Pencil beam scanning proton therapy: the significance of secondary particles

Stephen J. Dowdell

University of Wollongong

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PENCIL BEAM SCANNING PROTON THERAPY: THE SIGNIFICANCE OF SECONDARY PARTICLES

A Dissertation Submitted in Fulfillment of the Requirements for the Award of the Degree of

Doctor of Philosophy

from

UNIVERSITY OF WOLLONGONG

by

Stephen J. Dowdell

B.Sc. Adv (Hons)

Centre for Medical Radiation Physics
Faculty of Engineering
2011
CERTIFICATION

I, Stephen J. Dowdell, declare that this thesis, submitted in fulfillment of the requirements for the award of Doctor of Philosophy, in the Centre for Medical Radiation Physics, Faculty of Engineering, University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. The document has not been submitted for qualifications at any other academic institution.

(Signature Required)

Stephen J. Dowdell
January 2011
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Pencil Beam Scanning Proton Therapy: The Significance Of Secondary Particles

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A Thesis for Doctor of Philosophy
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ABSTRACT

The bulk of the energy deposition from a proton beam occurs at depth in the Bragg peak. The finite range of protons in tissue makes them an ideal candidate for the treatment of deep seated tumours and gives improved tissue sparing distal to the target volume compared to photons. However, the production of secondary neutrons and photons has the potential to deliver unwanted dose far outside the intended treatment volume. The findings of this thesis show that the magnitude of the doses from secondary neutrons and photons are small. The risk of second cancer from proton therapy treatments has been shown to be lower compared to photon techniques despite the presence of secondary neutrons. This thesis also demonstrates the potential advantages of using pencil beam scanning (PBS) compared to double scattering proton therapy. The neutron doses from PBS is significantly lower than double scattering even far from the primary field.

The rationale for using protons to treat cancer was examined. Treatment planning comparisons at a number of different clinical sites have shown the potential usefulness of proton therapy. A treatment planning comparison has demonstrated the potential use of protons for the treatment of prostate cancer. Through comparison of proton treatment plans with the best achievable photon plans, it was observed that protons can potentially deliver the same dose to the prostate target volume whilst reducing the dose in normal tissue.

Secondary neutrons deposit dose via charged secondary particles which often have high linear energy transfer (LET). The high range of neutrons in tissue combined
with the production of high-LET secondaries gives the potential of second malignancy induction external to the primary target volume. Secondary neutrons are produced in proton therapy through nuclear interactions in the treatment nozzle and or in the patient directly. The amount of neutron production in the patient is governed by the interaction cross-section. Phantoms which are used to represent human tissue in experimental studies need to be characterised as they have different chemical compositions which alters the amount of neutron production and the neutron energy spectrum. Monte Carlo simulations were used to determine the variation in neutron absorbed dose and dose equivalent from internally produced secondary neutrons in a series of different tissues and phantom materials. Large variations were observed in the neutron doses in the different materials suggesting the choice of phantom material for neutron dosimetry studies is significant for experimental studies, particularly in regions where the total dose is dominated by secondary neutrons generated internally.

A dedicated Monte Carlo code was developed for simulation of PBS treatments using the Geant4 Monte Carlo toolkit. The scanning treatment nozzle at Massachusetts General Hospital was included in the simulation code. Out-of-field doses in scanning treatments were previously approximated in Monte Carlo simulations by simulating a double scattering beamline and ignoring the contribution of secondary particles generated in the treatment nozzle. The dose deposition from protons, neutrons and photons was simulated for a field designed for the treatment of a deep seated tumour incident upon a Lucite phantom. The results of the simulations showed that the approximation used in previous studies is not valid close to the field edge where the wider penumbra from scanning plays a significant role. Further out-of-field, the approximation is more acceptable, as the total dose is dominated by internally produced secondary particles. The absorbed dose and dose equivalent out-of-field in scanning is approximately an order of magnitude lower than that delivered in double scattering. Employing a
patient-specific aperture in scanning reduces the penumbral width and the dose close to the field edge compared to scanning without an aperture by an order of magnitude.

