which thus exhibits correspondingly higher statistical uncertainties.

For comparison, dose calculations were also performed for the same geometry using a commercial treatment planning system for radiotherapy dose calculations (Eclipse 8.2, Varian Medical Systems) with the pencil beam convolution (PBC) algorithm. The phantom was defined in the system with the same densities as employed in the Monte Carlo calculations. A 6 MV divergent photon beam corresponding to a Varian 21 IX linear accelerator was used with the centre of the lesion at the isocentre. The maximum spatial resolution was used (i.e. a grid size of 1.25 mm; note this corresponds to a voxel size approximately twice that of the Monte Carlo model).
Table 5.9 The density and elemental composition (percentage by weight) of the various tissues modelled in this study. The lung carcinoma data was determined by combustion analysis of excised squamous cell lung carcinoma (Maughan et al. 1997) and other data is from the International Commission on Radiological Units (ICRU 1989). †The density of lung carcinoma is taken to be that of water (1 g.cm$^{-3}$).

<table>
<thead>
<tr>
<th></th>
<th>Soft tissue</th>
<th>Lung tissue</th>
<th>Lung carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>ρ (g.cm$^{-3}$)</td>
<td>1.06</td>
<td>0.26</td>
<td>1.00 †</td>
</tr>
<tr>
<td>H</td>
<td>10.2</td>
<td>10.3</td>
<td>9.9</td>
</tr>
<tr>
<td>C</td>
<td>14.3</td>
<td>10.5</td>
<td>19</td>
</tr>
<tr>
<td>N</td>
<td>3.4</td>
<td>3.1</td>
<td>4.5</td>
</tr>
<tr>
<td>O</td>
<td>70.8</td>
<td>74.9</td>
<td>65.45</td>
</tr>
<tr>
<td>Na</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1265</td>
</tr>
<tr>
<td>P</td>
<td>0.3</td>
<td>0.2</td>
<td>0.253</td>
</tr>
<tr>
<td>S</td>
<td>0.3</td>
<td>0.3</td>
<td>0.322</td>
</tr>
<tr>
<td>Cl</td>
<td>0.2</td>
<td>0.3</td>
<td>0.1955</td>
</tr>
<tr>
<td>K</td>
<td>0.3</td>
<td>0.2</td>
<td>0.253</td>
</tr>
</tbody>
</table>

5.5.3 Result
5.5.3.1 EGSnrc determination of under-dosage

Results are given as the ratio of doses at the boundaries of tumours (region facing beam, region where beam exits tumour and the four lateral sides of the tumour intersected by Cartesian axes) and a reference point, chosen to be the centre of the tumour, i.e.

$$R(d, FS, \bar{\Omega}_t, E) = \frac{D_{\text{boundary}}}{D_{\text{ref}}},$$

where R is the ratio of dose at the given boundary (Dboundary) to the (reference) dose at the centre of the tumour (Dref). R is effectively a function of the beam energy, E, the distance of tumour from chest wall, d, and field size, FS, the latter being dependent on the tumour diameter, \(\bar{\Omega}_t\). The tabulated results are those calculated with egsnrc. Table 5.10 and Table 5.11 present the dose ratios for 6 and 15 MV photon beams respectively. Each table is divided into three sections, corresponding to the ratios of the dose at the entrance, exit and lateral.
points of the tumour to the reference (central) point of the tumour. ‘Entrance’ and ‘exit’ refer to the closest and furthest points on the tumour with respect to the source of the beam. The statistical uncertainty ($1\sigma$ in each ratio) is given in parentheses. The calculation points are 1 cubic millimetre in volume and their locations are illustrated in Figure 5.43.

Figure 5.43 Diagram indicating the points of the tumour at which dose ratios are calculated (marked with a black x); illustrated through central cross-sections of the tumour volume. 'Prox' refers to the proximal (beam entrance) point, 'Dist' to distal (exit), 'Ref' to reference and 'Lat' to lateral points. The incident photon beam is indicated by the shaded area (a square field, directed along the z-axis). The x-y and x-z planes are shown, the latter also being equivalent to the y-z plane.
5.5.3.2 The ‘dose reduction factor’ (DRF)

Table 5.12 presents the estimated dose reduction factor (DRF) which is effectively the ratio of the mean of the total surface dose to that at the central point for a given arrangement. Calculations show that considering the dose to the total outer ‘shell’ of the tumour is equivalent (i.e. exhibits a statistically insignificant difference) to using weighted mean doses at the proximal, distal and four equispaced lateral points, such that:

\[
DRF = \frac{1}{6D_{ref}} \left( D_{\text{proximal}} + D_{\text{distal}} + \sum_{i=1}^{4} D_{\text{lateral},i} \right).
\]

This is relevant for clinical contexts such as arcs or multiple-field therapy where the beam is incident upon the tumour from numerous directions.

**Figure 5.44** (a) The dose reduction factor (DRF) for a 20 mm diameter tumour at various distances. Plotted alongside is equivalent calculated data within a homogeneous phantom composed entirely of soft tissue. This highlights the discrepancy between doses to the peripheral ‘shell’ and the centre of a tumour that arise purely from attenuative effects (the DRF for the homogeneous case remains within ~1 % of unity, which is indicative mostly of the curvature of a depth dose curve tail in soft tissue). (b) The ratio of dose to the centre of the tumour, to an equivalent point in a homogeneous (soft tissue) phantom. Expectedly, the points at further distances rise above unity due to the greater attenuation in the homogeneous case compared to that in lung tissue in the tumour model. The points at closer distances, roughly < 20 mm from the chest wall, are below unity, indicating the under-dosage due to effects of disequilibrium.
Table 5.10: The dose ratios, $R(d, FS, Ø_t, E)$, for a 6 MV photon spectrum. The ratios are presented for various tumour diameters ($Ø_t$), field sizes ($FS$) and distances from the chest wall to the tumour ($d$). The table is divided into three sections, corresponding to ratios of entrance-to-central dose, exit-to-central dose and lateral-to-central dose. The standard deviation, $σ$, is given in parentheses.

<table>
<thead>
<tr>
<th></th>
<th>Entrance dose</th>
<th>Exit dose</th>
<th>Lateral dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>$d$ (mm)</td>
<td>$Ø_t$ (mm) / $FS$ (mm$^2$)</td>
<td>$Ø_t$ (mm) / $FS$ (mm$^2$)</td>
<td>$Ø_t$ (mm) / $FS$ (mm$^2$)</td>
</tr>
<tr>
<td></td>
<td>10 / 30 x 30</td>
<td>16 / 35 x 35</td>
<td>20 / 40 x 40</td>
</tr>
<tr>
<td>5</td>
<td>1.0016 (± 0.01)</td>
<td>1.0405 (± 0.01)</td>
<td>1.0154 (± 0.01)</td>
</tr>
<tr>
<td>10</td>
<td>0.9835 (± 0.01)</td>
<td>1.0056 (± 0.01)</td>
<td>1.0315 (± 0.01)</td>
</tr>
<tr>
<td>20</td>
<td>0.9748 (± 0.01)</td>
<td>0.9667 (± 0.01)</td>
<td>1.0169 (± 0.01)</td>
</tr>
<tr>
<td>40</td>
<td>0.9628 (± 0.01)</td>
<td>0.9571 (± 0.01)</td>
<td>0.9739 (± 0.01)</td>
</tr>
</tbody>
</table>

| $d$ (mm) | $Ø_t$ (mm) / $FS$ (mm$^2$) | $Ø_t$ (mm) / $FS$ (mm$^2$) | $Ø_t$ (mm) / $FS$ (mm$^2$) |
| 5      | 0.9597 (± 0.01) | 0.9376 (± 0.01) | 0.9213 (± 0.01) | 0.9430 (± 0.02) | 0.8905 (± 0.02) |
| 10     | 0.9277 (± 0.01) | 0.9537 (± 0.01) | 0.9386 (± 0.01) | 0.9481 (± 0.02) | 0.8882 (± 0.02) |
| 20     | 0.9713 (± 0.01) | 0.9469 (± 0.01) | 0.9412 (± 0.01) | 0.9250 (± 0.02) | 0.9266 (± 0.02) |
| 40     | 0.9626 (± 0.01) | 0.9212 (± 0.01) | 0.9286 (± 0.01) | 0.9093 (± 0.02) | 0.9244 (± 0.02) |

| $d$ (mm) | $Ø_t$ (mm) / $FS$ (mm$^2$) | $Ø_t$ (mm) / $FS$ (mm$^2$) | $Ø_t$ (mm) / $FS$ (mm$^2$) |
| 5      | 0.9794 (± 0.005) | 0.9750 (± 0.005) | 0.9538 (± 0.005) | 0.9869 (± 0.008) | 0.9646 (± 0.01) |
| 10     | 0.9571 (± 0.005) | 0.9661 (± 0.005) | 0.9724 (± 0.005) | 0.9922 (± 0.008) | 0.9900 (± 0.01) |
| 20     | 0.9701 (± 0.005) | 0.9426 (± 0.005) | 0.9589 (± 0.005) | 0.9665 (± 0.008) | 1.0055 (± 0.01) |
| 40     | 0.9583 (± 0.005) | 0.9366 (± 0.005) | 0.9489 (± 0.005) | 0.9347 (± 0.008) | 0.9887 (± 0.01) |
Table 5.11 The dose ratios, $R(d, FS, \Phi, E)$, for a 15 MV photon spectrum. The ratios are presented for various tumour diameters ($\Phi$), field sizes ($FS$) and distances from the chest wall to the tumour ($d$). The table is divided into three sections, corresponding to ratios of entrance-to-central dose, exit-to-central dose and lateral-to-central dose. The standard deviation, $\sigma$, is given in parentheses.

### Entrance dose

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<thead>
<tr>
<th>$\Phi$ (mm)</th>
<th>$FS$ (mm$^2$)</th>
<th>$d$ (mm)</th>
<th>10</th>
<th>16</th>
<th>20</th>
<th>30</th>
<th>50</th>
<th>70 x 70</th>
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</thead>
<tbody>
<tr>
<td>5</td>
<td>0.9671 (± 0.01)</td>
<td>0.9654 (± 0.01)</td>
<td>0.9615 (± 0.01)</td>
<td>0.9346 (± 0.01)</td>
<td>0.9656 (± 0.02)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0.9670 (± 0.01)</td>
<td>0.9585 (± 0.01)</td>
<td>0.9391 (± 0.01)</td>
<td>0.9561 (± 0.01)</td>
<td>0.9772 (± 0.02)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>0.9450 (± 0.01)</td>
<td>0.9245 (± 0.01)</td>
<td>0.9281 (± 0.01)</td>
<td>0.9267 (± 0.01)</td>
<td>0.9814 (± 0.02)</td>
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<tr>
<td>40</td>
<td>0.9207 (± 0.01)</td>
<td>0.9053 (± 0.01)</td>
<td>0.9078 (± 0.01)</td>
<td>0.9182 (± 0.01)</td>
<td>0.9750 (± 0.02)</td>
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</table>

### Exit dose

<table>
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<th>$\Phi$ (mm)</th>
<th>$FS$ (mm$^2$)</th>
<th>$d$ (mm)</th>
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<th>16</th>
<th>20</th>
<th>30</th>
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</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.9379 (± 0.01)</td>
<td>0.9301 (± 0.01)</td>
<td>0.9219 (± 0.01)</td>
<td>0.9048 (± 0.01)</td>
<td>0.9236 (± 0.02)</td>
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<tr>
<td>10</td>
<td>0.9546 (± 0.01)</td>
<td>0.9251 (± 0.01)</td>
<td>0.9316 (± 0.01)</td>
<td>0.9331 (± 0.01)</td>
<td>0.9037 (± 0.02)</td>
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<td>20</td>
<td>0.9618 (± 0.01)</td>
<td>0.9254 (± 0.01)</td>
<td>0.9357 (± 0.01)</td>
<td>0.9293 (± 0.01)</td>
<td>0.9014 (± 0.02)</td>
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<tr>
<td>40</td>
<td>0.9613 (± 0.01)</td>
<td>0.9304 (± 0.01)</td>
<td>0.9499 (± 0.01)</td>
<td>0.9012 (± 0.01)</td>
<td>0.9112 (± 0.02)</td>
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</tbody>
</table>

### Lateral dose

<table>
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<th>$\Phi$ (mm)</th>
<th>$FS$ (mm$^2$)</th>
<th>$d$ (mm)</th>
<th>10</th>
<th>16</th>
<th>20</th>
<th>30</th>
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<tbody>
<tr>
<td>5</td>
<td>0.9470 (± 0.003)</td>
<td>0.9260 (± 0.003)</td>
<td>0.9141 (± 0.005)</td>
<td>0.8854 (± 0.005)</td>
<td>0.8914 (± 0.008)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0.9519 (± 0.003)</td>
<td>0.9078 (± 0.003)</td>
<td>0.8979 (± 0.005)</td>
<td>0.8940 (± 0.005)</td>
<td>0.8998 (± 0.008)</td>
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</tr>
<tr>
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<td>0.9413 (± 0.003)</td>
<td>0.8883 (± 0.005)</td>
<td>0.8898 (± 0.005)</td>
<td>0.8937 (± 0.005)</td>
<td>0.8714 (± 0.008)</td>
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</tr>
<tr>
<td>40</td>
<td>0.9206 (± 0.003)</td>
<td>0.8820 (± 0.005)</td>
<td>0.8971 (± 0.005)</td>
<td>0.8728 (± 0.005)</td>
<td>0.8820 (± 0.008)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Table 5.12: The estimated surface dose reduction factor, $DRF$, for 6 and 15 MV photon spectra. The standard deviation, $\sigma$, is given in parentheses. The lower uncertainty in the 15 MV case is borne of the fact that the uncertainty is a statistical one relating to the fluence. The variance is inversely proportional to the square of the number of particles, and since 15 MV photons have higher penetrative ability there are a greater number of particles contributing to scored quanta at ‘deeper’ points within the model (relative to the 6 MV case), and therefore the statistical uncertainty is lower.

<table>
<thead>
<tr>
<th>$6\text{ MV}$</th>
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<th>$\phi_i$ (mm)</th>
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</thead>
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<td>16</td>
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<td>0.98 (± 0.01)</td>
<td>0.98 (± 0.01)</td>
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<tr>
<td>10</td>
<td>0.96 (± 0.01)</td>
<td>0.98 (± 0.01)</td>
</tr>
<tr>
<td>20</td>
<td>0.97 (± 0.01)</td>
<td>0.95 (± 0.01)</td>
</tr>
<tr>
<td>40</td>
<td>0.96 (± 0.01)</td>
<td>0.94 (± 0.01)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>$15\text{ MV}$</th>
<th>$d$ (mm)</th>
<th>$\phi_i$ (mm)</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>0.951 (± 0.001)</td>
<td>0.940 (± 0.001)</td>
</tr>
<tr>
<td>10</td>
<td>0.958 (± 0.001)</td>
<td>0.931 (± 0.001)</td>
</tr>
<tr>
<td>20</td>
<td>0.949 (± 0.001)</td>
<td>0.913 (± 0.001)</td>
</tr>
<tr>
<td>40</td>
<td>0.934 (± 0.001)</td>
<td>0.906 (± 0.001)</td>
</tr>
</tbody>
</table>
5.5.3.3 Agreement between the two Monte Carlo transport codes

The results tabulated in this study correspond to those obtained using EGSnrc. Figure 5.46 shows the relation between results obtained with EGSnrc and GEANT4. The differences between the results from the two codes do not appear to be systematic, and may be attributed to the statistical uncertainties (which are larger for GEANT4) and the slightly different definition of the simulation geometry, exhibiting no consistent trends as a function of the various modelled geometric parameters.

5.5.3.4 Comparison with TPS prediction

For comparison, equivalent calculations of the \( DRF \) were undertaken with the pencil beam convolution algorithm (PBC). The ratio of the PBC values to those calculated using EGSnrc are shown in Figure 5.47 as a function of the distance, \( d \), for the various tumour diameters. The treatment planning system generates relatively high \( DRF \) values (i.e. close to unity), thus underestimating the peripheral under-dosage. For clinics with more advanced TPS dose calculation algorithms, similar evaluations of the \( DRF \) could be performed locally and compared with the Monte Carlo values presented in this work. It is difficult to identify any particular trends in the data; the reason for this is that the high degree of competition between effects of build-up, build-down, attenuation, varying charged particles ranges and so forth is highly complex.

**Figure 5.45** An example of the difference in under-dosage between the two different energy modalities, illustrated via the dose reduction factor (DRF) for a distance of 10 mm and various tumour diameters. The interesting relatively high value at \( \phi = 10 \) mm for the 15 MV beam is a consequence of the entirety of the tumour being in a ‘build-up’ region.
**Figure 5.46** An example of the agreement between EGSnrc and geant4. This figure shows the DRF (see main text for definition) for EGSnrc and geant4 data plotted against each other. The data is scattered about the line of y = x, the latter corresponding to ideal agreement. There does not appear to be any particular bias. The deviation from perfect agreement may be attributed to statistical variance and the slightly different definition of the simulation geometry.

**Figure 5.47** The ratio of DRF values calculated by the treatment planning system (pencil beam convolution, PBC) to those calculated with EGSnrc. This illustrates the limitations of the TPS, which inaccurately predicts the DRF – and thus underestimates the peripheral under-dosage – by up to approximately 4.5%. Data is shown for the various tumour sizes as a function of the distance, d.
5.5.4 Discussion

5.5.4.1 Clinical relevance
Currently, the leading type of cancer mortality is associated with the lung and bronchus. Recent data indicates lung cancers also account for approximately 15% and 14% of all new cancers in men and women respectively, and that 30% of cancer related deaths in men and 26% in women are due to lung cancer (Jemel et al. 2009). In the case of external beam radiotherapy of the lung, photon beams first penetrate soft tissue, then lung tissue – which has a density about one third that of soft tissue. For tumours within lung tissue (which have densities closer to soft tissue), complexities arise relating to the range of secondary electrons, which lead to inaccuracies if commercial treatment planning systems are employed to determine the dose distributions. This was highlighted recently by Timmerman et al (2009), who reported on the Radiation Therapy Oncology Group 0236 Phase II trial, whereby the prescribed 20 Gy per fraction dose (totalling 60 Gy) was found to be only 18 Gy per fraction (totalling 54 Gy) – an error that arose because of a lack of appropriate tissue heterogeneity. Haedinger et al (2005) reported similar discrepancies.