The radiation field external to the target volume for a clinical pancreatic field was characterised using a ΔE-E detector. Comparisons were made between double scattering and PBS. Distal to the spread out Bragg peak (SOBP), the neutron fluence is higher in double scattering, primarily due to the high amount of neutron production in the treatment nozzle for this modality. The wide penumbra in PBS leads to a higher particle fluence upon the detector close to the field edge. Further from the field edge, the neutron fluence is significantly higher from double scattering compared to scanning. Close to the primary field, the orientation of the detector was determined to be significant for double scattering. Depending on the chosen orientation, when operated in coincidence mode, the results are biased towards either detection of scattered protons from the primary field or neutrons generated in the treatment nozzle.

The time to undertake any treatment is important for radiotherapy and the efficiency of patient throughput. The time required for a PBS treatment has not been investigated previously. A series of equations are presented which allow calculation of the time required to deliver a pencil beam scanning treatment based on the system hardware. An SOBP is produced from a database of individual Bragg peaks generated from Monte Carlo simulations. Using a constant distance spacing between individual Bragg peaks in the SOBP allows the required dose conformality to be achieved with the fewest number of layers. The effect of each of the parameters in a clinical pencil beam scanning system on the total irradiation time was ascertained. Both a cyclotron and synchrotron were considered as possible beam sources. The equations allow optimisation of the irradiation time by observing the effect of altering the system hardware. The equations presented are facility independent and can be applied to any scanning system which uses two perpendicular scanning magnets to scan the beam laterally.
KEYWORDS: proton therapy, Monte Carlo, pencil beam scanning, secondary neutrons
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S. Dowdell, *Hardware Parameter Optimisation and Dedicated Monte Carlo Simulations for Proton Beam Scanning*, Presented at Physics Seminar, Massachusetts General Hospital, November 2010
List of Abbreviations

3D-CPT - Three dimensional conformal proton radiotherapy
BIS - Beam imaging system
BP - Bragg peak
CCD - Charge-coupled device
CGE - Cobalt Gray equivalent
CT - Computed tomography
CTV - Clinical target volume
CMRP - Centre for Medical Radiation Physics
DET - Distal edge tracking
DVH - Dose-volume histogram
DWA - Dielectric wall accelerator
FWHM - Full width at half maximum
GTV - Gross tumour volume
IC - Ionisation chamber
ICRP - International Commission on Radiation Protection
ICRU - International Commission on Radiation Units and Measurements
IMPT - Intensity modulated proton therapy
IMRT - Intensity modulated radiotherapy
LET - Linear energy transfer
MCA - Multichannel analyser
MGH - Massachusetts General Hospital
MLC - Multi-leaf collimator
MU - Monitor unit
NIST - National Institute of Standards and Technology
NPTC - Northeast Proton Therapy Center
OAR - Organ at risk
OED - Organ equivalent dose
PBS - Pencil beam scanning
pCT - Proton computed tomography
PET - Positron emission tomography
PLD - PBS layer definition
PSI - Paul Scherrer Institut
PT - Proton therapy
PTV - Planning target volume
Q - Quality factor
RBE - Radiobiological effectiveness
SAD - Source to axis distance
SOBP - Spread out Bragg peak
SSIMRT - Step-and-shoot IMRT
SVD - Single value decomposition
SWIMRT - Sliding window IMRT
TCP - Tumour control probability
TPS - Treatment planning system
TRAMP - Trajectory manipulation program
\(w_R\) - Radiation weighting factor
Chapter 1

Introduction

There is a consistent push in the radiotherapy community to improve the quality of treatments and investigate new technologies. These new technologies need to be compared to the current best available technology to ascertain the merit and benefit of adopting new technologies.

One such example is the use of proton therapy. Proton therapy is currently not available in Australia, however it is being more widely adopted internationally. There is optimism that using proton therapy may improve the quality of treatment for some clinical cancer sites and even potentially allow treatment of a number of clinical sites which cannot currently be successfully treated using photons. Chapter 2 presents the rationale for using proton therapy for cancer treatment of different clinical sites. One of the major concerns raised against the use of protons has been the background of secondary neutrons produced in the treatment head and in the patient (Hall 2006). Secondary neutrons are the focus of the work presented in Chapters 3-6. There is also interest in moving to active methods of beam delivery, which will reduce the neutron dose delivered to the patient (Schneider et al. 2002). The use of active delivery methods are also investigated in Chapters 4-7.
1.1 Aims and objectives

1.1.1 Using protons to treat cancer

Intensity modulated radiotherapy (IMRT) represents the current state-of-the-art therapy available to Australian patients.