5.5.4.2 Influences on dose inhomogeneity
Describing the effect on the dose to the periphery of the tumour is not straightforward. At the proximal region of the tumour, there is electronic disequilibrium borne of the fact that there are less forward scattered electrons from the preceding lung tissue, which has a relatively low density. At lateral points at the periphery of the tumour, there is a lack of lateral equilibrium which results in under-dosage. There is also less forward- and back-scatter which results in longitudinal disequilibrium. At the distal region of the tumour, the doses are consistently lower than the central doses, resulting from the attenuative effect within the tumour volume and loss of backscatter at the exit of the tumour.

Figure 5.44 illustrates the dose differences between the lung tumour model and a homogeneous phantom. The inhomogeneity of the dose distribution over the tumour volume may be illustrated by the ratio of the peripheral dose to the dose at the centre of the tumour.

We have defined a dose reduction factor (DRF) of the peripheral region. Consideration of this reduction due to secondary electron disequilibrium would be particularly important if dose were to be prescribed to a covering isodose shell. It is important to recognise that the dose to the centre of the tumour may also be affected by the electronic disequilibrium arising from the presence of surrounding lung tissue. In the case of small tumours, there is insufficient build-up within the tumour to reach equilibrium, reducing the dose there, but this effect is
lessened in large tumours or those close to the chest wall within range of forward-scattered electrons. Competing with this, the reduced attenuation of the photon beam in the overlying lung tissue increases the dose the tumour centre, relative to the homogeneous soft-tissue case. Thus, the tumour centre is used as a reference point as a measure for the \textit{DRF} describing the dose deficiency at the tumour periphery. The absolute dose effect at the centre of the tumour must be considered separately by comparison, for example, to the doses at similar points in a homogeneous soft-tissue medium, as illustrated in Figure 5.44(b).

5.5.4.3 \textit{Effect on typical treatment}
A typical treatment might involve use of either an arc, or a multi-field arrangement with of the order of nine fields (Hiraoka \textit{et al.} 2007; Timmerman \textit{et al.} 2007a). In the few cases where the front surface dose is higher than the central dose, such as larger tumours close to the chest wall treated with a 6 MV beam (see Table 5.10), the effect will be somewhat offset by the lower exit region dose when averaged (as intended by the treatment design). In general, however, the lower entrance and exit doses to these lung tumours compound, when treated from multiple directions, to produce an overall under-dosed peripheral region. From observation of Table 5.12, showing the \textit{DRF}, it is evident that over all arrangements of tumour size, $\phi_t$, and distance, $d$, that the dose to peripheral regions of the tumour is, on average, about 3\% lower than that to the centre for the 6 MV case and 7\% lower for the 15 MV case. With a 6 MV beam, the under-dosage increases from about 2\% to 5\% with increasing distance, and decreases from 4\% to 2\% with increasing tumour size. For a 15 MV beam, the under-dosage increases from about 7\% to 8\% with increasing distance, and increases from 5\% to 8\% with increasing tumour size.

5.5.4.4 \textit{The influence of linac energy}
The range of secondary electrons from the 15 MV beam are more than double that from the 6 MV beam for the nominal energies, and about a factor of two and one-quarter higher for the mean energies, in all the media studied. The ratios, $R$, are presented for the 15 MV beam in Table 5.11. The most pronounced difference with comparison to the 6 MV case is that, for 15 MV, $R(d, FS, \phi_t, E) < 1$ for all arrangements. For the exit regions of the tumour, there is little observed difference between the ratios for 15 MV and 6 MV. It is evident that for both the entrance and lateral regions of the tumour, the ratios for 15 MV are on average approximately 7\% lower than those for 6 MV (see Figure 5.45). Relative doses to the entrance point of the tumour increase with tumour diameter and decrease with distance from the chest wall. For the
exit region, $R$ decreases with tumour size but does not exhibit any significant trend with changing chest wall distance. For the lateral regions of the tumour, the dose is consistently lower than that at the centre, with $R$ decreasing for increasing tumour size and chest wall distance. To illustrate the difference between energy modalities, an example has been provided in Figure 5.46, which shows the dose reduction factor as a function of tumour diameter for both 6 MV and 15 MV at a distance of 10 mm.

5.5.4.5 Application of the DRF
Most commercial treatment planning systems would not be able to predict the magnitude of dose reduction in the periphery of a solid tumour accurately as the calculation grid size is too coarse and most algorithms are not designed to calculate dose distributions in the presence of inhomogeneities on a millimetre scale. The DRF defined here provides a first estimate of the potential under-dose compared to the centre of the lesion, the dose to which is usually better estimated by conventional treatment planning. This is of particular relevance when prescribing dose to covering isodoses.

5.5.5 Conclusions
The objective of this work was to develop an easy-to-use Dose Reduction Factor for clinicians and treatment planners to estimate the degree of under-dosing of lung tumours that can occur as a result of electronic disequilibrium due to tissue inhomogeneities but may not be evident from clinical treatment planning calculations. Such a factor will be useful for dose prescription as well as plan evaluation. Calculations were performed with two Monte Carlo radiation transport codes (EGSnrc and GEANT4). Ultimately, doses to peripheral zones of the tumour volume may be up to 12% lower than the dose to the centre of the tumour. The disparity is generally more significant if a 15 MV treatment beam is used than for a 6 MV treatment beam.
5.6 Chapter summary

This chapter has described the characterisation of stereotactic fields, facilitated by Monte Carlo radiation transport calculations. These have been generated for a large number of fields shaped with the mini-multileaf collimator. Specifically, this includes the investigation of beam characteristics in air, both in and beyond the primary field, including:

- Photon spectra,
- Contaminant electron spectra,
- Spatial variation of mean photon energy,
- Spatial variation of mean electron energy, and
- Angular distribution of photons.

Spectral data in water at several depths (5, 10 and 15 cm) has also been calculated, including:

- Photon energy fluences,
- Electron energy fluences, and
- Mean energy distributions.

Further data has been compiled for comparison using ‘backed-up’ field, i.e. jaws set at the same field opening as the MMLC. Mean energy, spectral and angular distributions were calculated for several representative cases.

Summarised here are the key findings for the in-air study:

- Out-of-field photon fluence ~1 % of primary beam fluence.
- Out-of-field electron fluence ~30 % of primary beam fluence.
- Photon fluence has sharp gradient at field edge.
- Electron (contaminant) fluence does not have a sharp gradient at field edge.
- ‘Structure’ evident in fluence profiles just beyond the primary beam (due to interleaf leakage through collimator).
- Mean energy of primary photon field lower than surrounding peripheral regions (due to beam hardening by collimators) for small fields; mean energy drops again in far out-of-field regions.
- Photon energy fluence varies with field size, most notably at low energies (below ~1 MeV).
- The photon beam is more forward directed for smaller fields, as evidenced by the primary field angular photon distributions (in fact, for the 9.8 x 9.8 cm² field the distribution peaks at approx. 3º rather than 0 º).
- The photons outside the primary field are much less forward-directed.
When fields are backed-up by jaws, the spectral distributions of photons and electrons in-field are similar to the non backed-up case.

Out-of-field, the mean energies differ significantly between the backed-up and non backed-up fields.

The angular distribution of photons at the patient plane is significantly different, being more forward-directed for small fields but less so for large fields, relative to the non backed-up case.

Summarised here are the key findings for the in-water study:

- Photon spectra harden with depth in water.
- Electron spectra harden with depth in water.
- Mean energy of primary photon beam decreases with increasing field size (6 x 6 mm$^2$ beam is 30% harder than 98 x 98 mm$^2$ beam).
- Out-of-field mean photon energies (at 12 cm off-axis distance) decrease with increasing field size (6 x 6 mm$^2$ beam is 250% harder than 98 x 98 mm$^2$ beam).
- The fraction of total photons in the low energy regime increases with field size (98 x 98 mm$^2$ beam has ~1000% more photons with energies < 250 keV than 6 x 6 mm$^2$ beam).
- Electron spectrum varies with field size, most notably in the low-energy regime (< 1 MeV), such that larger fields have a larger fluence of low-energy electrons.

To illustrate the relevance of varying spectra, several illustrative studies were carried out. These included:

- An investigation of the effect of changing secondary electron spectra on the mean restricted stopping power ratios relevant to ionisation chamber measurements,
- The energy dependence of measurements taken using radiographic film, and
- The energy-dependent effective atomic number of TLD-100 thermoluminescent dosimeters.

The effect of the investigation into spectral effects as relevant to ionisation chamber measurements showed that the typical assumption of unchanging spectra (field size independence) was typically acceptable, with deviation from the reference field case all sub-percent. The discrepancy worsens with decreasing field size but is nonetheless acceptable. However, this only applies to in-field measurements. Out-of-field, spectral variations result in discrepancies > 1%, being worst for larger field sizes. A further consequence of the spatial variation of the spectrum is demonstrated in the context of radiographic film dosimetry. A Monte Carlo investigation indicates that the film over-responds to the incident stereotactic
fields relative to water, but the extent of the over-response varies spatially for the aforementioned reason. A third study compares the effective atomic numbers ($Z_{\text{eff}}$, calculated using the method described for gel dosimeters in Chapter 3) of TLD-100 and water indicates that the greatest discrepancy in $Z_{\text{eff}}$, approximately 80%, coincides with the peak of the photon energy spectrum.

In addition to the Monte Carlo studies of beam characteristics, two ‘case studies’ were undertaken – the first a gel dosimetry investigation of stereotactic (intracranial) radiotherapy, the second an in silico investigation of lung tumour under-dosage relevant for stereotactic body (extracranial) radiotherapy. Measurement of three-dimensional dose distributions in an anthropomorphic head phantom using gel dosimetry was shown to be feasible for treatment plan verification. Agreement with treatment planning system (pencil beam algorithm) calculations was demonstrated for high dose regions (above the 90% isodose, $\gamma$ evaluation indicated 96% agreement for criteria of 2%/2mm). The outcome of the lung under-dosage study was a ‘look-up’ table for a range of parameters (including beam energy, field size, tumour size and distance of tumour from chest wall) that allows clinicians to estimate the level of under-dosage not predicted by simplistic treatment planning algorithms. This dataset is also useful for the interpretation of clinical trial data (to estimate the true doses actually delivered), in which pencil beam convolution algorithms have often been employed.
CHAPTER SIX

I should have been a pair of ragged claws
Scuttling across the floors of silent seas.†

TS Eliot

† I haven’t, in this instance, contrived any particular reason for the inclusion of this quotation; just a beautiful line from Eliot’s *The Love Song of J. Alfred Prufrock*. 
CHAPTER 6

Characterisation of stereotactic fields: Out-of-field

Peripheral doses from small fields and the potential for radiocarcinogenesis
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6.1 Chapter overview

Thus far, the focus of this thesis has been the in-field characterisation of stereotactic fields, which is associated with significant complications as a result of difficult dose measurement and calculation. Poor assessment of the characteristics of stereotactic fields can have serious detrimental consequences for the patient. Not only does this present a problem to clinicians, but radiation delivery to cancer patients for radiotherapy is invariably accompanied by unwanted radiation to parts of the patient that are far from the primary field. Traditionally, considerable effort has been made to calculate and measure the radiation dose to the target as well as to nearby critical structures. Only recently has attention been focused also on the relatively low doses that exist far from the primary radiation beams. In several clinical scenarios such doses have been associated with cardiac toxicity as well as an increased risk of secondary cancer induction. Out of field dose is a result of leakage and scatter and generally difficult to predict accurately.

A thorough review indicates that the out of field dose from stereotactic fields in particular has received relatively little attention in the published scientific literature. There are three main investigations presented in this chapter:

- A comprehensive review of published literature pertaining to out-of-field doses, identifying trends that may be exploited for risk-minimisation.
- A systematic investigation of out-of-field doses from stereotactic beams, as a function of a range of treatment parameters.
- An investigation of stereotactic radiotherapy of paediatric patients, for whom out of field doses are of particular significance in terms of long-term health effects.

While the literature review does not constitute a ‘novel’ scientific study, it is of clinical interest; data has been extracted from a large number of studies and presented in a comparative manner for a range of treatment parameters, such as treatment type, machine type, field size et cetera. The advantage of this comparative investigation is that it facilitates exploitation of known low out-of-field dose scenarios such that associated risks (such as radiocarcinogenesis) may be minimised.

What is also clear from the review, however, is that out-of-field doses from (particularly linac-based) stereotactic fields are less well known.

A novel investigation of out-of-field doses from linac-based stereotactic fields has been presented in a systematic fashion. The variation of out-of-dose with field size, source-surface
distance, depth in phantom and spatial orientation has been investigated. Higher doses were associated with increasing field sizes and shallow phantom depths, whilst variation of source-surface distance did not exhibit a significant effect. Furthermore, it is demonstrated that if the patient lies along the x-plane then out-of-field doses may be reduced by up to an order of magnitude compared to the y-plane (where planes are defined by the direction of jaw motion). For a stereotactic treatment with dose to the target of the order of tens of Gy, the out-of-field doses are of the order of cGy – which is a significant dose in radiation protection terms. An example of the clinical consequences is provided for the case of radiation-induced cancer of the thyroid following intracranial stereotactic radiotherapy.

A further novel study presented in this chapter investigates the out-of-field doses in the context of stereotactic radiotherapy of paediatric patients. As discussed in the following sections, children are at particular risk of latent effects following radiation therapy. A number of key results are shown that may be exploited to reduce the risk of secondary cancer in children. Choice of linac may affect the out-of-field dose by 40 %, appropriate choice of collimator rotation can reduce out-of-field dose by 40 %, appropriate choice of treatment technique can reduce out-of-field dose by an order of magnitude and simple shielding arrangements can reduce the out-of-field dose by 50 %. Interestingly, the out-of-field dose resulting from large fields and small stereotactic fields is actually comparable far from the primary field. The clinical advantages of electing the appropriate treatment parameters are demonstrated via examples of secondary cancer risk reduction calculations under different treatment scenarios.
6.2 Out-of-field doses far from the targeted volume

In the case of radiological imaging, the dose delivered to the patient as a consequence of the imaging process is entirely detrimental. In the case of radiotherapy, it is the cell-killing function of ionising radiation that is the desirable effect for the destruction of a targeted tumour. However, as has been discussed, doses to healthy tissues can have a carcinogenic effect. This is not only of interest in the immediate regions around the targeted volume, but also in critical structures that are quite distant from the primary field, but that nonetheless receive a dose from scattered and or leakage radiation.

Numerous studies have been undertaken measuring the out-of-field dose from different radiotherapy machines and modalities over the past few decades. About 25 % of 56 publications reviewed are concerned solely with neutron doses, about 15 % deal with both photons and neutrons, and the remaining 60 % or so deal solely with photon doses. Intracranial radiotherapy (which constitutes the predominant application of stereotactic radiotherapy) typically implements 6 MV beams, and thus out of field photon doses are given greater emphasis in the subsequent discussions.

The majority of studies involve measurement of out-of-field doses, but many also make calculations of such doses using Monte Carlo radiation transport simulation, analytical approaches, or combinations of these, as indicated in Figure 6.1. To help simplify the discussion somewhat, a summary of the literature is given heretofore in two sections – the first is concerned with what might be called ‘classical’ or ‘conventional’ treatment techniques, the second addresses studies that incorporate more recent techniques (namely, intensity modulated radiotherapy and stereotactic radiotherapy).

![Figure 6.1](image)

**Figure 6.1** A representation of the percentage of studies (out of 56 selected publications) that have undertaken measurement or calculation (analytical or Monte Carlo) of out-of-field dose.
In the following sections an overview of studies of out-of-field dose is presented. The objective of this is multifold:

- To highlight the interest and common concerns in out-of-field dose from radiotherapy treatments,
- To note trends and thus identify exploitable means for risk-reduction, and
- To place the (relatively few) investigations of stereotactic out-of-field dose specifically into context.

Much of the work presented in this section has been published by the candidate (Taylor and Kron 2011).

### 6.2.1 Conformal radiotherapy and other conventional techniques

Interest in the out-of-field radiation doses from different machines seems to have started more seriously from about the 1970s. The focus of the studies is typically either dose to the environment from an occupation radiation safety perspective (particularly in early works), or doses to untargeted critical structures in the patient. As mentioned previously, the focus of the present study is the dose due to photons, because the peak energy of photons employed is 6 MeV and the neutron contribution is thus negligible. The concise discussion presented here consequently focuses primarily on out-of-field photon doses.

Fraass and Van de Geijn (1983) investigated the peripheral dose for a $^{60}$Co beam, as well as 4 MeV, 6 MeV and 8 MeV photon beams. Doses were reported for water tank measurements for multiple field sizes at a range of distances from the field edge. Transmission and in-patient scatter were separated, and found to be of similar magnitude. Thermoluminescent dosimetry (TLD) was also performed during treatment of patients. Kase et al (1983) similarly studied a $^{60}$Co beam, as well as 4 MeV and 8 MeV photon beams. Kase et al also attempted to differentiate head-leakage and scattered radiation, finding that collimator scatter may contribute up to about 40% of the dose outside the treatment field. Francois et al (1988) parameterised dose distributions for different beam energies as a function of depth, distance from the edge, field size and shape. An algorithm was thus developed to determine the dose to organs outside the beam from 10 to 50 cm from the field edge. The measurements were undertaken with TLD (calibrated against a Farmer-type ionisation chamber) in an anthropomorphic phantom. Measurements were also taken in a large water phantom for the various fields. Some limited Monte Carlo calculations were also performed. The American Association of Physicists in Medicine (AAPM) report TG-36 (Stovall 1995) studied foetal
doses in pregnant women treated with radiotherapy, for a range of delivery conditions. Van der Giessen (1996) measured doses in a water phantom for four Cobalt machines and 37 linear accelerators to investigate variation in peripheral doses amongst machines from seven different manufacturers. Variation of leakage radiation dose was found to be small amongst the varying designs, however, collimator dose was found to vary up to 50% depending on the collimator / flattening filter design. In his PhD thesis, Van der Giessen (1997a) provides results from studies of various machines (with a focus on $^{60}$Co), mostly using water phantoms to collect data or by evaluation of published data and leakage / collimator scatter data provided by other clinics / institutions. Dose was also measured on patients’ perinea using TLD. The studies constituting his thesis were published separately as articles mostly in *Int. J. Radiat. Oncol. Biol. Phys.* (Van der Giessen and Hurkmans 1993; Van der Giessen 1994; 1996; 1997b; Van der Giessen and Bierhuizen 1997).