The use of proton therapy has been hypothesised to give improved treatments compared to IMRT and other photon techniques for a number of different clinical sites. The use of protons has been shown to be beneficial for head and neck tumours (Steneker et al., 2006; Lomax et al., 2003a), ocular tumours (Dendale et al., 2006), breast tumours (Lomax et al., 2003b) and in paediatrics (MacDonald et al., 2008; St Clair et al., 2004).

There is discussion in the proton therapy community as to any potential benefit of using protons to treat prostate cancer. A proposed advantage of proton therapy over IMRT for prostate cancer is the reduced integral dose (Trofimov et al., 2007; Fontenot et al., 2008). Due to the physical characteristics of protons, proton therapy can achieve the same or improved conformality compared to IMRT using fewer beam angles (Cella et al., 2001).

Research Question:

What is the rationale for using proton therapy for the treatment of cancer?

Chapter 2 presents comparisons of radiotherapy treatments using proton therapy and IMRT for different treatment sites.

1.1.2 Phantom materials for secondary neutron dosimetry

The dose resulting from secondary neutrons in proton therapy has been measured using a number of various techniques for both passive and active delivery methods. (Schneider et al., 2002; Trompier et al., 2007; Wroe et al., 2007, 2009). These experimental
studies all employ tissue substitutes to represent human tissue. The production of neutrons is directly related to the nuclear reaction cross sections, which are defined by the composition of the material. Once the neutron doses have been measured in the tissue substitute, approximations of the dose to human tissue are then made based on the values measured or simulated in these materials.

**Research Question:**

> How suitable are the tissue substitutes commonly available in radiotherapy departments as analogs for human tissue in terms of secondary neutron generation and dosimetry?

Chapter 3 presents a series of Monte Carlo simulations which compare the absorbed dose and dose equivalent in a variety of tissue substitutes and tissues defined by the International Commission on Radiation Protection (ICRP) to determine the suitability of each of the considered phantom materials.

### 1.1.3 Monte Carlo simulations of pencil beam scanning proton therapy

As they are charged particles, magnetic fields can be used to control the trajectory of protons. This is the basis for pencil beam scanning (PBS) \cite{Kooy2010}. Combining the ability to scan the beam laterally using magnetic fields with the ability to change the beam energy, there is theoretically no need for the use of patient specific hardware to conform the beam to the target volume. This is in contrast to double scattering proton therapy which relies on the use of patient specific apertures and compensators to conform the dose to the target \cite{Koehler1975, Koehler1977}.

Previous Monte Carlo studies typically simulate PBS by ignoring the secondary particles produced in the nozzle of a double scattering simulation \cite{Clasie2009}.
This methodology has been denoted as the “passive-internal” approximation.

**Research Question:**

*What are the differences in neutron dose when using a full pencil beam scanning simulation compared to the “passive-internal” approximation?*

Chapter 4 outlines the implementation of a dedicated simulation code for PBS proton therapy treatments. The geometry of the PBS beamline at the Francis H. Burr Proton Therapy Center at Massachusetts General Hospital was incorporated into the simulation code.

This dedicated PBS simulation code was then used in combination with the previously published double scattering code of Paganetti *et al.* (2004) to ascertain the differences in neutron dose between double scattering proton therapy, PBS and the “passive-internal” approximation. The results of these simulations are presented in Chapter 5.

### 1.1.4 Characterisation of the radiation field external to the target volume in proton therapy

The main contributions to the dose external to the primary field in proton therapy are primary protons which have undergone scattering through wide angles and neutrons produced in the nozzle and in the patient (Clasie *et al.* 2009). The contribution of photons can also be significant and needs to be accounted for, especially in PBS. Any additional dose deposited outside the intended treatment volume may increase the risk of second cancer induction (Hall 2006; Zacharatou Jarlskog *et al.* 2008). It is of interest to determine the particle types present out of field as different particles are known to have different radiobiological effectiveness (RBE), which can have large implications on the risk of second cancer induction. It is also of interest to quantify the differences in the external radiation field in double scattering and PBS treatments.
to determine if there is any advantage in using a particular modality.

**Research Question:**

*How does the radiation field external to the target volume differ in double scattering and PBS treatments?*

Chapter 6 presents measurements performed at the Francis H. Burr Proton Therapy Center at Massachusetts General Hospital. These measurements used $\Delta E-E$ detectors (Cornelius *et al.* 2006) to characterise the mixed radiation field at various positions out of field for a clinical double scattering and PBS treatment. Measurements were made both distal and lateral to the spread out Bragg peak.