Broadly, regarding photon doses outside the treatment volume for ‘classical’ methods, one may conclude that: the photon dose decreases with decreasing field size and drops approximately exponentially away from the field edge. Neutron doses (less relevant here) are more dependent on beam energy than distance from the field edge.

### 6.2.2 Intensity modulated radiotherapy

The advent of intensity modulated radiotherapy (IMRT) has given rise to concerns over the fact that the total number of monitor units used is often greater than for treatments for equivalent cases using, for instance, three-dimensional (3D) conformal radiotherapy. The additional monitor units may result in additional scattered or transmitted dose, and thus increase the dose to untargeted critical structures. Contemporary IMRT delivery is typically undertaken with multileaf collimators (MLC) or mini-multileaf collimators (MMLC) attached as tertiary / quaternary collimators on a linear accelerator. Many of the works discussed here involve measurements to investigate the influence of the MLC on out-of-field doses, as well as in the specific context of IMRT. Note again that the focus of the discussion remains with peripheral photon doses.

Followill *et al* (1997) undertook a study of doses outside the treatment fields for IMRT with 6 MeV, 18 MeV and 25 MeV beams, for which the photon whole body equivalent doses per cGy were 80 $\mu$Sv, 6.5 $\mu$Sv and 10 $\mu$Sv respectively. The respective neutron doses were 0.0 $\mu$Sv, 46 $\mu$Sv and 76 $\mu$Sv. Using risk values recommended by the National Council on Radiation Protection and Measurements (NCRP) they calculated worst-case scenario risks of
cancers to be between 1 % (for the 6 MeV beam) and 24.4 % (for the 25 MeV beam). Stern (1999) investigated whether the presence of an MLC would influence the peripheral dose when positioned at the field edge defined by the jaws. For 6 MeV and 18 MeV beams at all depths and distances studied, configuring the MLC leaves at the field edge yielded a reduction in peripheral dose of 6 – 50 % compared to the MLC leaves fully retracted. In the latter case, peripheral doses matched those for a linac without an MLC. As mentioned earlier, the AAPM report TG-36 can be used to estimate the peripheral dose distributions (Stovall 1995). Mutic and Klein (1999) undertook a number of measurements with an ionisation chamber in a water-equivalent plastic phantom with various MLC leaf settings including full retraction. Peripheral dose distributions with the MLC fully retracted and collimator rotated to 180 degrees were similar to TG-36 data, but lower with MLC field shaping. They also showed that rotating the collimator to 90 degrees with full MLC retraction may reduce the peripheral dose up to a factor of three (compared to TG-36).

Chibani and Ma (2003) employed MCNPX to study the dose from photon-induced nuclear particles (neutrons, protons and alpha particles). Varian beams are found to produce more particles than the Siemens, due to higher primary electron energies. Neutrons are found to contribute more than 75 % of the total dose equivalent ratio. Chibani and Ma compare the model to measurements. The dose equivalent from leakage neutrons (at 50 cm off-axis distance) represent 1.1, 1.1 and 2.0 % likelihood of fatal secondary cancer from a 70 Gy treatment delivered by the Siemens 18 MV, Varian 15 MV and Varian 18 MV beams respectively. Vanhavere et al (2004) performed measurements in air, at different depths in a plexi-phantom and using a Rando-Alderson phantom for gammas and neutrons with an 18 MV linac. Organ equivalent doses and effective doses (estimated by different methods) were evaluated for a range of organs. For a prostate cancer IMRT treatment, the effective dose (using Rando-Alderson phantom) was found to be about 30 mSv per 2 Gy target dose, 13 % of which is attributed to neutrons.

Sharma et al (2006a) noted that dynamic fields (consisting of constant-width strips moved from one bank to the other) required between two and fourteen times as many monitor units as static fields to achieve the same dose at isocenter, for various arrangements. Peripheral doses were between two and fifteen times higher for the dynamic case, depending on field size et cetera. They also compared patient specific intensity modulated fields with uniform dynamic MLC fields with similar jaw settings, and discovered that the two are sufficiently similar to use the dynamic MLC data to predict out-of-field doses for comparable patient-specific cases (Sharma et al. 2006b). Kry et al (2006) identified that the dose to the patient outside the treatment field is important, however determination of such out-of-field doses
requires tedious measurement or calculations that exhibit high uncertainty. They used the MCNPX Monte Carlo code to model a Varian Clinac 2100 operated at 6 MV, modelling dose distributions away from the central axis and measuring dose distributions with an ionisation chamber (in a water phantom) and TLD (in an acrylic phantom). In a different publication, Kry et al (2007b) describe a similar study for 18 MV photons. In the latter work, discussion of neutron dose was also included.

Wiezorek et al (2007) performed point dose measurements at different depths in a solid phantom at 29 cm off-axis distance, for a Siemens Oncor Impression linac with energies of 6 and 15 MeV. Peripheral doses associated with artificial fluence distributions were compared with open beam contributions. Measurements were performed with two types of TLD to quantify photon and neutron dose separately. Neutrons were only detected for 15 MV. The photon contribution to peripheral dose increased (compared to open field) when using segmented multi-leaf modulation (sMLM) for IMRT, and even further when using compensators.

IMRT treatments sometimes require between 3 and 5 times the number of monitor units to deliver (compared to a conventional treatment). Kry et al (2005b) measured the photon and neutron out-of-field dose equivalents to various organs from different treatment strategies, energies and accelerators. Photon dose decreased exponentially away from primary field; neutron dose was found to be independent of the distance from treatment field. Neutrons contributed significantly to out-of-field dose for $E > 15$ MeV. Considering out-of-field doses, Kry et al (2005a) found that the maximum risk of fatal secondary malignancy was 1.7 % for conventional radiation, 2.1 % for IMRT with 10 MeV x-rays and 5.1 % for IMRT with 15 MeV x-rays. Kry et al (2007a) also examined the uncertainty in risk estimates relating to out-of-field doses, with the result that risk estimates for secondary malignancy were subject to very large uncertainties. It was shown, however, that it is possible with relatively good accuracy to identify preferable modalities based on the ratio of risk estimates. In a recent study at the William Buckland Radiotherapy Centre (The Alfred Hospital, Melbourne), Ruben et al (2008) compared IMRT with three-dimensional CRT in terms of carcinogenic risk. Equivalent plans were constructed for prostate, breast and head-and-neck treatments. The risk of radiation induced malignancies in organs outside the target volume was calculated using two dose-response models for radiocarcinogenesis. Ultimately, the risks were found to be comparable between the two modalities. Depending on the technique and region of interest, risks ranged between 1 and 2 % for one risk model, and between 0.5 and 1 % for the other model. There is a significant body of literature covering epidemiological studies of cancer induction in radiotherapy patients, an overview of which is given in the subsequent
section. Reft et al (2006) performed in vivo patient and phantom measurements of the secondary out-of-field photon and neutron dose equivalent for 18 MV IMRT treatments. It was found that the photon dose drops by a factor of two from 10 cm to 20 cm from the field edge while the neutron dose remains the same (within experimental uncertainties). There is an indication that 18 MV IMRT results in higher neutron doses (factor of 2 to 3) compared to 3DCRT. Klein et al (2006) collected peripheral dose data in a phantom at distances ranging from 5 to 72 cm away from the field edges of small (2 to 10 cm) IMRT fields. Micro- and cylindrical ionisation chambers were arranged in a phantom representing a 3 yr old at locations corresponding to the thyroid, breast, ovaries and testes. Distant peripheral dose (dominated by head scatter) was higher than predicted. Doses to the testes were three to five times higher for IMRT compared to conventional treatment.

6.2.3 Stereotactic radiotherapy

Relevant to the present study is the existence of peripheral doses from intracranial stereotactic radiotherapy (SRT). The doses/fraction involved in SRT are generally much higher than those in IMRT treatments, and are delivered in relatively few fractions (note that stereotactic radiosurgery involves a single fraction only). The out-of-field doses from these high dose treatments are thus of significant interest.

Ioffe et al (2002) quantified the dose rate as a function of distance from the isocenter in a RANDO phantom for Gamma-Knife treatments. Hasanzadeh et al (2006) constructed an anthropomorphic phantom and undertook TLD measurements of dose in untargeted organs for Gamma-Knife radiosurgery. Petti et al (2006) developed Cyber-Knife plans for a thorax lesion and brain lesion in an anthropomorphic phantom and measured the dose at various depths and distances outside the treatment field using TLD. Peripheral doses were found to be 2 to 5 times higher than a comparable Gamma-Knife treatment and up to 4 times higher than an IMRT treatment. The relatively large peripheral dose is attributed to greater leakage of the Cyber-Knife unit. Chuang et al (2008) investigated reduction of out-of-field doses from the Cyber-Knife system resulting from a shielding upgrade, with the observation that doses were generally reduced by 20 to 55%.

The latter studies mentioned have focused on the Cyber-Knife and Gamma-Knife systems. Maarouf et al (2005) examined the radiation exposure of organs at risk and assessed the risk of late effects (such as secondary tumours or hereditary disorders) following stereotactic linac radiosurgery of intracranial tumours. TLDs were placed superficially on patients’ (N = 21) eyelids, thyroid, breast and regions of the ovary / testes. The organ receiving the highest doses
was the eye lens (276 ± 200 mGy), then the thyroid (155 ± 83 mGy), breast (47 ± 22 mGy), ovary (12 mGy) and lastly the testes (9 ± 3 mGy). The absorbed doses thus ranged between 0.025 and 0.76% of the target dose. They recommended the use of conformal beams employing micro-multileaf collimators and avoiding beams directed toward the trunk. Solberg et al (2001) compared conventional non-coplanar arc, static field conformal and dynamic arc field shaping approaches to radiosurgery. In terms of peripheral dose, it was found to decrease as additional beams or arc degrees are added with either of the conformal approaches. Ultimately, dynamic arc shaping was found to be preferred in efficiency and efficacy in delivery of a homogenous dose whilst minimising peripheral dose, for radiosurgery applications.

Comparatively, there has been little study of out-of-field doses from stereotactic fields than other treatment approaches.

6.2.4 Contributions to out-of-field dose
Out-of-field dose is essentially the combination of leakage from the accelerator head, scatter from collimators, from within the patient and from the rest of the treatment room. If, for example, a different accelerator, patient orientation or treatment type is considered, it is logical that the out-of-field dose will not necessarily be the same as another arrangement. As such, it is possible to reduce out-of-field doses (and corresponding risks to the patient) by careful choice of treatment arrangement. To help facilitate this, the main influences on out-of-field dose are discussed here.

6.2.4.2 The influence of accelerator type
Because out of field dose to untargeted regions of a patient is a result of a combination of leakage and scatter, it is logical that different linac models will have different shielding designs and that the out-of-field doses they generate may then differ. Figure 6.2 illustrates this quite clearly for a Siemens Primus, Varian 2100 and Philips SL-C operated at 18 MV (listed in order of decreasing out-of-field photon dose).

Figure 6.4 illustrates the differences between Siemens and Varian machines, with the latter delivering out-of-field doses only 20-50% of that delivered by the Siemens Primus (Chibani and Ma 2003). Neutron doses are clearly higher with the Varian machine, however (see Figure 6.2). The different contributions to out-of-field dose from collimator scatter for a range of machines are given in Figure 6.6. Kry et al (2005a) found that intensity modulated
radiotherapy (IMRT) in 6 MV mode with Varian and Siemens linacs resulted in risks of fatal secondary cancer of 2.9 % and 3.7 % respectively.

6.4.2.3 The influence of field size

Intuitively, one would expect that for larger field sizes more dose would be delivered to out-of-field regions, as a result of purely geometric reasons and increased patient-scatter. Generally this is indeed the case. This is shown in Figure 6.3 (note that Figure 6.3 shows the distance from field edge not from isocentre); another interesting note is that the discrepancy decreases with distance. The conclusion one may draw from this is that the field size dependent influences on out-of-field dose (i.e. collimator and patient scatter) become less important at large distances. This means that at large distances head leakage is the dominant influence on out-of-field dose. Figure 6.5 also shows the influence of field size on patient scatter (Van der Giessen and Hurkmans 1993) and collimator scatter and leakage (Van der Giessen 1994).

![Figure 6.2](image_url)

**Figure 6.2** Data from Reft et al (2006) shows the difference between linac models in terms of out-of-field dose for 18 MV IMRT of the prostate. *In vivo* measurements were undertaken measuring both photon (solid) and neutron (cross-hatched) doses; the data shown here corresponds to doses at a distance of 20 cm from the field edge. Measurements were performed for the same model accelerator at different centres (reflected by the number *n*).
6.4.2.4 The influence of energy mode

The energy mode also influences out-of-field dose. One might expect that because higher energy photons have higher penetrative ability, and are thus less attenuated by shielding and collimator devices, that out-of-field dose at high energies may be greater. However, this is not the case, as evidenced by Figure 6.2, Figure 6.3(b) and Figure 6.4.

Lower energy modes tend to result in greater out-of-field photon doses than higher energy modes. This is because lower energy photons are less forward scattered than higher energy photons (consider the Klein-Nishina (1929) formula). As such, one would expect patient scatter in low-energy modes to result in greater out-of-field dose. One would also expect, however, that this would be pronounced at intermediate distances but less so at far distances, since from the previous section we expect patient scatter to be less influential far out-of-field. Indeed, from Figure 6.4 it is clear that the Varian linac in 15 MV and 18 MV mode generate comparable out-of-field dose at far off-axis distances. The problem with high energy modes, however, is that the photonuclear effect may generate neutrons that contribute to the out-of-field dose. This is illustrated in Figure 6.2. It has been shown that neutron doses may not
significantly increase the risk of radiocarcinogenesis for IMRT with a linac operated in 18 MV rather than 6 MV mode (Kry et al. 2009).

Figure 6.4 An indication of the variation in neutron dose that exists between operating at 15 and 18 MV modes, and between different linac manufacturers. This data shows MCNPX calculated neutron doses along the plane of the couch for a Varian 2100C (15 MV and 18 MV) and Siemens Primus (18 MV) (Chibani and Ma 2003). Also shown are several measured data points for the Varian 15 MV. The sub-plot below the primary figure shows the ratio of these doses to the Siemens 18 MV case.

6.4.2.5 The influence of leakage, collimator and patient scatter
The influence of leakage, collimator and patient scatter may be inferred to some extent by the influence of field size. A number of authors have made explicit attempts to determine separate influences of these. Figure 6.5(a) directly indicates that the (percentage of central axis, CAX) dose attributable to patient scatter decreases with increasing distance. Van der Giessen (1994) treated the collimator scatter and leakage together, and from Figure 6.5(b) it is clear that the different field sizes converge far from the primary beam and the contribution to out-of-field dose plateaus.
Figure 6.5 (a) The percentage contribution of patient scatter to out-of-field dose for a range of field sizes from a $^{60}$Co unit (Theratron 780) (Van der Giessen and Hurkmans 1993). (b) The contribution of collimator scatter and head leakage (as a percentage) to out-of-field dose for a range of field sizes from a 6 MV treatment beam (GE Saturne 41) (Van der Giessen 1994).

Figure 6.6 The contribution of out-of-field dose as a result of collimator scatter varies amongst linac designs. This figure shows data adapted from Van der Giessen (1996) indicating this variation. The percentage contribution of collimator-scattered dose (at an off-axis distance of 50 cm) relative to the dose at the central axis is given for seven different linac types. Measurements were taken at different centres with various models; the total number of measurements is given as $n$ in the figure. The doses correspond to a standard field size of $10 \times 10 \text{cm}^2$. 
6.4.2.6 The influence of treatment type

The nature of the treatment affects the out-of-field dose. Intensity modulated radiotherapy (IMRT) is of particular interest in this regard (Hall 2006; Ruben et al. 2008), as discussed earlier, because it typically involves a greater number of monitor units than other delivery methods. Wang and Xu (2008) found that out-of-field doses are indeed significantly higher for an IMRT treatment than for conformal radiotherapy (CRT), as shown in Figure 6.7(a). Sharma et al. (2006a) showed that achieving an equivalent field size with a sliding field rather than a static MLC can result in an increase in out-of-field dose of up to an order of magnitude; see Figure 6.7(b). Hall and Wu (2003) found that IMRT of prostate cancer rather than conventional radiotherapy resulted in double the risk of fatal secondary cancer (3 % Sv\(^{-1}\) compared to 1.5 % Sv\(^{-1}\)). Kry et al. (2005a) found that 18 MV IMRT with a Varian unit resulted in a risk of fatal secondary cancer of 5.1 % Sv\(^{-1}\), while the risk for 18 MV conventional radiotherapy was 1.7 %.

![Figure 6.7(a)](image1)

**Figure 6.7 (a)** A comparison of IMRT with conformal (CRT) techniques based on data adapted from Wang and Xu (2008). Far from the primary field, the IMRT treatment generates more dose than the CRT deliveries. The sub-plot beneath the primary figure is a ratio plot of the 6-field CRT and IMRT deliveries compared to the 4-field CRT delivery. Note that the number of monitor units employed for the 4- and 6-field CRT and IMRT treatments were 1260, 1308 and 2850 respectively. (b) This data, adapted from Sharma et al. (2006a), shows the difference between achieving a 14 x 14 cm\(^2\) field with a static MLC or with a sliding window technique (in this case, a 0.5 cm strip field that moves dynamically to achieve a field equivalent to that generated with the static MLC. The sub-plot beneath the main figure shows the ratio of the sliding window to static case; achieving an equivalent field with the sliding window generates up to an order of magnitude more out-of-field dose.
6.2.5 Summary
There is a large body of literature associated with the measurement of out-of-field doses from radiotherapy with a medical linear accelerator. However, this is of little use or interest without consideration of the potential consequences for the patient. Untargeted structures in the patient, including critical organs, may receive a dose (albeit small) as a result of such scattered and leaked radiation. This can lead to radiation-induced cancer growth. This is a dynamic and complex area of research. In the following chapter, a summary of the data sources for dose response behaviour is given, along with an explanation of approaches for risk estimation.

6.3 Radiocarcinogenesis
In the previous sections it has been shown that measurements and radiation transport simulations indicate doses exist well beyond the treatment field. There is epidemiological evidence to suggest these may give rise to secondary cancers, as can doses to healthy tissues in the immediate vicinity of the targeted tumour volume. Radiation induced cancer is of increasing clinical interest, as reflected by Figure 6.8.