### 1.1.5 Calculation of pencil beam scanning proton therapy treatment times

The time required to deliver of a PBS field in proton therapy is related to the hardware components of the given facility. In a clinical setting it is of interest to optimise treatment time to maximise patient throughput, of course without compromising the quality of the treatment which the patient receives. There are a number of pieces of equipment and various parameters which when varied will alter the time taken to deliver a given PBS field.

**Research Question:**

*How does altering the system hardware effect the time required to deliver a PBS field?*

Chapter 7 presents a series of equations which calculate the time to deliver a PBS field based on the system hardware. The value of each of the hardware parameters incorporated into the calculation was varied to ascertain its effect on the irradiation time.
1.2 Getting to this point...

The research presented in this thesis was undertaken at the Centre for Medical Radiation Physics (CMRP), University of Wollongong and at the Department of Radiation Oncology, Massachusetts General Hospital (MGH) & Harvard Medical School. The measurements and Monte Carlo simulations related to comparisons of double scattering and PBS proton therapy were performed at MGH. The calculation of the irradiation times and hardware optimisation for PBS was undertaken at MGH. The Monte Carlo simulations of the various tissue substitutes and the planning comparison of IMRT and proton therapy were carried out at the CMRP.

1.3 Proton therapy

1.3.1 History

The use of protons for treatment of cancer was first suggested by Robert Wilson (Wilson [1946]). The first treatments of human patients using protons occurred in the mid 1950s at the University of California Lawrence Berkeley Laboratory (Tobias et al., 1958).

Radiosurgical techniques using protons were first developed at the Gustaf Werner Institute in Uppsala, Sweden in the late 1950s (Larsson et al., 1958). This group performed radiosurgery for brain tumours and were the first to use range modulation to give conformal dose to the target. They were also the first to use beam scanning to produce relatively large proton fields.

Radiosurgery treatment of intracranial targets began at the Harvard Cyclotron Laboratory in 1961 (Kjellberg et al., 1962). This program was the precursor to the Northeast Proton Therapy Center (NPTC), now the Francis H. Burr Proton Therapy Center, operating at Massachusetts General Hospital in Boston, USA.
1.3. Proton therapy

Early proton therapy facilities were confined to physics research departments. The first hospital based proton therapy facility was built at Loma Linda, USA and began treatments in 1990 (Slater et al. 1991). According to the website of the Particle Therapy Co-operative Group (PTCOG 2009), there are 30 proton therapy facilities currently operating with a further 23 either proposed or under construction.

1.3.2 Motivation for Proton Therapy

The rationale for using protons in radiotherapy is primarily due to the physical characteristics of protons themselves. Unlike photons, protons have a finite range in tissue which presents potential for improved dose sparing of critical structures distal to the intended target. The range of a proton beam is dependent on the primary energy and the physical characteristics of the target material. Figure 1.1 shows the proton range in water as a function of incident proton energy.

![Figure 1.1: Proton range (in g/cm$^2$) as a function of initial energy. The data used is from ICRU (1993).](image)

Protons have a relatively low ionisation density at shallow depths where the bulk
1.3. Proton therapy

of the dose from a single photon beam is delivered. The ionisation density of protons increases with increased depth, leading to the deposition of the majority of the energy at depth, inside the target. This narrow region of high ionisation density at the end of the proton range is known as the Bragg peak. A proton Bragg peak generated using a Monte Carlo simulation is shown in Figure 1.2.

![Figure 1.2: Depth dose distribution for a single proton Bragg peak. The Bragg peak was generated from the Astroid treatment planning system at Massachusetts General Hospital.](image)

Multiple monoenergetic Bragg peaks can be superimposed to produce a spread out Bragg peak (SOBP) \cite{Koehler1975}. Using a SOBP yields a region of uniform dose to be conformed to the target whilst largely retaining the dose sparing capabilities of protons. The superposition of multiple Bragg peaks leads to higher doses proximal to the target than those from a single monoenergetic Bragg peak but the sharp falloff in dose distal to the Bragg peak is retained. An example of a proton SOBP is shown in Figure 1.3. The SOBP shows the

![Figure 1.3: Example of a proton SOBP.](image)

The ability to produce a region of uniform dosage from a single beam angle implies that radiotherapy treatments using protons can incorporate fewer beams than photon
1.3. Proton therapy

Figure 1.3: Depth dose distribution for a Spread out Bragg Peak (SOBP) prescribed to deliver 2 Gray to a target volume of depth 10-20cm. The Bragg peak was generated from the Astroid treatment planning system at Massachusetts General Hospital. The relative contributions of the individual Bragg peaks within the SOBP are also shown.

techniques, further assisting in the sparing of normal tissue.