![Figure 6.8](image-url) An illustration of the increasing interest in radiocarcinogenesis, as reflected by a PubMed search of the terms "radiation induced cancer", presented over the past six decades.
In the first instance it is useful to know such peripheral doses so that treatments may be compared and optimal methods identified, but calculation of cancer induction risks associated with radiotherapy is the ultimate desired outcome. This typically takes the form of a dose response function. There is a linear increase of cancer risk with dose between around 0.1 and 2.5 Sv, as evidenced from the atomic bomb cohort data (Ron et al. 1994; Thompson et al. 1994; Preston et al. 2003; Preston et al. 2004; Preston et al. 2007). Beyond 2.5 Sv the relationship between dose and risk is less well known. There is evidence to suggest that the curve may be somewhat bell-shaped, with an ultimate decrease in cancer induction risk because of the relatively high likelihood of cell-killing compared to the induction of transformed cells. In the following sections, an introduction to the mechanisms of and influences on radiocarcinogenesis is given, since this is typically considered the gravest potential consequence of out-of-field dose to untargeted organs. The various dose response models will be discussed.

6.3.1 Mechanisms of radiocarcinogenesis

It is well accepted that even low doses of ionising radiation may induce cancer (ICRP 2005; BEIR 2006). This has been evidenced by documented studies of radiation exposure to populations as a result of war, accidents, occupation or from the diagnosis and treatment of disease. Cell damage occurs as a result of discrete interactions whereby electrons lose their kinetic energy via ionisation events. There is scientific consensus that the cytotoxic effect of ionising radiation on cells results from damage to deoxyribonucleic acid (DNA) (Latarjet 1972; Hutterman et al. 1978; Teebor et al. 1984; Errera 1985; Thacker 1986). Strands of DNA can be broken directly or indirectly, via interaction with free radicals. The term ‘direct action’ applies to ionisation that occurs within the DNA molecule. The fraction of cell-killing resulting from direct action is of the order of 80 % for high linear energy transfer (LET) radiation (Roots et al. 1985). Indirect damage to DNA is caused by free radicals that are generated from the radiolysis of water – the predominant reaction in living systems for low LET radiation. Free radicals are a highly reactive chemical species. Although most free radicals formed in these reactions recombine to form oxygen and water in a time scale of ~ $10^5$ seconds, some may interact with other chemical compounds and result in damaging biological effects. Of the products of water radiolysis, the hydroxyl (OH$^-$) radical (an oxidising species) is the most important radical in terms of damage to DNA (Cadet et al. 1999).
The lesions in DNA that result from ionising radiation include: (i) double or single strand breaks of the duplex molecule, (ii) chemical alteration of the bases, (iii) chemical alteration of the sugar moieties and (iv) cross linking to DNA related matrix proteins or nucleotides in the DNA molecule itself (Ward 1985). Single strand breaks are generated at a rate of about 1000 per Gy of ionising radiation, whereas double strand breaks occur at a rate of 15 – 60 breaks per Gy (Ward 1990). Single strand breaks are typically easily and rapidly repaired, whereas double strand breaks are less readily repaired. The latter can eventuate from the simultaneous scission of both strands close together, or by the interaction of two adjacent single strand breaks. About 25 % of repairs are misrepairs in the case of double strand breaks (Lobrich et al. 1995), depending on the mechanism of repair, and can result in mutations that may ultimately lead to cell death. In the case of damage not resulting in cell death, the daughter cells can carry a radiation-induced mutation. It is generally accepted that unrepaired or misrepaired double strand breaks are of principal importance in terms of the induction of chromosomal abnormalities and gene mutations (ICRP 2005). Much of the current scientific understanding of low dose radiobiological effects that is described in the recent ICRP Report 103 (2007) is similar to the earlier Report 60 (1991). One important feature of radiation damage that has been recognised only more recently is that of damage clusters. The latter may incorporate a single strand break or double strand break associated with base damage, as well as far more complex associations including multiple densely clustered double strand breaks. This concept is illustrated in Figure 6.9. Approximately 30 % of double strand breaks induced by low linear energy transfer radiation (such as photons) are complex in nature, involving multiple double strand breaks (Nikjoo et al. 1999; Nikjoo et al. 2000; Nikjoo et al. 2001; Nikjoo et al. 2002; ICRP 2005). This clustering effect associated with ionising radiation does not seem to occur with chemical carcinogens.
Such mutation resulting from ionising radiation is effectively the first stage of the carcinogenic process, known as initiation. The second stage, promotion, involves the acquisition of new properties, such as immortalisation, resistance to hypoxia and so on. This comes about by the accumulation of a number of faults in the genome. Subclones can arise from clones of initiated cells in which mutations have occurred. Amongst subclones there is what Tubiana (2009) describes as Darwin-esque competition, which allows the subclones of more rapid growth to gain dominance. Ultimately, new subclones emerge with greater autonomy, growing more rapidly, until finally a subclone of cells exists which may proliferate autonomously. Following this stage is progression, in which the cells proliferate frequently despite the absence of stimuli. Cells eventually gain the potential for invasion of peripheral tissues or metastasis.

Generally accepted as being of single-cell origin, the development of cancer occurs as a result of successive mutations and extensive proliferation. The period of time over which cancer develops (i.e. the latency) is in the order of decades for solid tumours, and relies on the unregulated proliferation of mutated cells that are not removed over time via apoptosis or immune system action. A clinically-diagnosed cancer will be constituted by of the order of
several billion cancerous cells. The low doses to untargeted healthy organs in the human body that occur as a result of scattered and leaked radiation in radiotherapy have the potential to induce cancer (and other health complications) as a result of the treatment. This is a typical stochastic effect whereby the probability of cancer induction is dependent upon the dose whilst the severity is independent. Radiocarcinogenesis is the most serious potential consequence of out-of-field doses, thus it is appropriate to discuss the different influences on the risk of radiocarcinogenesis so as to better understand the contexts in which out-of-field dose reduction may be especially important.

6.3.2 Dose response models

Within a population, there is an incidence of cancers that is expected to occur naturally. The objective is to determine the potential for an increase in incidence as a result of radiation exposure. This is facilitated by use of a dose-response relationship from which one may obtain risk coefficients. An additional consideration is the nature of the assumption(s) made about the mechanisms of radiocarcinogenesis.

There are multiple dose-response models. Their applicability is mostly dependent upon the dose regime of interest. For low doses, the most appropriate model is a linear relationship between dose and risk. At higher doses there is evidence for quadratic behaviour. At high doses where cell-killing becomes the dominant biological effect, there is evidence that the risk of cancer induction decreases with dose.

‘Relative risk’ (RR), defined in Equation 6.8, describes the excess risk of the disease as the ratio of the incidence of disease in equivalent exposed ($I_1$) and non-exposed ($I_0$) groups.

$$RR = \frac{I_1}{I_0}$$  \hspace{1cm} (6.8)

Also worth mentioning is the ‘excess relative risk’ (ERR). This is equal to the rate of cancer incidence (or mortality, etc) in an exposed population, divided by the rate in an unexposed population, minus one (i.e., $ERR = RR - 1$). The Committee on the Biological Effects of Ionizing Radiation (BEIR 1990) concluded some time ago that the RR model is the most appropriate model for analysis and projection of radiation-induced cancer incidence (1988; Shimizu et al. 1990).
6.3.3 Sources for radiocarcinogenesis data and associated risk relationships

Radiation studies using experimental animals have been performed since the 1930s or so, and only the key observations will be discussed here. Most early data suggests that the incidence rate increases significantly at low dose levels, that the relationship exhibits a complex non-linear behaviour, and decreasing incidence is often found for doses beyond the maximum. Later (more accurate) data indicates that the initial slope at low dose levels is linear.

Key findings of animal studies include (Upton 1986):

- the fact that neoplasms of almost any type may be induced via irradiation under appropriate conditions;
- incidence rises steeply with dose and is less dependent on dose rates of high linear energy transfer (LET) radiations than low LET radiation (such as $\gamma$-rays);
- the effects of radiation on the development of neoplasms can be modified by other physical / chemical agents;
- at high doses the dose-incidence curve appears to ‘bend over’ as a result of sterilisation of potentially transformed cells, and
- the time in which radiation-induced tumours appear depends on a large number of variables other than the conditions of radiation exposure, such as tumour type and the genetic background of the animal et cetera.

There are a range of in vitro experiments that can be performed that model the cellular transformation process. As described above, the transformation of a single cell into one which is potentially cancerous is an initial part of a larger process, which is subject to influences from other modifying effects in the organism. It should be noted that in vitro investigation of the transformation aspect of the process neglects these influences arising from the organism’s response. However, cell culture studies have shown interesting results for dose fractionation – namely, that the transformation frequency is decreased via dose fractionation.

There is also data available from medically-exposed persons. A brief overview of risk estimates based on epidemiological data is given in Table 6: the risk estimates for subjects treated with external-beam radiation sources, for leukaemia, stomach, breast, thyroid and lung cancer.
Table 6.1 Some risk estimates (ERR per Gy) from selected studies for cancer of the stomach, breast, thyroid, lung and leukaemia following exposure to external-beam radiation. The average dose in the treatment, as well as the number (N) of cases and in the control population is given (where available).

<table>
<thead>
<tr>
<th>Study</th>
<th>Average dose (Gy)</th>
<th>N (cases)</th>
<th>N (control)</th>
<th>ERR (Gy⁻¹), 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stomach cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Boice et al. 1989)</td>
<td>2</td>
<td>348</td>
<td>658</td>
<td>0.54, [0.05, 1.5]</td>
</tr>
<tr>
<td>(Mattsson et al. 1997)</td>
<td>0.66</td>
<td>14</td>
<td>1,216</td>
<td>1.3, [0, 4.4]</td>
</tr>
<tr>
<td>(Weiss et al. 1994)</td>
<td>3.2</td>
<td>127</td>
<td>1,745</td>
<td>-0.004, [-0.05, 0.05]</td>
</tr>
<tr>
<td>(Carr et al. 2002)</td>
<td>8.9</td>
<td>11</td>
<td>1,859</td>
<td>0.20, [0, 0.73]</td>
</tr>
<tr>
<td><strong>Breast cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Boice et al. 1991)</td>
<td>0.79</td>
<td>147</td>
<td>2,573</td>
<td>0.61, [0.3, 1.01]</td>
</tr>
<tr>
<td>(Mattsson et al. 1995)</td>
<td>5.8</td>
<td>47</td>
<td>-</td>
<td>1.63, [0.77, 2.89]</td>
</tr>
<tr>
<td>(Shore et al. 1986)</td>
<td>3.8</td>
<td>51</td>
<td>601</td>
<td>0.40, [0.2, 0.7]</td>
</tr>
<tr>
<td>(Travis 2002)</td>
<td>22</td>
<td>67</td>
<td>122</td>
<td>0.15, [0.04, 7.3]</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Weiss et al. 1994)</td>
<td>0.59</td>
<td>42</td>
<td>-</td>
<td>3.56, [-0.3, 0.65]</td>
</tr>
<tr>
<td>(Howe and McLaughlin 1996)</td>
<td>2.13</td>
<td>578</td>
<td>-</td>
<td>0.40, [0.13, 0.77]</td>
</tr>
<tr>
<td>(Doody et al. 2000)</td>
<td>0.11</td>
<td>70</td>
<td>4942</td>
<td>2.7, [-0.2, 9.3]</td>
</tr>
<tr>
<td><strong>Thyroid cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Ron et al. 1989)</td>
<td>0.09</td>
<td>98</td>
<td>10,834</td>
<td>30.0, 90% CI: [0, 0.9]</td>
</tr>
<tr>
<td>(Schneider et al. 1993)</td>
<td>0.6</td>
<td>309</td>
<td>234</td>
<td>3.00, N/A</td>
</tr>
<tr>
<td>(Shore et al. 1993)</td>
<td>1.36</td>
<td>37</td>
<td>2,657</td>
<td>9.00, 90% CI: [4, 24]</td>
</tr>
<tr>
<td>(Ron et al. 1995)</td>
<td>-</td>
<td>700</td>
<td>58,000</td>
<td>7.7, [2.1, 28.7]</td>
</tr>
</tbody>
</table>
Table 6.1 cont. Some risk estimates (ERR per Gy) for cancer of the stomach, breast, thyroid, lung and leukaemia following exposure to external-beam radiation. The average dose in the treatment, as well as the number (N) of cases and in the control population is given.

<table>
<thead>
<tr>
<th>Study</th>
<th>Average dose (Gy)</th>
<th>N (cases)</th>
<th>N (control)</th>
<th>ERR (Gy⁻¹), 95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Inskip et al. 1994)</td>
<td>4.6</td>
<td>61</td>
<td>120</td>
<td>0.20, [−0.62, 1.03]</td>
</tr>
<tr>
<td>(Mattsson et al. 1997)</td>
<td>0.75</td>
<td>10</td>
<td>1,216</td>
<td>0.38, [0, 0.6]</td>
</tr>
<tr>
<td>(Gilbert et al. 2003)</td>
<td>20</td>
<td>146</td>
<td>271</td>
<td>0.15, [0.06, 0.39]</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Weiss et al. 1994)</td>
<td>8.88</td>
<td>282</td>
<td>-</td>
<td>0.09, [0.03, 0.15]</td>
</tr>
<tr>
<td>(Howe 1995)</td>
<td>1.02</td>
<td>1,178</td>
<td>25,007</td>
<td>0.00, [−0.06, 0.07]</td>
</tr>
<tr>
<td>(Carr et al. 2002)</td>
<td>1.1</td>
<td>21</td>
<td>-</td>
<td>0.43, [−0.12, 1.35]</td>
</tr>
<tr>
<td><strong>Leukaemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Boice 1985)</td>
<td>7</td>
<td>143</td>
<td>745</td>
<td>0.88, (std. error: 0.69)</td>
</tr>
<tr>
<td>(Inskip 1993)</td>
<td>0.59</td>
<td>4</td>
<td>1,407</td>
<td>0.50, [−0.6, 3.3]</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Weiss et al. 1995)</td>
<td>4.38</td>
<td>35</td>
<td>1,745</td>
<td>12.4, [2.25, 52.1]</td>
</tr>
</tbody>
</table>

In the present work, low out-of-field doses from radiotherapy are of particular interest. For a comprehensive overview, the Board on Radiation Effects Research (BEIR) Report VII: *Health Risks from Exposure to Low Levels of Ionising Radiation* provides a detailed review of studies of second cancer incidence resulting from radiotherapy (BEIR 2006). In this study, the BEIR (2006) risk estimates have been adopted as being the most appropriate for low-dose exposures. Much of their work is based on data from the atomic bomb cohort.
By far the best data on human exposure comes from the ‘atomic bomb cohort’, – the survivors of the nuclear weapon detonations in Nagasaki and Hiroshima, Japan. This study is often referred to as the Life Span Study (LSS). This group has been studied in detail for many decades. The LSS cohort is composed of a sample of around 195,000 residents of Hiroshima and Nagasaki who responded to the atomic bomb survivor census (conducted in 1950) and about 32,000 people who were not in the city at the time of the bombing (as identified in a further consensus conducted between 1950 and 1953). Some studies of cancer incidence in atomic bomb survivors have been published in *Radiation Research*: including an overview of use of the tumour registries for incidence studies (Mabuchi *et al.* 1994), a study of solid tumour incidence (Thompson *et al.* 1994), a study of leukaemia, lymphoma and multiple myeloma (Preston *et al.* 1994) and a comparison of cancer incidence and mortality (Ron *et al.* 1994). Preston *et al.* (2003) have published the thirteenth report on the mortality of atomic bomb survivors, including solid cancer and non-cancerous disease mortality, as well as the effect of recent changes in atomic bomb survivor dosimetry on mortality risk estimates (Preston *et al.* 2004).

The LSS cohort is a unique data source in that the population is very large and was not selected on the basis of disease etc, there has been a long follow-up period, both sexes are included as are all ages. This allows investigation of the different factors by comparison of risks amongst the various sub-groups. The doses are fairly well known, and the cohort incorporates a large group exposed to low-doses, which are of particular relevance in this study. The subjects received a whole-body exposure, which facilitates investigation and inter-comparison of organ-specific cancer risks.

For low dose levels, the best data for radiation-induced cancer risk in humans is the LSS data. Some key inferences one may draw from this dataset are that:

- the risk of radiation-induced cancer increases with post-irradiation time;
- the risk of radiocarcinogenesis decreases with increasing age at time of exposure;
- females exhibit a greater risk than males and
- there is an increased risk of fatal cancer for doses ranging up to 2 Sv that is consistent with a linear relationship.

Figure 6.10 shows the solid cancer incidence arranged according to the percentage of the total incidence and the excess relative risk.
Figure 6.10 Solid cancers for specific cancer site or organ system arranged according to (a) percentage of total solid cancer incidence and (b) excess relative risk (per Sv). Data from (Thompson et al. 1994).
Shimizu et al investigated cancer mortality amongst atomic bomb survivors. Highlighting the dose intervals where a statistically significantly higher cancer mortality is observed, Figure 6.11 shows the estimated relative risk compared to the control (0 Gy) group, given for dose bins less than 2 Gy.

The issue of latency is also worth mentioning. Radiation-induced leukaemia typically manifests two or three years after exposure, with peak occurrence within six to eight years, after which there is a decrease with time. The latency period for radiation-induced solid tumours is typically longer than leukaemia – generally fifteen years or more. It is for this reason that paediatric patients are of particular concern in terms of radiation-induced cancer, and for this reason later sections of this work deal specifically with doses to paediatric patients.

![Figure 6.11](image.png)

**Figure 6.11** The estimated relative risk of mortality for the atomic bomb cohort for doses less than 2 Gy. This highlights the dose intervals where the observed mortality is statistically higher than the control (0 Gy) group. Data from (Shimizu et al. 1993).
6.3.4 The nominal risk per Sievert
Risk models generally allow for the variation in excess risk that occurs with influencing factors such as sex, age at exposure and attained age. The *nominal* risk coefficients presented here are derived from averaging sex and exposure-age lifetime risk estimates for combined Euro-American and Asian populations (ICRP 2007). The lifetime cancer risks are determined from risk estimates for site-specific cancers. Table 6.2 shows the whole-population, sex-averaged nominal risk of fatal, non-fatal and total tumour incidence. The risks are given for the oesophagus, stomach, colon, liver, lung, bladder, breast, ovary, thyroid and bone marrow from BEIR VII (2006) data. For gonads (heritable) risks, BEIR data was unavailable and ICRP (2007) data was used. Remaining tissues were grouped as ‘other’ solid cancers.

**Table 6.2** The whole-population, sex-averaged nominal risk (% per Sv) of fatal, non-fatal and total cancer incidence according to the BEIR VII report (2006). Note that a dose and dose rate effectiveness factor (DDREF) of 1.5 is used by the BEIR committee.
* Note that BEIR VII did not consider lifetime risk estimates for gonads and so these values are from the ICRP (2007).

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Total</th>
<th>Fatal</th>
<th>Non-fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophagus</td>
<td>0.141</td>
<td>0.131</td>
<td>0.01</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.963</td>
<td>0.798</td>
<td>0.165</td>
</tr>
<tr>
<td>Colon</td>
<td>0.745</td>
<td>0.356</td>
<td>0.389</td>
</tr>
<tr>
<td>Liver</td>
<td>0.4</td>
<td>0.382</td>
<td>0.018</td>
</tr>
<tr>
<td>Lung</td>
<td>1.369</td>
<td>1.218</td>
<td>0.151</td>
</tr>
<tr>
<td>Bladder</td>
<td>0.519</td>
<td>0.15</td>
<td>0.37</td>
</tr>
<tr>
<td>Breast</td>
<td>1.119</td>
<td>0.329</td>
<td>0.789</td>
</tr>
<tr>
<td>Ovary</td>
<td>0.115</td>
<td>0.065</td>
<td>0.05</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.32</td>
<td>0.021</td>
<td>0.299</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>0.419</td>
<td>0.28</td>
<td>0.139</td>
</tr>
<tr>
<td>Other solid cancers</td>
<td>1.633</td>
<td>0.801</td>
<td>0.832</td>
</tr>
<tr>
<td>Gonads (heritable) *</td>
<td>0.2</td>
<td>0.16</td>
<td>0.04</td>
</tr>
<tr>
<td>Total</td>
<td>7.943</td>
<td>4.691</td>
<td>3.252</td>
</tr>
</tbody>
</table>
6.3.5 Risk estimation for non-cancerous diseases based on LSS data

The Life Span Study data also shows evidence for a link between radiation exposure and non-cancer disease mortality. This is discussed in detail elsewhere (Shimizu et al. 1999). Preston et al (2003) showed that a linear (L) fit for the dose response is a suitable model, with the linear-quadratic (LQ) model not fitting significantly better. Table 6.3 shows the cause-specific excess relative risk per Sv for mortality from non-cancer diseases, based on LSS data.

Table 6.3 Excess relative risk (ERR per Sv) of mortality for non-cancer diseases, identified for individual causes, shown with the 90% confidence interval (CI). Based on LSS data (Preston et al. 2003).

<table>
<thead>
<tr>
<th>Cause</th>
<th>ERR (Sv⁻¹)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td>0.17</td>
<td>0.08, 0.26</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.12</td>
<td>0.02, 0.22</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>0.18</td>
<td>0.06, 0.32</td>
</tr>
<tr>
<td>Digestive disease</td>
<td>0.15</td>
<td>0.00, 0.32</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>-0.02</td>
<td>-0.2, 0.25</td>
</tr>
<tr>
<td>Other (non-blood) diseases</td>
<td>0.08</td>
<td>-0.04, 0.23</td>
</tr>
<tr>
<td>All non-cancer diseases</td>
<td>0.14</td>
<td>0.08, 0.2</td>
</tr>
</tbody>
</table>

6.3.6 Summary

Various data sources for radiocarcinogenesis are available, including experimental animal studies, in vitro tissue studies and epidemiological data from human exposures including medical, occupational, accidental and atomic bomb exposures. For low doses, a linear dose-response model is appropriate for solid-tumour induction. Here, the BEIR VII Phase 2 risk estimates are chosen to be most appropriate. Much of this data is based on the atomic-bomb cohort. There are also risks of noncancerous diseases related to radiation exposure, and these have been summarised.
6.4 The lack of data for out-of-field doses from stereotactic fields

In the previous sections, a detailed review has been given of studies investigating out-of-field dose and of the risks for detrimental side-effects that may occur far from the primary field, in low-dose regions. It is evident from this overview that despite the fervent interest in out-of-field doses and the potential for radiation-induced carcinogenesis from low doses, there is relatively little data pertaining to such doses from small fields, such as those used in stereotactic radiotherapy.

Intuitively, one might expect that out-of-field doses from a stereotactic radiotherapy treatment may be lower than, for instance, a whole-brain radiotherapy treatment. However, this does not necessarily imply that the former may generate out-of-field doses which are entirely without an associated increased risk to the patient of detrimental effects, such as radiation-induced cancer. In fact, as the novel studies undertaken in this work show, far from the primary field the doses are not dependent on field-size (see the following sections), negating such dismissive points of view.

As such, it seems prudent that any comprehensive study – such as this one – characterising the doses from small fields must also investigate out-of-field doses. The least-studied stereotactic out-of-field doses are those delivered using linac-based radiotherapy. In the following sections, peripheral doses from mini-multileaf collimator shaped stereotactic fields are characterised in a systematic way, as a function of various parameters such as field size, depth in phantom, source-surface distance and so on. Additionally, since it is paediatric patients whom are at most risk of developing latent radiation-induced cancers, doses to critical organs are measured in a paediatric phantom subjected to small-field treatments, and corresponding cancer risks are calculated.
6.5 Systematic evaluation of the peripheral doses from stereotactic fields

Despite the highly localised doses that may be delivered via stereotactic radiotherapy, a small dose is nonetheless delivered to out-of-field regions, which may cause detriment to the patient. In this work, a systematic set of dose measurements have been undertaken up to a distance of 45 cm from the isocentre, for stereotactic fields shaped by a BrainLAB mini-multileaf collimator (MMLC) mounted on a Varian 600C linear accelerator. A range of treatment parameters were varied so as to determine the factors of greatest influence and establish relationships with dose. The commercial treatment planning software (TPS) miscalculates the dose to out-of-field regions. Measured dose decreases consistently out to 45 cm, whereas the TPS decreases out to 10-15 cm, at which point the predicted dose is constant. At 5-10 cm off-axis distance (OAD), measurements indicate doses of about 5-10 % of the dose at isocentre, 1 % at 15 cm OAD and 0.1 % at 45 cm OAD. There are several observed trends. Greater MMLC field sizes (with static jaw) result in higher out-of-field dose, as do shallower depths. The source-to-surface distance does not greatly influence peripheral dose. However, the results given in this work do indicate that simple treatment arrangements, such as preferable collimator rotation, would in certain cases reduce out-of-field dose by an order of magnitude. Peripheral dose raises questions of treatment optimisation, particularly in cases where patients have a long life expectancy in which secondary effects may become manifest, such as in the treatment of paediatric patients or those with a non-malignant primary. For instance, for a 20 Gy hypo-fractionated treatment, dose to out-of-field regions is of the order of cGy – a substantial dose in radiation protection terms.

Note that for the sake of scientific integrity, this section of the chapter repeats the associated publication verbatim (Taylor et al. 2010c).
6.5.1 Introduction

The function of stereotactic radiotherapy is to deliver highly localised doses to small lesions; however, treatment of these conditions nonetheless results in a small amount of dose being delivered to untargeted regions. The unfortunate irony of contemporary radiotherapy is that its increasing efficacy is successfully lengthening patients’ lifetimes, and thus there is greater time in which radiation-induced cancers may become manifest. The potential for radiocarcinogenesis due to doses received outside the primary field is of particular importance for paediatric patients and those with a non-malignant primary condition, and knowledge of such doses may influence the choice of treatment options adopted.

Treatment planning systems (TPS) are normally commissioned using measured data that extend only a few centimetres beyond the field edge, with penumbra defined as 80% to 20% of the maximum dose for the field. Dose extending outside the field is not intended to be used for the overall calculation of the dose distribution or contribute to the inverse optimisation procedure. Therefore, one would expect the dose distributions predicted by the TPS to be inaccurate in regions far from the primary field.

A large body of published literature exists pertaining to the measurement and calculation of doses to out-of-field regions for various modes of external beam radiotherapy (Xu et al. 2008). There is, however, relatively little literature relating to peripheral doses from stereotactic radiotherapy. Intensity-modulated radiotherapy typically uses doses of the order of a couple of Gy over a large number of fractions so as to achieve a total of 60 – 70 Gy. In contrast, stereotactic radiotherapy often employs high doses (10 – 20 Gy per fraction) in a hypofractionated regime of few fractions. As such, the out-of-field doses from each high dose single fraction is of interest. Ioffe et al (2002) quantified the dose rate as a function of distance from the isocenter in a RANDO phantom for Gamma-Knife treatments. Hasanzadeh et al (2006) constructed an anthropomorphic phantom and undertook thermoluminescent dosimeter (TLD) measurements of dose in untargeted organs for Gamma-Knife radiosurgery. Petti et al (2006) developed Cyber-Knife plans for a thorax lesion and brain lesion in an anthropomorphic phantom and measured the dose at various depths and distances outside the treatment field using TLD. Peripheral doses were found to be 2 to 5 times higher than a comparable Gamma-Knife treatment and up to 4 times higher than an IMRT treatment. The relatively large peripheral dose is attributed to greater leakage of the Cyber-Knife unit. Chuang et al (2008) investigated reduction of out-of-field doses from the Cyber-Knife system resulting from a shielding upgrade, with the observation that doses were generally reduced by 20 to 55%. The latter studies mentioned have focused on the Cyber-Knife and Gamma-Knife systems. Maarouf et al (2005) examined the radiation exposure of organs at risk and assessed
the risk of late effects (such as secondary tumours or hereditary disorders) following stereotactic linac radiosurgery of intracranial tumours. TLD were placed superficially on patients’ eyelids, thyroid, breast and regions of the ovary / testes, with measured doses in the order of cGy and mGy.

Ultimately, there have been few studies of out-of-field doses from linac-based stereotactic radiotherapy. The present study characterises the peripheral doses from a BrainLAB (Feldkirchen) m™ mini-multileaf collimator (MMLC) used for stereotactic radiotherapy. Doses were measured at various points in a water phantom up to 45 cm from the central axis. A range of field sizes was employed along with variation of other parameters, such as source-surface distance and depth in water, so as to determine the factors of greatest influence and establish relationships with dose. The doses at these positions were also calculated with the BrainLAB iPlan treatment planning system.

A set of results have been presented as concisely as possible here, to indicate the general behaviour of peripheral doses from stereotactic fields and demonstrate the influence of typical treatment parameters. A comparison with the treatment planning software dose calculation indicates the limitations thereof, and preferable treatment options are identified to limit unnecessary patient dose.

6.5.2 Dose measurement and Calculation
6.5.2.1 Experimental method
At the William Buckland Radiotherapy Centre (Alfred Hospital, Melbourne), stereotactic radiotherapy is performed using a BrainLAB m™ mini-multileaf collimator mounted on a Varian 600C as a tertiary collimation device. The maximum effective field size is 9.8 x 9.8 cm² at isocenter, shaped by 26 leaf pairs: 14 of width 3 mm, six of width 4.5 mm and an outer set of six with 5.5 mm width. The leaves move orthogonally to the beam axis, and have a complex tongue and groove cross-section. This cross section is also shaped to match the beam divergence across the field. The leaf edges are not curved, but rather have three angled straight edges, the total length of which is 6 cm. The middle section is milled parallel to the beam axis to match the (non-) divergence of the beam when centred. The upper section is at an angle corresponding to the beam divergence when the leaf is fully extended (5 cm beyond the centre), and the angle of the lower section corresponds to full retraction (5 cm back from the centre).
The dose was measured with ionisation chambers IC3 and IC13 (Wellhöfer, Schwarzenbruck) at 5 cm steps along a line (in both the x- and y-planes) from the isocentre (0 cm) to 45 cm away. The smaller IC3 was used in the near out-of-field region to elucidate expected structure, while the larger IC13 was used in the far out-of-field region. For consistency the same measurement points were used for all field sizes, with 5 cm distance from the central axis being the nearest out-of-field distance of interest for the set of field sizes studied. The detectors were placed inside a large (50 x 50 x 50 cm$^3$) water-filled tank (Wellhöfer, Schwarzenbruck) and their position controlled via the scanning mechanism. This was undertaken for various combinations of delivery parameters, as indicated in Table 6.4. Measuring in a homogenous water phantom (water-tank) allows for the systematic characterisation of peripheral doses. This facilitates isolation of geometrical parameters from other compounding effects introduced when measuring in more realistic situations, such as in vivo or with anthropomorphic phantoms. These include six field sizes shaped with the MMLC (with a static 9.8 x 9.8 cm$^2$ jaw), three source-surface-distances (SSD) and three depths with collimator rotations of 0° and 90°. All measurements were taken with sufficient monitor units (hundreds to thousands) to obtain a dose in the order of at least mGy, and were corrected for electrometer leakage, temperature, pressure and daily linac output variation; repeated measurements indicate variations of ~0.5 %.

**Table 6.4** The comprehensive set of measurement parameters varied in this study, including source-surface distance (SSD), depth in water tank and MMLC field size (with static 9.8 x 9.8 cm$^2$ jaw setting).

<table>
<thead>
<tr>
<th>Direction</th>
<th>Cross-plane and in-plane</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSD (cm)</td>
<td>85, 90 and 100</td>
</tr>
<tr>
<td>Depth (cm)</td>
<td>2, 5, 10 and 20</td>
</tr>
<tr>
<td>Field sizes (mm$^2$)</td>
<td>0 x 0, 24 x 24, 42 x 42, 60 x 60, 80 x 80 and 98 x 98</td>
</tr>
</tbody>
</table>

**6.5.2.2 iPlan dose calculation**

Treatment plans were generated with iPlan RT Dose version 3.0 (BrianLAB, Feldkirchen) dose calculation software, which has been commissioned according to the manufacturer’s specifications. Note that this commissioning does not incorporate data more than a few centimetres from the field edge. The iPlan pencil beam algorithm uses photon beam data calculated by Mohan *et al* (1985; 1986; 1987). In this method, the incident beams are subdivided into small ‘beamlets’. For each beamlet, a radiological path length correction is applied to correct for density inhomogeneity. A fast Fourier transform (FFT) is applied for the beam kernel convolution with the fluence distribution of the beam.
6.5.3 Results and Discussion

6.5.3.1 Overview of results

The results presented here have been chosen to best indicate the trends of out-of-field dose from stereotactic fields, and to demonstrate the influence of typical treatment parameters, such as depth in phantom, field size, SSD and collimator rotation (data was taken along the x- and y-planes, as defined by the direction of jaw motion). The dose per monitor unit (MU) is given as a function of distance from isocentre for these various parameters, as shown in Figure 6.12. In the same fashion, a comparison with treatment planning software predictions is given in Figure 6.13, and an indication of the discrepancies between measurement and dose calculation is given in Table 6.5. The discussion of results is broken up into sections, each discussing the influence of the different delivery parameters. A brief discussion of the potential for detrimental radiation-induced effects is also given, facilitated by an example for a paediatric patient treated for an arteriovenous malformation.

Table 6.5 This table summarises the discrepancies between the doses (relative to the dose at isocentre) as measured and as calculated with the treatment planning system (TPS) at selected distances from the isocentre. The data shown incorporates maximum (max.) and mean doses (with standard deviation, $\sigma$) over multiple depths along both the x- and y-planes for 98 x 98 mm$^2$ field. The TPS-calculated out-of-field doses plateau beyond a certain distance (as evidenced in Figure 6.13). In order to generate comparable data, a large number of monitor units were employed in the TPS calculation; it should be noted that with a lower number of monitor units (such as that for a typical treatment) the TPS assumes zero dose far from the primary field. In most contexts, therefore, the TPS significantly underestimates peripheral dose.

<table>
<thead>
<tr>
<th>Distance from isocentre (cm)</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max. measured dose (rel. to isocentre dose)</td>
<td>81 %</td>
<td>4.80 %</td>
<td>1.81 %</td>
<td>0.05 %</td>
</tr>
<tr>
<td>Mean measured dose (rel. to isocentre dose)</td>
<td>35 %</td>
<td>2.19 %</td>
<td>0.85 %</td>
<td>0.03 %</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>30 %</td>
<td>1.64 %</td>
<td>0.62 %</td>
<td>0.01 %</td>
</tr>
<tr>
<td>Max. TPS calculated dose (rel. to isocentre dose)</td>
<td>58 %</td>
<td>5.01 %</td>
<td>2.03 %</td>
<td>1.11 %</td>
</tr>
<tr>
<td>Mean TPS calculated dose (rel. to isocentre dose)</td>
<td>38 %</td>
<td>2.27 %</td>
<td>0.89 %</td>
<td>0.59 %</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>24 %</td>
<td>1.68 %</td>
<td>0.67 %</td>
<td>0.32 %</td>
</tr>
<tr>
<td>Ratio of max. relative doses (measured / TPS)</td>
<td>1.39</td>
<td>0.96</td>
<td>0.89</td>
<td>0.05</td>
</tr>
<tr>
<td>Ratio of mean relative doses (measured / TPS)</td>
<td>0.94</td>
<td>0.97</td>
<td>0.95</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Figure 6.12  Plot of dose per monitor unit (MU) as a function of distance from isocentre, indicating the influence of measurement depth on the peripheral dose. Example taken along the y-plane direction for a 24 x 24 mm$^2$ field at an SSD of 90 cm.  

(b) Plot of dose per monitor unit (MU) as a function of distance from isocentre, indicating the influence of SSD and measurement plane (x-direction, x, or y-direction, y) on the peripheral dose. Example taken for a 24 x 24 mm$^2$ field at a depth of 10 cm.

(c) Shows the off-axis doses from a closed (0 x 0 mm$^2$) field compared to a 24 x 24 mm$^2$ field at a depth of 10 cm for 90 cm SSD, along both the x- and y-plane directions.  

(d) Plot of dose per monitor unit (MU) as a function of distance from isocentre, indicating the influence of stereotactic field size (in mm$^2$) on peripheral dose. Example taken along the x-plane direction at an SSD of 90 cm.
Figure 6.13 Plot of dose per monitor unit (MU) as a function of distance from isocentre, which indicates the poor dose prediction of the treatment planning system for a selection of field sizes at 10 cm depth and 90 cm SSD. Beyond the field edge the dose calculation either overestimates or underestimate the peripheral dose.