1.3.3 Beam delivery techniques

When the proton beam enters the treatment room, it is typically a pencil beam of small size and angular divergence. Beam delivery systems are typically defined as either passive or active, depending on how this pencil beam is conformed to the target. Passive deliveries involve scattering the beam and using a series of blocks and apertures to achieve dose conformality. Active deliveries typically involve scanning a narrow pencil beam over the tumour volume.

1.3.3.1 Double scattering proton therapy

Passive systems achieve conformity in the target by scattering and degrading the primary pencil beam. A diagram of a double scattering beamline is shown in figure
1.3. Proton therapy

1.4. Obtaining dose uniformity in depth requires modulation of the beam. This is typically achieved in passive systems by varying the thickness of absorber material which the beam traverses. This can be done using a range modulator wheel (Koehler et al., 1975). The range modulator wheel is a rotating disc consisting of steps of varying thickness which when traversed by the proton beam alters its range.

Typically, a pair of scattering foils are employed to increase the width of the primary beam. The first scatters the primary pencil beam, yielding a Gaussian distribution with high intensity in the centre of the field. The second scatterer is a composite scatterer which converts the Gaussian distribution to a homogeneous circular distribution (Koehler et al., 1977). Blocks and apertures are then used to collimate the beam produced by the scatterers to the required target shape based on a two dimensional projection of the target volume on the patient surface. A patient specific compensator is finally used to shape the dose distribution to the distal edge of the target volume.

Passive techniques are somewhat limited in that conforming the dose to the distal edge of the target volume implies that the same distribution is also applied to the proximal target edge. This can lead to some tissue immediately proximal to the intended target volume receiving close to the full treatment dose. The patient-specific hardware should be placed as close as possible to the skin to reduce the lateral scattering which degrades the beam penumbra.
1.3. Pencil beam scanning proton therapy

Pencil beam scanning (PBS) uses magnetic fields to scan the proton beam laterally across the target (Pedroni et al., 1995). Combining this capability with the ability to change the energy allows conformality in three dimensions. This is in direct contrast to double scattering proton therapy which cannot conform the dose distribution to both distal and proximal edges of the target volume. A diagram of an example PBS beamline is shown in figure 1.5. There are two principle methods of beam scanning, spot scanning and continuous scanning. For both these techniques, the irradiation is typically delivered as a series of two-dimensional layers.

Spot scanning involves the delivery of dose from pencil beams in finite steps. After the delivery of each individual pencil beam, the beam is switched off while the elements which steer the beam are reconfigured to deliver dose to the next voxel. This reconfiguration may require a change in the beam position or energy or both, depending on the individual facility and the scanning methodology employed. The method of changing the beam energy depends on how the proton beam is generated. If a synchrotron is used, the energy can be changed dynamically, whereas if a cyclotron is used, an energy selection system can be employed. Absorbers which degrade the beam energy may also be placed in the beam delivery system.

Voxel positions should be separated by less than 80% of the pencil beam’s full width half maximum to ensure uniformity in the dose distribution (ICRU, 2007).
Smaller separation reduces the sensitivity to fluctuations in the pencil beam position but increases treatment time.

The principal difference between continuous scanning and spot scanning is that in continuous scanning, the beam remains on when the position needs to be changed. The beam remains on whilst each layer is irradiated. The beam is then interrupted while the energy is changed. The beam is then turned back on, allowing irradiation of the next layer. This process continues until the target has been fully irradiated.