6.5.3.2 Influence of depth

Figure 6.12(a) indicates the relationship between the peripheral dose and the measurement depth (2, 5, 10 and 20 cm). This is shown for a 24 x 24 mm2 field at 90 cm SSD along the y-plane direction; similar data (not shown) has also been measured for other field sizes (including a closed field) and the x-plane direction. Generally, the peripheral dose is higher for shallower depths – as shown in Figure 6.12 (a), at a distance of 45 cm from the isocentre, the dose per MU is about five times higher at a depth of 2 cm than that at 20 cm. This is not unexpected, and may be explained more or less by attenuation. As evidenced by typical depth dose curve measurements, the attenuation of the primary beam along the central axis results in a dose at 20 cm depth of about 2.6 times less than that at 2 cm depth. For the out-of-field regions, such data is relatively less well-known. A dosimetrically matched Monte Carlo model of the 600C linac constructed using BEAMnc (Rogers et al. 1995; Kawrakow and Rogers 2006) indicates that the primary beam has a mean energy of around 2 MeV, and far from the primary field, the spectral qualities of the beam change quite significantly, having a much lower mean energy (of the order of 0.5-0.6 MeV). The detector response is quite flat, and would change by only about 1 % – thus not significantly affecting the results. Consideration of simple linear attenuation in water (Attix 2004) gives a factor of 2.4 difference between 2 cm and 20 cm depth for a 2 MeV beam, and a factor of 5.7 for a 500
keV beam. The attenuation at an off-axis distance of 45 cm is thus more pronounced, providing some explanation for the differences observed in out-of-field dose for the different measurement depths as illustrated in Figure 6.12(a).

6.5.3.3 Influence of SSD
Figure 6.12(b) demonstrates the relationship between the peripheral dose and the source-to-surface distance (SSD). In this case, data is shown along the x-plane and y-plane directions for a 24 x 24 mm$^2$ field at a depth of 10 cm. From the data, it is evident that the SSD has a negligible influence on the out-of-field dose. The slight differences between curves can also be partially attributed to the uncertainty in the measurements taken in these very low fluence regions (where doses are fractions of mGy).

6.5.3.4 Influence of collimator rotation
Unlike the SSD, collimator rotation has a significant effect on the peripheral dose, as indicated in Figure 6.12(b) and (c). Close to the primary field, as one would expect, doses do not vary significantly with collimator rotation. With increasing off-axis distance, however, doses along the y-plane are up to an order of magnitude higher than those along the x-plane. The jaws are thick and, as a result, one pair is mounted above the other (such that the y-jaws sit almost 9 cm vertically above the x-jaws (top-to-top), both being approximately 8 cm thick). While this does not appear have an effect on in-field doses (Metcalfe et al. 1993), there is clearly a difference for out-of-field doses. The difference in height may have some influence, in as far as a particle interacting in the x-jaws and scattering arbitrarily into the primary field may be scattered outside of the field if it interacted at an equivalent point in the upper jaws and scattered at the same angle. The upper jaws are also exposed to greater primary radiation than the lower jaws, which are somewhat shadowed by the former, and thus generate more scatter. Because the lower jaws are oriented perpendicularly to the upper jaws, this scatter is un-collimated along the y-direction. The MMLC construction has a strong influence on the level of disparity between the x and y directions, with differences being more pronounced for small field sizes (field size differences are discussed in the following section). The leaves move in the x-plane direction, the drive machinery lies beneath the x-jaws and the leaf bank is slightly longer in that direction. For larger fields where the relative influence of in-phantom scatter from the primary beam is higher, the difference between x and y is less pronounced.
At about 10 cm off-axis distance, the out-of-field dose from a small field along the y-plane is a factor of three higher than that along the x-plane, and at 45 cm off-axis distance it is almost an order of magnitude higher. As such, the clinical recommendation is that, where possible, for a couch orientation of 0° one should employ a collimator rotation of 0°. For each field, the collimator rotation should be preferentially chosen such that the x-plane is aligned with the craniocaudal axis of the patient (i.e. parallel to the couch).

6.5.3.5 Influence of field size

Figure 6.12 (c) and (d) show the relationship between the peripheral dose and the size of the stereotactic field. The most strikingly different field is of course the closed field (0 x 0 mm²), which is compared to the 24 x 24 mm² field in Figure 6.12 (c) along both the y- and x-plane directions. The difference between doses in the x- and y-planes has been discussed in the previous section and, as with open fields, the dose with closed leaves is still significantly higher along the y-plane than the x-plane. Consider first doses along the x-plane, in which direction the MMLC leaves move. At isocentre, the 24 x 24 mm² field clearly results in a dose significantly higher (two orders of magnitude) than the closed field. However, at about 5 cm off-axis the dose from the closed field is a factor of about one and a half times higher than the small field. The reason for this is that the MMLC leaves close such that the isocentre is best shielded, with one bank fully extended and the other bank fully retracted. The slight airgap between the two banks of leaves allows some leakage which results in the relatively higher dose at about 5 cm from the isocentre. Beyond this point, the dose from the closed field is lower than the 24 x 24 mm² field until about 30 cm off-axis distance, at which point the dose again rises above that of the small field. A trigonometric calculation suggests that this corresponds to scatter beneath the jaws passing behind the fully-extended leaf bank. Doses along the y-plane agree with what one would intuitively expect, i.e. the dose due to the 24 x 24 mm² field is higher than the closed field, the difference decreasing with increasing off-axis distance.

In Figure 6.12(d), data is shown along the x-plane direction for five different field sizes at a depth of 10 cm and an SSD of 90 cm. The general trend is that dose per MU decreases with distance in a consistent manner for the various field sizes, with the larger field sizes clearly resulting in higher out-of-field dose. While head leakage will be a significant contributor to out-of-field dose, this is expected to remain more or less consistent regardless of the field size, since the jaws are static. As such, the ‘vertical shift’ of the dose curves for different field sizes may be attributed chiefly to the change in primary fluence. The dose at a distant point is...
related to the energy and fluence of the radiation scattered there (and the mass energy absorption coefficient of the medium). Considering the primary beam incident upon the phantom, the dominant interaction mode for this energy ($E \approx 2$ MeV) is inelastic photon scattering. The scattered photon fluence at the distant point is related to the primary fluence, by a proportionality constant incorporating the Klein-Nishina (1929) cross section for the Compton effect, an inverse-square law factor and an attenuation factor. From a practical perspective, if one wishes to estimate the increase in out-of-field dose resulting from an increased field size in a clinical context, the results show an increase proportionate to the increase in side-length of the field. Compare, for instance, the $24 \times 24$ mm$^2$ field to the $98 \times 98$ mm$^2$ field. The $98$ mm side length is four times the $24$ mm side length, and the peripheral dose is four times higher. This approximate trend is also exhibited by other ratios of field sizes (within around ten or fifteen percent).

6.5.3.6 Limitations of the treatment planning dose calculation software

Figure 6.13 illustrates the limited capacity of the treatment planning software to calculate out-of-field doses. This is shown for various field sizes at 90 cm SSD and a depth of 10 cm along the x-plane. Beyond the field edge, the dose calculation either overestimates or underestimates the peripheral dose. The treatment planning software effectively does not calculate dose beyond about 10 cm from the isocentre. Selecting a large number of monitor units (MU) and then observing the dose per MU indicates that iPlan simply assumes that the dose plateaus beyond a given distance. There is generally under-prediction of the peripheral dose close to the primary field, and over-prediction far from the primary field (because of the dose plateau). In order to generate comparable data, a large number of monitor units were employed in the TPS calculation (up to $10^3$); it should be noted that with a lower number of monitor units (such as that for a typical treatment) the TPS assumes zero dose far from the primary field. In most contexts, therefore, the TPS significantly underestimates peripheral dose.

6.5.3.7 Implications and recommendations

Aside from the normal tissue complications that may arise in the vicinity of the treatment zone, low doses to untargeted regions may result in harmful long-term effects, such as radiocarcinogenesis. The patients of most concern are those whose lifetimes might otherwise be quite long, and hence have a greater time period in which radiation-induced cancers may become manifest, such as paediatric patients or those without a primary malignancy. For example, consider paediatric patients treated for arteriovenous malformations (AVM); for
small AVMs, minimum target doses of 20 to 25 Gy are not unusual (Aoyama et al. 2001; Chang and Adler 2001). To illustrate the potential for detriment, in this case consider a dose of 18 Gy applied to a 12 year old patient delivered with a 6 cm$^2$ field (see, for instance, the study by Maity et al (2004)). Making an estimate from the out-of-field dose data presented in this study, the dose to the thyroid (about 12 cm from mid-brain) would be of the order of 70 mGy. Using the preferred model for risk estimation of thyroid cancer (for low doses) based on the study by Ron et al (1995), and recommended by the Committee on the Biological Effects of Ionizing Radiation (BEIR 2006), the increased relative risk of thyroid cancer as a result of the treatment would be increased by a factor of 1.2 or 1.3 for a male or female patient respectively. While few would argue against the notion that the curative effects of radiotherapy outweigh the potential negative consequences, the results nonetheless highlight the importance of maintaining an awareness of out-of-field doses, and by employing a simple treatment arrangement, out-of-field dose to the patient may be minimised.

6.5.4 Conclusions
A systematic set of measurements of out-of-field dose have been undertaken for various fields of relevance to stereotactic radiotherapy shaped with a BrainLAB m$_3$ MMLC mounted on a Varian 600C. The treatment planning software was shown to considerably miscalculate doses beyond the primary field. Higher peripheral doses are associated with increasing field sizes and shallow phantom depths, while varying the SSD was shown to have a negligible influence on out-of-field dose. Furthermore, it is recommended that clinical treatments are undertaken in such a fashion that the patient lies along the x-plane direction, where peripheral doses to untargeted regions may be up to an order of magnitude lower than along the y-plane direction. For a stereotactic treatment with a treatment dose in the tens of Gy, out-of-field doses are of the order of cGy, which is a considerable dose in radiation protection terms.
6.6 Small-field radiotherapy of paediatric patients: Doses to untargeted critical structures and the risk of radiation-induced carcinogenesis

The objective of this study is to characterise out-of-field doses in paediatric radiotherapy, and to identify simple means by which out-of-field dose may be minimised, with a view to reducing the risk of secondary cancers. With the aim of characterising peripheral doses under different treatment conditions, dose measurements in an anthropomorphic child phantom were taken in various organs and critical structures outside the primary field using thermoluminescent dosimetry. Doses from Varian 600C and Varian Trilogy linear accelerators (linacs), both at 6 MV, were investigated. Larger field sizes are shown to result in higher peripheral doses close to the primary beam, with the difference becoming less considerable at large distances, indicating that most of out-of-field dose is due to head leakage and collimator scatter beyond 40 cm from the primary field. The use of lead shields is shown to reduce the absorbed dose resulting from leakage. Aligning the craniocaudal axis of the patient with the x-plane of the collimator results in a dose reduction of 40 %, for both machines. Out-of-field doses from the Varian Trilogy were shown to be approximately 40 % higher than those from the 600C, despite being operated at the same energy. Out-of-field doses to paediatric patients may be minimised by employing simple treatment options, such as using the single energy mode linac rather than the multi-mode, orienting the couch and collimator such that the patient lies along the x-plane, and avoiding fields directed along the trunk of the body.

Note that for the sake of scientific integrity, this section of the chapter repeats the associated publication verbatim (Taylor et al. 2011c).
6.6.1 Introduction
The most common fatal disease in children is cancer. In fact, after accidents, it is the leading cause of death in children between the ages of one and fourteen years (Bleyer 1990; Jemal et al. 2009). There are a number of treatment options available, such as surgery, chemotherapy or radiation therapy (radiotherapy). However, there are long term negative potential consequences from treatment – via any modality – of childhood cancers. Survivors of childhood cancer are prone to social difficulties in later life, being more likely to require special education services and having a reduced likelihood of undertaking tertiary education, marrying as a young adult and finding employment (Pang et al. 2008; Gurney et al. 2009). Also concerning is the potential for late health complications, in particular, those that arise as a result of the treatment for the primary disease. Such cases are of interest to clinicians because they are amenable to risk minimisation by careful choices regarding the nature of the treatment.

In Australia, approximately 28 % of children under the age of 15 diagnosed with cancer are treated with radiotherapy (Ahern and Berry 2003). In radiotherapy, it is the cell-killing function of ionising radiation that is the desirable effect for the destruction of a targeted tumour. However, unwanted doses to untargeted healthy tissues can have deleterious consequential effects, such as respiratory and cardiac complications or radiocarcinogenesis. This is not only of interest in the immediate regions around the targeted volume, but also in critical structures that are quite distant from the primary field, which nonetheless receive a dose from scattered and leaked radiation. In the case of paediatric patients, the issue of doses to untargeted tissues is of particular concern. Normal tissues in children have the capacity not only to repair but to grow, and are affected by radiation to a greater extent than adult tissues. Furthermore, the long potential lifetimes of paediatric patients means that there is greater time in which radiation-induced cancers may become manifest.

Strong interest in out-of-field radiation doses from medical linear accelerators (linacs) seems to have started from about the 1970s. The focus of earlier studies is typically from an occupational radiation safety perspective. More recently, there has been greater acknowledgement and interest in doses to untargeted critical structures in the patient. For a review of out-of-field doses from external photon beams, the reader is referred to the recent paper by Xu et al (Xu et al. 2008). In the present study, the objective is to identify straightforward treatment arrangements that may be readily applied clinically to reduce the level of unnecessary dose to untargeted organs in the patient. This has been achieved by experimental measurement of out-of-field doses undertaken for a range of treatment arrangements using a paediatric phantom.
6.6.2 Method

6.6.2.1 Thermoluminescent dosimetry in paediatric phantom

Dose measurements were taken in a 5 yr old paediatric phantom (CIRS Incorporated, Virginia USA). The phantom is made using tissue-equivalent material with homogeneity of bone and lung equivalent materials better than 1 and 3 %, over an energy range of 30 keV to 20 MeV (ICRU 1984a). The phantom incorporates a set of 5 mm holes designed for organ dosimetry using thermoluminescent detectors (TLD). LiF:Mg,Cu,P TLD-100H chips (Harshaw, Kansas USA) were employed, and display less variation in response with photon energy than standard TLD-100 LiF:Mg,Ti. This TLD is highly sensitive in the low-dose regime (Duggan et al. 2004). Multiple TLDs were placed at each of the following anatomic locations: the right and left lenses of the eye, optic nerve, brain, thyroid, lungs, heart, kidneys, abdomen and gonads (Table 6.6). Calibration was performed at 6 MV with TLDs at 1.5 cm depth in solid water, using a 10 x 10 cm$^2$ field at 100 cm source-surface distance (SSD). For each set of measurements, the calibration group had two TLDs that received zero dose, four received 0.1 Gy and another four received 1 Gy. The reproducibility of TLD measurements was better than 2 % (1σ). Using multiple TLDs for calibration yielded an overall uncertainty of 4 % at the 95 % confidence level for a given dose reading. Read-out was performed using a Harshaw automatic TLD reader.

6.6.2.2 Radiation delivery arrangements

Measurements of out-of-field dose were taken in the paediatric phantom for a range of delivery conditions. Multiple measurements were taken for several combinations of treatment parameters, over different days. Two static-field deliveries were applied to the phantom with a target in the posterolateral region of the brain: one with a posterior and lateral field (1:1 weighting), the other incorporating a third field along the vertex (2:2:1 weighting). A twin-arc treatment was also applied (1:1 weighting). For each case, irradiations were performed with a 0.5 x 0.5 cm$^2$ field (total of 5 Gy delivered) and a 5 x 5 cm$^2$ field (total of 2.5 Gy delivered), chosen for generality and reproducibility. Identical irradiations were performed on both a Varian™ Clinac 600C and Trilogy operated at 6 MV. Both upright and supine patient positions were investigated, as were collimator rotations of 0° and 90°. The patient positions are illustrated in Figure 6.14. A whole-brain radiotherapy (WBRT) field was also applied (20 x 10 cm$^2$) for comparison, since it is often employed in the treatment of metastases or acute lymphocytotic leukaemia. The use of a shielding block placed on the couch next to the phantom was studied in terms of the potential for reduction of leakage dose to the torso of the patient.
Figure 6.14 A schematic indicating the three different phantom orientations employed in this study: (a) supine (the typical arrangement), (b) upright and (c) prone. For clarity, not all treatment fields have been illustrated. The two-field treatments are indicated in (a) and (b), and the whole-brain radiotherapy (WBRT) field is illustrated in (c). Note the presence of the lead (Pb) shielding block in the latter arrangement. The uncertainties in each measurement point are better than 4 % at the 95 % confidence limit.

6.6.3 Results
The results are presented as graphs of dose as a function of distance in the phantom from the isocentric plane. Note that at each distance there are multiple data – corresponding to dose measurement points in organs in the same plane and hence same distance (see Table 6.6). The uncertainty at each point is better than 4 % (95 % confidence interval) and the spread of values at a given distance represents the dose to different organs at the same superior-inferior distance or different doses at multiple locations within a single organ.
Table 6.6 The TLD locations for the small field and whole-brain radiotherapy (WBRT) field treatments.

<table>
<thead>
<tr>
<th>Location</th>
<th>Small fields</th>
<th></th>
<th>WBRT fields</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># measurement points</td>
<td>Sup/inf distance from field centre (cm)</td>
<td># measurement points</td>
<td>Sup/inf distance from field centre (cm)</td>
</tr>
<tr>
<td>Right and left lenses of the eye</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Optic nerve</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Mid-brain</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Cord C spine</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Mouth</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Thyroid</td>
<td>2</td>
<td>16.5</td>
<td>2</td>
<td>16.7</td>
</tr>
<tr>
<td>Upper Lung</td>
<td>2</td>
<td>21.5</td>
<td>2</td>
<td>21.5</td>
</tr>
<tr>
<td>Cord T spine</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>21.5</td>
</tr>
<tr>
<td>Anterior heart</td>
<td>2</td>
<td>29</td>
<td>2</td>
<td>29</td>
</tr>
<tr>
<td>Lower Lung</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>29</td>
</tr>
<tr>
<td>Kidneys</td>
<td>4</td>
<td>36.5</td>
<td>4</td>
<td>36.5</td>
</tr>
<tr>
<td>Abdomen</td>
<td>2</td>
<td>46.5</td>
<td>4</td>
<td>46.5</td>
</tr>
<tr>
<td>Gonads</td>
<td>2</td>
<td>56.5</td>
<td>2</td>
<td>56.5</td>
</tr>
<tr>
<td>End of phantom (mid upper thigh)</td>
<td>2</td>
<td>61.5</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

The peripheral doses from two different linacs were studied – a Varian 600C and a Varian Trilogy. The results show that doses from a Trilogy are about 40% higher than those from the 600C (at a distance of > 20 cm), and that doses along the x-plane (defined by the direction of jaw motion) are 40% less than doses along the y-plane. This result is consistent with data recently reported elsewhere for stereotactic fields (Taylor et al. 2010c). Aligning the craniocaudal axis of the patient with the x-plane so as to minimise dose effectively requires setting a collimator angle of 90° for a couch rotation of 0°. To illustrate this, Figure 6.15 shows the dose from these two linacs, with collimator rotations of 0° and 90°.
Figure 6.15 The out-of-field dose at various distances for a 5 x 5 cm\(^2\) two-field treatment delivered with two different linacs. (a) and (b) Dose with collimator rotations of 0° and 90° from the 600C and Trilogy respectively. (c) The ratio of the dose with a collimator rotation of 90° to that with 0° for both machines (with a couch rotation of 0°), while (d) shows the ratio of dose from the Trilogy to that from the 600C for both collimator rotations. The uncertainties in each measurement point are better than 4 % at the 95 % confidence limit.

Two field sizes are compared, as shown in Figure 6.16 – a 5 x 5 cm\(^2\) field and a 0.5 x 0.5 cm\(^2\) field. With equivalent deliveries, the large field is shown to result in significantly more peripheral dose in closer proximity to the isocentre, however, with increasing distance there is less disparity. The reason for this is that, for out-of-field regions which are close to the primary field, there is a relatively large amount of patient/collimator scatter from a large field compared to a small field. Patient and collimator scatter are field size dependent; the convergence of dose due to small and large fields with increasing distances indicates that the field size dependent components become less important than leakage. As can be seen in Figure 6.16(c), the contribution to out-of-field dose from leakage is higher for the Trilogy.
The structure of the treatment head differs between the 600C and the Trilogy, the latter having notable differences such as interchangeable electron targets and a flattening filter entirely beneath (rather than extending into) the primary collimator. Another significant difference is the fact that the 600C has a standing vertical waveguide, whilst the Trilogy incorporates a bending magnet to facilitate the longer horizontal waveguide that is necessary for higher operating energies. The significantly different structure and in particular the different head shielding between the two linacs is the most likely source of the considerable disparity in out-of-field dose; the fact that the difference is most pronounced at far distances where head leakage is of greater influence than patient scatter supports this hypothesis.

**Figure 6.16** Illustrates the difference in out-of-field dose for a small field (0.5 x 0.5 cm$^2$) irradiation compared to a relatively larger field (5 x 5 cm$^2$) irradiation. Data from the Trilogy linac is shown in (a) while the 600C doses are plotted in (b). The ratio of the small-field doses to the large-field doses is plotted in (c). A further study was carried out to investigate the influence of the patient orientation relative to the accelerating structure – and so a comparison of the typical supine orientation of the phantom on the couch was made with an upright orientation, shown in (d). The uncertainties in each measurement point are better than 4% at the 95% confidence limit.
An investigation of the distance from the accelerating structure was also investigated by orienting the phantom in an upright position in addition to the typical supine arrangement. Doses in the supine orientation were about 40% lower than those with the phantom sitting upright, as shown in Figure 6.16 (d).

Three delivery methods were compared – a two-field treatment, a three-field treatment involving a vertex field and a twin-arc treatment. Both arcs had an initial angle of $0^\circ$ (vertex field for the phantom placed upright on the couch) and an arc angle of $90^\circ$. With couch positions of $0^\circ$ and $90^\circ$ the resultant stop position was a lateral and posterior field, respectively. Figure 6.17 indicates that the doses away from the target due to the three-field and arc deliveries are an order of magnitude greater than the two-field treatment that avoids the trunk of the body.

**Figure 6.17** The variation of out-of-field dose with the type of the applied field. The examples shown are a comparison of (a) two arcs to two static fields with the Trilogy (measured along y-plane) and (b) a three-field treatment (including a low-weighted vertex field) to a two-field treatment on the 600C (measured along the x-plane). Note the doses presented are mean doses at each particular plane. The uncertainties in each measurement point are better than 4% at the 95% confidence limit.
Figure 6.18 The out-of-field dose for a whole-brain radiotherapy field (WBRT) of 20 x 10 cm$^2$. In (a), this is plotted against a 5 x 5 cm$^2$ field for comparison. Doses measured with a Pb block between the patient and linac (at a distance of 45 cm from the isocentre) indicates the potential for shielding. In (b), the mean doses at each distance with the shielding block placed between the phantom and linac are plotted as a ratio of the WBRT field with no block. This illustrates the shielding possible, with the block placed approximately 45 cm from the isocentre. The uncertainties in each measurement point are better than 4 % at the 95 % confidence limit.

As shown in Figure 6.18, an additional investigation of out-of-field doses from WBRT fields indicated significantly higher (an order of magnitude) out-of-field dose than the small-field treatments. The use of a lead shielding block at 40-45 cm from the isocentre reduced out-of-field dose by around 50 % for those points covered by the lead, indicating the amount of peripheral dose that may be attributed to leakage (rather than patient scatter), and the efficacy of simple shielding techniques for far out-of-field anatomy.

6.6.4 Discussion

The key concern with out-of-field doses in general is that epidemiological evidence indicates that there is an increased probability of contracting cancer as a result of radiation exposure, relative to the normal background rate. The likelihood of radiation-induced cancer is higher for children than for patients exposed as adults. The results presented in this study indicate that for a given treatment, this risk could be halved just by employing the various simple treatment arrangements suggested here.

One such approach would be the preferential use of a vertical straight waveguide linac (such as the 600C). The reason for the notable disparity in out-of-field dose between the two linac
models has been suggested in the Results section. There are significant differences in the construction of a low-energy single-mode linac, such as the 600C, and a high-energy multi-mode linac operated in low-energy mode, such as the Trilogy. While in-field doses should be equivalent (except for small differences in the beam spectra), the difference in head design evidently leads to differences in out-of-field dose. In the case of the Trilogy, the electrons are accelerated in the first third of the accelerating waveguide, which lies in a plane parallel to the patient. A bending magnet directs the beam towards the patient, and contributes additional bremsstrahlung radiation. The 600C has a waveguide that is smaller, directed toward the isocentre and shielded by the linac head. As an interesting side note, one would expect the problem of leakage to be greater (in a relative sense) when operated at 6 MV as opposed to the higher energy modes. From purely theoretical considerations, the expected dose due to leakage photons relative to that at the isocentre would be higher when operating in low energy modes because of the inverse relationship between the energy of the electrons and angle of peak radiation intensity. In other words, as the electron energy increases, the resulting bremsstrahlung photon distribution becomes more forward-peaked. For instance, the angle of deviation from the initial electron trajectory corresponding to the bremsstrahlung peak from a 6 MV beam would be about a factor of three greater than the angle for an 18 MV beam. Thus, the leakage radiation in 6 MV mode would be generated on a path less tangential to the arc of the bending magnet than in the higher energy modes – i.e. more towards the patient plane. Ultimately there will also be differences in the structure of the head shielding which would likely contribute significantly to the disparity in out-of-field dose between the two linacs.

An additional means of risk reduction is alignment of the craniocaudal axis of the patient with the x-plane of the collimator. This may be explained in terms of the geometrical arrangement of the secondary and tertiary collimators in the linac head. The y-jaws in a Varian linac are located above the x-jaws. The upper (y) jaws move in an arc trajectory about a point defined by the linac target such that the angle of the face matches the divergence of the photon beam. The lower (x) jaws slide in a straight line along a direction perpendicular to the beam axis, tilting such that the faces of the jaws match the field divergence. The primary field (defined by the opening of the jaws) is quite flat, but a difference is observed in the out-of-field dose. The lower jaws are shadowed to a degree by the upper jaws, which would result in less transmission in the direction of the lower jaw motion. Furthermore, simple geometrical considerations indicate a greater spread of angles of particles borne of interactions in the upper jaws are able to scatter into regions outside the primary field, compared to those which have interacted in the lower jaws. In addition, beneath the secondary collimators is a mini-multileaf collimator, the leaf bank of which is slightly longer in the direction of leaf travel.
The latter is aligned with the x-axis, thus providing an additional level of attenuation/shielding for radiation scattered in the x-plane.

It must be noted that these explanations are only applicable to Varian linear accelerators of the type studied. Linear accelerators of other manufactures (or other Varian designs) may have different properties which need to be studied. While the aim of the present work is to alert to the potential of dose reduction the methods suggested may not be readily applicable to other equipment.

Further risk reduction is possible by using beam directions that provide equivalent target coverage but avoid the trunk of the patient. This result is no doubt intuitively expected. While out-of-field dose due to leakage and collimator scatter would be equivalent under any such arrangement (assuming the same beam-on time), the dose due to the primary field and patient scatter differ. Calculations (not shown) using a Monte Carlo model of a dosimetrically-matched Varian 600C linac show that at a depth of 0.3 metres in water, doses due to a 6 MV photon field are still > 20 % of the maximum. Furthermore, the mean energy of a 6 MV beam is approximately 2.1 MeV, and the dominant interaction process in this energy regime is inelastic (Compton) scattering. At such energies the Klein Nishina formula (Klein and Nishina 1929) predicts generally forward-directed secondary radiation. These combined effects encourage the use of fields that are not directed along the craniocaudal axis of the patient. summarises the simple considerations that may be made when treating paediatric patients with radiotherapy so as to minimise the dose to untargeted organs. The present data was acquired using only equipment of one manufacturer. It will be necessary to study these effects. Table 6.7 in each centre using the equipment available for other manufacturers or configurations.
Table 6.7 Lists the various considerations that may function as simple means to reduce the out-of-field dose to patients in paediatric radiotherapy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Influence on peripheral dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collimator rotation</td>
<td>Out-of-field doses along the x-plane (defined by direction of jaw-motion) are 40% less than those along the y-plane for both linacs studied.</td>
</tr>
<tr>
<td>Treatment technique</td>
<td>A three-field treatment involving a vertex field or an arc treatment increases the dose beyond the thyroid by an order of magnitude compared to a two-field treatment avoiding the trunk of the body.</td>
</tr>
<tr>
<td>Field size</td>
<td>The study on field size indicates that beyond 40 cm distance from the isocentre, about half of the out-of-field dose is due to leakage (i.e. less dependent on field-size).</td>
</tr>
<tr>
<td>Linac</td>
<td>Using the Trilogy (bending magnet) linac operated at 6 MV results in doses higher 40 % higher than the (straight waveguide) 600C for both collimator rotations.</td>
</tr>
<tr>
<td>Shielding</td>
<td>The use of a shielding block on the couch between the patient and linac may halve the out-of-field dose.</td>
</tr>
</tbody>
</table>

As mentioned, associated with these out-of-field doses is the grave potential clinical consequence of radiation-induced carcinogenesis. Children are at particular risk because of their long potential lifetimes, in which latent secondary cancers have greater time to become manifest, and because there is evidence of increased radiosensitivity in children. In fact, though the data is sparse, it is thought that the greatest risk of cancer induction in children may be as a result of radiotherapy (BEIR 2006). For a five year old patient, which the anthropomorphic phantom employed in this study is intended to represent, the lifetime probability of death attributable to low radiation doses (such as peripheral doses from a radiotherapy treatment) is about 16 % Gy^{-1} for females and 13 % Gy^{-1} for males. This risk is approximately a factor of five greater than that for an adult of age 50 years (ICRP 1991). The risk that a child may contract a second cancer as a result of radiotherapy may be as high as 12 % in 25 years (Tucker et al. 1991) and up to 51 % in 50 years (Wong et al. 1997) after the initial cancer. Also reported, based on a cohort presenting with malignant tumours within 2 years of diagnosis of the first tumour, was an increased risk of bone cancer, demonstrating a relative risk of 2.7 at the 95 % confidence interval (CI)(Tucker et al. 1987). Soft tissue sarcoma has been reported with an odds ratio of 19 at 95 % CI (Menu-Branthomme et al. 1987).
Melanoma (Guerin et al. 2003) and thyroid cancer (De Vathaire et al. 1999) have been reported with odds ratios of 1.4 to 13 at 95% CI and relative risks between 4 and 26 at 90% CI (depending on dose) respectively.

To illustrate the differing risks of radiocarcinogenesis for various techniques, an example is given (based on the results presented in this work) for dose to the thyroid from the 5 x 5 cm\(^2\) fields delivering 3 Gy to isocentre in different arrangements. For a 5 year old patient aligned with the x-plane and exposed to a 2 field treatment with the Trilogy, the lifetime attributable risk of cancer incidence (per 100,000 people) is approximately 4.3 for males and 23.5 for females. When aligned with the y-plane, the lifetime attributable risk of cancer incidence (per 100,000 people) is reduced to approximately 2.5 for males and 13.8 for females. For a patient treated using 2 fields on the 600C, the lifetime attributable risk of cancer incidence (per 100,000 people) is approximately 4 and for males and 22 for females. When a 3 field treatment is used, these risks increase to approximately 8.5 and for males and 47 for females. These estimates are combined estimates based on relative and absolute risk transport, adjusted by a DDREF of 1.5 (BEIR 2006). These examples indicate the potential for detriment arising from out-of-field doses and the reduction in risk that is achievable by implementation of some of the simple recommendations suggested in this paper.

6.6.5 Conclusion
This work has characterised out-of-field doses in paediatric radiotherapy of brain lesions under various treatment conditions, and has identified several straightforward means of reducing dose to untargeted organs. For typical treatment fields used in paediatric radiotherapy, the disparity in out-of-field dose between small fields and large fields decreases with increasing distance from the primary field. This could be attributed to the fact that, at larger distances, the dominance of leakage and collimator scatter increases relative to patient scatter. Simple methods such as choice of linac, collimator angle and external shielding can help to reduce these out-of-field doses, and therefore reduce the associated risks of radiation-induced health complications (including radiocarcinogenesis), which are known to be of particular importance in the context of paediatric radiotherapy. These methods are also of great utility in the context of adult radiotherapy – especially for treatments for non-malignant disease which typically have long survival times and hence radiation protection must be taken very seriously.
6.7 Summary and clinical recommendations

There is a demonstrated interest in out-of-field doses from radiotherapy procedures. However, thus far the consideration of out-of-field dose from (in particular, linac-based) stereotactic radiotherapy has been limited, perhaps because of the assumption that such doses will be significantly lower than other techniques. While it is certain that at near- and mid-field distances this may indeed be the case, it has been demonstrated that doses far from the primary field are comparable because of a reduced field size dependence. In this chapter, the current literature pertaining to out-of-field doses from radiotherapy and theory of radiocarcinogenesis has been reviewed. Out-of-field doses have been characterised in a systematic fashion for linac-based stereotactic radiotherapy. These results show:

- The systematic variation of out-of-field dose with field size, source-surface distance, depth in phantom and collimator orientation.
- Higher doses are associated with increasing field sizes and shallow phantom depths.
- Variation with source-surface distance is not significant.
- If the patient lies along the x-plane then out-of-field doses may be reduced by up to an order of magnitude.
- For a stereotactic treatment of tens of Gy, the out-of-field dose is of the order of cGy (a significant dose in radiation protection terms).

In addition to this, out-of-field doses in the context of small-field radiotherapy of paediatric patients has also been investigated, since children are more susceptible to and have greater lifetimes in which radiation-induced cancer may become manifest. Key clinical recommendations that may be made based on the results presented here include:

- Out-of-field dose reduction of approximately 40 % may be achieved by using a single-mode (vertical waveguide) linac as opposed to a multi-mode.
- Appropriate choice of collimator rotation can reduce out-of-field dose by 40 %.
- Appropriate choice of treatment technique can reduce out-of-field dose by an order of magnitude (step-and-shoot, without field along craniocaudal axis, results in less out-of-field dose than arc delivery).
- Simple shielding can reduce out-of-field dose by 50 %.
- Field size has a reduced influence far from the primary field (i.e. out-of-field doses from stereotactic fields deliver similar doses to larger-field treatments at large distances from isocentre).
- Examples have been given illustrating that implementing these approaches can reduce relative risks of cancer induction by over 50 %.
- The Paediatric Unit of Peter MacCallum Cancer Centre (Aust.) is planning changes to treatment protocols based on these results.
CHAPTER SEVEN

Let us not conjecture at random about the most important things. †

Ἡράκλειτος ὁ Ἐφέσιος

† Pragmatic advice from Heraclitus of Ephesus, if indeed we can trust the account of Heraclitus’ thoughts provided by Diogenes Laërtius.
CHAPTER 7

Conclusions and recommendations

Final comments on the significance of the work and recommendations regarding the characterisation of stereotactic radiotherapy fields
7.1 Stereotactic radiotherapy

The objective of this thesis has been to characterise the small radiation fields employed in stereotactic radiotherapy. Specifically, this refers to spectral, fluence and dosimetric properties in the primary beam and its immediate periphery (in-field) as well as far from the primary field (out-of-field).

Stereotactic radiotherapy (SRT) is an increasingly popular treatment modality for tumours both intracranial and, more recently, of extracranial anatomic locations. Stereotactic radiotherapy procedures are also often used for benign intracranial lesions. In this thesis and an associated review paper submitted to *Acta Oncologica*, the following definition of stereotactic radiotherapy has been proposed:

*Stereotactic radiotherapy may be defined as the use of beams of ionising radiation from multiple directions intersecting at a target (usually intracranial), spatially defined using a three-dimensional coordinate system.*

Comparing, for instance, to an alternative advanced mode of radiotherapy such as intensity modulated radiotherapy (IMRT), stereotactic radiotherapy has several notable differences. The doses delivered per fraction in SRT (and stereotactic body radiotherapy, SBRT) are typically much higher, ranging from approximately 5 – 25 Gy, compared to 1.8 – 3 Gy for IMRT. The number of fractions is fewer, typically 1 – 5 fractions as opposed to 10 – 30. Furthermore, the margins in conventional radiotherapy may be of the order of centimetres, whilst in SRT the margins are of the order of millimetres.

The point of mentioning this is to emphasise that we are concerned with large doses which must necessarily be delivered with high spatial accuracy. As such, the issues of dosimetry (whether pertaining to measurement or calculation) are of critical importance for efficacious treatments, and thus improved patient outcomes.

There are a number of complexities associated with dosimetry for the small fields employed in stereotactic radiotherapy. Considering first conventional dose calculation with a treatment planning system (TPS), the accuracy of dose distributions calculated for stereotactic fields may be questionable because of issues of charged particle equilibrium in particular (especially where the field size employed approaches the range of secondary electrons). Furthermore, calculations performed by the TPS are ‘informed’ by linac-specific parameters that have been experimentally measured under broad-beam reference conditions. The extrapolation to small-
fields may not always be accurate/appropriate. Additionally, the direct measurement of dosimetric characteristics of small fields is often difficult, and a common clinical approach might be to undertake multiple measurements of the same arrangement with different detector types and average the results. A further issue is that the treatment planning system is not designed to accurately determine dose to the patient far from the primary field, and such out-of-field doses are not incorporated into routine treatment optimisation. Associated with these doses is an increased risk of health complications, including radiocarcinogenesis.

Thus it is evident that to facilitate the thorough characterisation of stereotactic fields both in-field and out-of-field, which is the ultimate aim of the present work, it is necessary to adopt more specialised methodologies for measurement and calculation, which may be less common clinically.

7.2 The measurement and calculation of dose and other quantities

The objective of this thesis is to characterise stereotactic radiotherapy fields and has focused on two approaches in particular:

- Three-dimensional gel dosimetry for measurement, and
- Monte Carlo radiation transport methods for calculations.

Gel dosimetry is a promising dosimeter for small-field dosimetry as relevant to the characterisation of stereotactic radiotherapy fields. Ideally, gel dosimeters yield three-dimensional dose information, are not subject to issues of detector volume averaging, and function as both the phantom and dosimeter material and thus do not perturb the radiation field. However, there are a number of complexities associated with gel dosimetry that currently limit routine clinical implementation. In this thesis, two key issues were identified: (i) The extent to which the radiological properties of gels matched water or soft tissue (i.e. water equivalence), and (ii) The absence of a standard for gel dosimeter calibration in the published literature.

With respect to the former, the effective atomic number ($Z_{\text{eff}}$) was investigated in its oft-employed capacity as an indicator of the radiological properties of gel dosimeters. Inspection of the literature indicated inconsistent and dubious methods for the calculation of $Z_{\text{eff}}$. A novel methodology for calculating the $Z_{\text{eff}}$ of gel dosimeters was described in this thesis, and energy-dependent values were determined for total and partial photon and electron
interactions in a range of biological media, water and fourteen Fricke and polymer gel dosimeter types. The key findings were:

- The typical power-law method by which one generates a single-valued $Z_{\text{eff}}$ is of limited usefulness for the broad spectrum of energies involved in radiotherapy.
- Conclusions drawn by comparison of $Z_{\text{eff}}$ values in this way are of questionable validity, even in the intended regime (low-energy) of applicability.
- The smooth correlation between interaction cross section and atomic number may be exploited to yield an effective atomic number for a given composite medium.
- When required, a single-valued $Z_{\text{eff}}$ may be obtained by weighting against the radiation spectrum of interest.
- Broadly, gel dosimeters may be considered to be water-equivalent over a broad energy range, for both photon and electron interaction processes.
- The BANG-1 gel is found to be most water-equivalent.

Having thus established gel dosimeters as being appropriate from a radiological perspective, the next key issue requiring resolution prior to implementation was that of gel calibration. Inspection of the literature revealed a number of published techniques, none of which were considered a ‘standard’. Furthermore, there was little justification for the common assumption that the gel composition and containment vessel would not result in deviations from water equivalence. High resolution Monte Carlo radiation transport methods were employed to investigate the influence of containers and different gel compositions on the level of water equivalence. This yielded several key findings:

- Under strict conditions specified in this thesis, the majority of published methods may be employed to calibrate gels with a tolerance of [-1%, 1%] at the 95% confidence interval.
- The most appropriate method is that of a ‘large tub’ of gel, with dose read out at $D_{\text{max}}$ (though away from $D_{\text{max}}$, the error increases significantly).
- The least suitable method is the approach employing a long test tube in water to yield a depth-dose curve within the gel (exhibiting errors > 2%).
- The most appropriate gel formulations are BANG-1 and Fricke.

Resolution of these two issues (described in Chapter 3), radiological properties and calibration, provided the confidence to employ gel dosimetry for stereotactic field measurements, as described later.
The limited accuracy of treatment planning systems for the calculation of small-field doses, doses in the vicinity of interfaces, and the infeasibility of calculating or measuring spectral qualities, prompted the development of a Monte Carlo model (described in Chapter 4). A model of a Varian 600C linear accelerator with mounted BrainLAB mini-multileaf collimator was constructed using EGSnrc. This was commissioned using experimental data measured at the Alfred Hospital (Melbourne, Australia). The advantage of the Monte Carlo model is that it facilitates:

- Confident calculation of dose distributions for small fields as relevant to stereotactic radiotherapy.
- More accurate determination of doses at interfaces of heterogeneous media.
- Determination of photon spectra, mean energy and angular distributions.
- Determination of contaminant and secondary electron spectra, mean energy and angular distributions.

The Monte Carlo model is thus critical for the thorough characterisation of stereotactic fields. In short, it facilitates: (i) Accurate determination of dose distributions resulting from stereotactic fields (where the treatment planning system may be of limited accuracy), and (ii) Determination of beam spectra both in air and in water (which is not measurable due to high beam fluxes).

7.3 Characterisation: In-field
Characterisation of stereotactic radiation fields is the primary objective of this thesis. The difficulties of measuring spectral characteristics in megavoltage photon beams are circumvented with use of a dosimetrically-matched Monte Carlo model. Highly systematic characterisation (described in Chapter 5) has been undertaken.

Data have been generated for a large number of fields shaped with the mini-multileaf collimator.

Beam characteristics in air, both in and beyond the primary field were investigated, including:

- Photon spectra,
- Contaminant electron spectra,
- Spatial variation of mean photon energy,
- Spatial variation of mean electron energy, and
- Angular distribution of photons.
Spectral data in water at several depths (5, 10 and 15 cm) has also been calculated, including:

- Photon energy fluences,
- Electron energy fluences, and
- Mean energy distributions.

Further data has been compiled for comparison using ‘backed-up’ field, i.e. jaws set at the same field opening as the MMLC. Mean energy, spectral and angular distributions were calculated for several representative cases.

Summarised here are the key findings for the in-air study:

- Out-of-field photon fluence ~1 % of primary beam fluence.
- Out-of-field electron fluence ~30 % of primary beam fluence.
- Photon fluence has sharp gradient at field edge.
- Electron (contaminant) fluence does not have a sharp gradient at field edge.
- ‘Structure’ evident in fluence profiles just beyond the primary beam (due to interleaf leakage through collimator).
- Mean energy of primary photon field lower than surrounding peripheral regions (due to beam hardening by collimators) for small fields; mean energy drops again in far out-of-field regions.
- Photon energy fluence varies with field size, most notably at low energies (below ~1 MeV).
- The photon beam is more forward directed for smaller fields, as evidenced by the primary field angular photon distributions (in fact, for the 9.8 x 9.8 cm² field the distribution peaks at approx. 3º rather than 0 º).
- The photons outside the primary field are much less forward-directed.

With regards to backed-up fields:

- Spectral distributions of photons and electrons for backed-up field show strong similarity in-field.
- For smaller fields, the mean energy distributions beyond the primary field differ noticeably.
- Mean energies typically increase closer to the field edge than the non backed-up case.
- For the backed-up case, mean energies are low in the shadow of the MMLC then remain higher far from the primary field.
- Notable difference in angular distributions of photons at the patient plane, being more forward-directed for smaller fields but less so for larger fields, relative to the non backed-up case.
A number of observations were made regarding the spectra in water:

- Photon spectra harden with depth in water.
- Electron spectra soften with depth in water.
- Mean energy of primary photon beam decreases with increasing field size (6 x 6 mm$^2$ beam is 30% harder than 98 x 98 mm$^2$ beam).
- Out-of-field mean photon energies (at 12 cm off-axis distance) decrease with increasing field size (6 x 6 mm$^2$ beam is 250% harder than 98 x 98 mm$^2$ beam).
- The fraction of total photons in the low energy regime increases with field size (98 x 98 mm$^2$ beam has ~1000% more photons with energies < 250 keV than 6 x 6 mm$^2$ beam).
- Electron spectrum varies with field size, most notably in the low-energy regime (< 1 MeV), such that larger fields have a larger fluence of low-energy electrons.

To illustrate the relevance of varying spectra, several illustrative studies were carried out. These included:

- An investigation of the effect of changing secondary electron spectra on the mean restricted stopping power ratios relevant to ionisation chamber measurements,
- The energy dependence of measurements taken using radiographic film, and
- The energy-dependent effective atomic numbers of TLD-100 thermoluminescent dosimeters.

The effect of the investigation into spectral effects as relevant to ionisation chamber measurements showed that the typical assumption of unchanging spectra (field size independence) was typically acceptable, with deviation from the reference field case all sub-percent. The discrepancy worsens with decreasing field size but is nonetheless acceptable. However, this only applies to in-field measurements. Out-of-field, spectral variations result in discrepancies > 1%, being worst for larger field sizes. In the case of the response of radiographic film, the degree of over-response of film (relative to water) is of the order of ~1%. The difference between the radiological properties of TLD-100 and water are highlighted using the energy-dependent effective atomic number ($Z_{eff}$, see Chapter 3). Of particular note is the fact that the peak photon fluence coincides with the maximum discrepancy in $Z_{eff}$.

As described in the previous section, gel dosimeters were hypothesised as being suited to the measurement of small-field dose distributions. This was demonstrated in a study (described in Chapter 5), investigating stereotactic radiotherapy for treatment of small, intracranial lesions. The potential for stereotactic treatment validation using normoxic polymer gel dosimetry (with optical-CT readout) in an anthropomorphic head phantom was assessed. A 12-field
stereotactic treatment plan for meningioma was recalculated onto a computed tomography scan of the head phantom with gel insert and was delivered using a Varian 2100 linear accelerator with mounted BrainLAB mini-multileaf collimator:

- Using quantitative comparison using indices such as percentage pixel agreement and gamma analysis, it is demonstrated that 3D gel dosimetry may be readily employed for assessment of PTV coverage.
- Agreement with treatment planning system (pencil beam algorithm) calculations was demonstrated for high dose regions (above the 90% isodose, $\gamma$ evaluation indicated 96% agreement for criteria of 2%/2mm).
- Gamma analysis showed that above the 80% isodose line, 94% of the gamma values were less than unity (for criteria of 5%/5mm).
- Poorer agreement was observed at low isodoses, most likely because in these regions: (i) the gel is receives only low doses and may exhibit nonlinearity, (ii) the effects of slight misregistration of the plan and gel dose distributions may be more pronounced, (iii) optical scatter and (iv) the treatment planning system may not accurately calculate dose adjacent to the container.

An additional study was undertaken in the context of stereotactic body radiotherapy. Lung tumours present challenges in terms of treatment planning dose calculations, because of the juxtaposition of high and low density media. This may affect the minimum dose received by lesions and is particularly important when prescribing dose to covering isodoses. This work (see Chapter 5) quantified under-dosage in key regions around a hypothetical target using Monte Carlo dose calculation methods, and developed a factor for clinical estimation of such under-dosage. A systematic set of calculations were undertaken using two Monte Carlo radiation transport codes (EGSnrc and GEANT4):

- Discrepancies in dose were determined for a number of parameters, including beam energy, tumour size, field size and distance from chest wall.
- Calculations were performed for 1 mm$^3$ regions at proximal, distal and lateral aspects of a spherical tumour, determined for a 6 MV and a 15 MV photon beam.
- The simulations indicate regions of tumour under-dose at the tumour-lung interface.
- Comparison with TPS data (pencil beam convolution) indicates such under-dosage would not have been predicted accurately in the clinic.
- A Dose Reduction Factor (DRF) as the average of the dose in the periphery in the six cardinal directions divided by the central dose in the target, the mean of which is 0.97 and 0.95 for a 6 MV and 15 MV beam respectively.
– The *DRF* can assist clinicians in the estimation of the magnitude of potential discrepancies between prescribed and delivered dose distributions as a function of tumour size and location.

– Calculation for a systematic set of ‘generic’ tumours allows application to many classes of patient case, and is particularly useful for interpreting clinical trial data.

7.4 Characterisation: Out-of-field

As shown by the detailed literature review provided in Chapter 6, there is an increasing interest in out-of-field doses from radiotherapy procedures. This is because the higher cure rates, longer patient survival and better follow-up raise the awareness of associated latent risks such as cardiac or respiratory complications, or radiation-induced cancer.

However, thus far the consideration of out-of-field dose from (in particular, linac-based) stereotactic radiotherapy has been limited. In this thesis, the current literature pertaining to out-of-field doses from radiotherapy and theory of radiocarcinogenesis has been reviewed. Out-of-field doses have been characterised in a highly systematic fashion for linac-based stereotactic radiotherapy. These results show:

– The systematic variation of out-of-field dose with field size, source-surface distance, depth in phantom and collimator orientation.

– Higher doses are associated with increasing field sizes and shallow phantom depths.

– Variation with source-surface distance is not considerable.

– If the patient lies along the x-plane then out-of-field doses may be reduced by up to an order of magnitude.

– For a stereotactic treatment of tens of Gy, the out-of-field dose is of the order of cGy.

In addition to this, out-of-field doses in the context of small-field radiotherapy of paediatric patients has also been investigated, since children are more susceptible to and have greater lifetimes in which radiation-induced cancer may become manifest. Key clinical recommendations that may be made based on the results presented here include:

– Out-of-field dose reduction of approximately 40% may be achieved by using a single-mode (vertical waveguide) linac as opposed to a multi-mode.

– Appropriate choice of collimator rotation can reduce out-of-field dose by 40%.
– Appropriate choice of treatment technique can reduce out-of-field dose by an order of magnitude (step-and-shoot, without field along craniocaudal axis, results in less out-of-field dose than arc delivery).
– Simple shielding can reduce out-of-field dose by 50%.
– Field size has a reduced influence far from the primary field (i.e. out-of-field doses from stereotactic fields deliver similar doses to larger-field treatments at large distances from isocentre).

The results provided in this thesis show uncomplicated means of reducing out-of-field doses and corresponding risks to both adult and, or particular importance, paediatric patients. This outcome is one of the results with direct clinical utility, as described in the following section on Impact.

### 7.5 Clinical significance

There are a number of results presented in this thesis that extend beyond issues of purely academic interest, and have direct clinical impact.

These are summarised here:

(i) **Effective atomic number of gels.** Although it was initially not anticipated to be a groundbreaking study, the investigation of the effective atomic number of gel dosimeters has stirred significant interest in the scientific community. This is evidenced not solely by citations, but by the large number of personal communications from researchers internationally inquiring about the work.

(ii) **Calibration of gel dosimeters.** Until this publication, there has been no strong justification for one calibration method over another beyond issues of convenience. This thesis describes the most appropriate and accurate means of calibration, facilitating improved absolute dosimetry.

(iii) **Spectral qualities of stereotactic fields and clinical consequences.** Until now, there has been no systematic investigation of stereotactic field spectra from the BrainLAB mini-multileaf collimator. Such spectral information has clinical consequences, most notably in the use of dosimeters which exhibit energy dependence. In particular, the investigation of systematic errors in ionisation chamber calibration resulting from the assumption of unchanging secondary electron spectra described in this thesis has – to the best of the author’s knowledge – not been published elsewhere.
(iv) *Lung tumour under-dosage lookup table.* Clinicians have already shown interest in obtaining the tabulated estimates of lung tumour under-dosage presented in this thesis, to inform judgements regarding prescribed doses and retrospective analysis.

(v) *Methodologies for reducing the risk of radiation-induced cancer.* The straightforward approaches detailed in this thesis allow significant reduction of out-of-field doses and corresponding risks of radiocarcinogenesis (and other complications). Based on the results in this thesis, the Paediatric Unit of the Peter MacCallum Cancer Centre (Melbourne, Australia) is planning changes to treatment protocols. The impact of this study is also reflected by recent media interest.

7.6 Outlook

This thesis has been successful in characterising the radiation fields used in stereotactic radiotherapy, both in- and out-of-field. Spectral characteristics for small fields may be used to inform interpretation of measured data, the potential of radiosensitive gels for stereotactic dosimetry of small and complex dose distributions has been demonstrated, and clinical recommendations have been made to exploit the spatial anisotropy of out-of-field doses and minimise risks of cancer induction.

In this thesis, the focus has related to spectral and dosimetric characterisation. However, stereotactic radiotherapy is a field that has grown dramatically over the last couple of years and many different radiation tools are available. In such a multifaceted field, there are many challenges that may be addressed in order to generate an improved treatment and the present thesis must therefore have limitations that should be noted.

For instance, there remain a number of challenges associated with gel dosimetry that restrict routine clinical implementation. This includes the requirement for a chemical handling and gel preparation laboratory, equipped with acid safe, chemical disposal facilities, fume cupboard, and so on. It may be difficult for some centres to maintain such a facility. Other issues include the fact that each batch requires individual calibration, the dosimeters are single-use and MRI readout may not always be readily available, necessitating optical readout (which for polymer gels may be nontrivial depending on the scanner and scatter corrections employed). The recommended method for dose calculation is Monte Carlo radiation transport. The only real limitation is that the computationally-demanding nature of the Monte Carlo approach requires supercomputer access for efficient calculations. Although, as has
been reviewed in this thesis, there are several commercially available treatment planning system implementations of Monte Carlo codes – these are yet to undergo rigorous comparison with full Monte Carlo codes. As a further note, anecdotal evidence from using, for example, the iPlan Monte Carlo algorithm on a standard desktop computer (as used in the clinic) suggests that to achieve the recommended accuracy of 1%, a given patient plan requires days to finish computation.

More than this, there are various difficulties associated with stereotactic radiotherapy that are beyond the scope of this thesis; in particular, the handling of tumour motion. All tumours move to some extent, but tumours in the thoracic cavity, for instance, may undergo significant intrafraction motion. If not accounted for, this would have serious consequences for tumour coverage and normal tissue complications. A cursory inspection of recent issues of medical physics journals indicates that this is a dominant challenge facing physicists and clinicians in contemporary stereotactic body radiotherapy. There are a number of studies investigating the efficacy of real-time image guidance, respiratory gating and so on, being undertaken both internationally and locally at RMIT University by the Medical Physics Research Group.

However, it is hoped that the work presented in this thesis and the associated publications will contribute to more accurate dosimetry in small radiation fields. While primarily concerned with stereotactic radiotherapy fields, the findings of this thesis are also applicable to other areas in radiotherapy where small fields and field segments are used. Intensity modulated radiotherapy is such an example. Most importantly, however, it is hoped that the outcomes of this thesis will help to make the treatment of patients more accurate and reproducible. By considering both theory and measurement, it is also hoped that building blocks for future work that further enhances treatment approaches have been created.
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