As a scanned beam is delivered, organ motion can cause fluctuations in the dose distribution via “interplay effects” (Bortfeld et al., 2002). These effects arise in PBS because the beam delivery as well as the target change with time. If a cell within an organ moves in the same direction as the beam is being scanned, it will receive more dose than intended. If the movement is opposite to the direction the beam is being scanned, it will receive less dose than was prescribed. These effects can be large, effecting the dose distribution by as much as 10% (Bortfeld et al., 2002). Interplay effects typically arise when the frequency of organ motion and the beam scan are similar. Organ motions typically have a period between less than one to a few seconds. The delivery of a scanning beam has three dimensions, the two lateral dimensions and the range. It is likely that one of these three dimensions may have a period of the same order as organ motion. To minimise the role which interplay effects have, repainting can be implemented. This involves repeating the delivery of the pencil beams a number of times. This may not be necessary if a large number of treatment fractions are delivered as the interplay effects tend to average out (Bortfeld et al., 2002).
1.3.4 Intensity modulated proton therapy

Intensity modulated proton therapy (IMPT) is the proton equivalent of IMRT and is only possible using active methods of beam delivery such as PBS. IMPT involves the simultaneous optimisation of all fields used in a particular treatment. This is in contrast to other methods which optimise the delivery such that each individual field delivers a homogeneous dose to the target \cite{Kanai1980}. The optimisation process in IMPT leads to non-uniform distributions from the individual beams which when superimposed yield a uniform dose distribution in the target \cite{Lomax1999}. Figure 1.6 shows the different variations of IMPT.

1.3.4.1 2D IMPT

2D IMPT is defined as the delivery of IMPT fields with fixed modulation, as is the case for double scattering proton therapy, see figure 1.6(a). In similarity to double scattering, the width of the SOBP is constant throughout the field and the dose is conformed to the distal edge of the target. The term “intensity modulation” applies to the calculation and application of a two-dimensional matrix of intensities. The modulation of the pencil beams only occurs in the transverse plane. Each of the intensities is assigned to an individual pencil beam (with fixed SOBP width). This is effectively the proton equivalent of intensity modulation for photons.

1.3.4.2 2.5D IMPT

The term “2.5D IMPT” is used to describe the intensity modulation of SOBPs with variable thickness, figure 1.6(b). Using this methodology, the dose is conformed to both distal and proximal edges of the target volume. This highlights one of the advantages of PBS over double scattering in that the modulation width does not need to be fixed. Modulating the width of the SOBP reduces the dose delivered immediately proximal
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(a) 2D IMPT

(b) 2.5D IMPT

(c) Distal Edge Tracking

(d) 3D IMPT

Figure 1.6: Different methods for intensity modulation of protons. The circles represent positions of individual Bragg peaks and the circle diameters symbolise relative intensities. Example depth-dose curves for each modulation method are also shown. Adapted from (Lomax et al., 1999).

to the target volume without comprising the quality of the dose distribution in the target itself. The free modulation of pencil beams occurs in the transverse plane and the change in SOBP width means that the depth-dose characteristics also vary in the transverse plane.

1.3.4.3 Distal edge tracking

Distal edge tracking (DET) was originally proposed by Deasy et al. (1997). This method uses only pristine Bragg peaks which are delivered to the distal edge of the target volume (figure 1.6(c)). Modulation by varying the intensities of the Bragg peaks
and using multiple beam angles leads to a homogeneous dose distribution throughout the target volume. As with 2D IMPT, modulation only occurs in the transverse plane. This methodology gives the lowest dose outside the target volume of any of the IMPT delivery methods ([Lomax et al. 1999](#)). The reduced number of Bragg peaks, combined with the exclusion of SOBPs from this modality makes it more susceptible to target motion. It has been shown that target motion can lead to large variations in the dose distribution using DET and homogeneity in the target volume can be greatly reduced ([Lomax 2008b](#)).

### 1.3.4.4 3D IMPT

3D IMPT, see figure [1.6(d)](#), fully utilises intensity modulation in that modulation is performed in three dimensions. Each individual pencil beam, regardless of its position in the target volume is included in the optimisation process. The spot positions are optimised such that the dose is conformed to both proximal and distal edges of the target, as in 2.5D IMPT. The extra dimension comes from the ability to optimise the weight of each spot delivered in the irradiation. In theory, this methodology is the most flexible of the IMPT methods described above as the number of variables which can be optimised is higher.

### 1.3.5 Biology of proton beams

The principle rationale for proton therapy lies in the improved dose distributions and reduced integral dose compared to photon modalities. However, the relative biological effectiveness (RBE) of protons is also slightly higher than that of photons. The RBE of any radiation type is dependent upon the dose, dose rate, fractionation and the tissues which are being irradiated. It also must be specified to a particular clinical endpoint.
The increase in RBE is primarily due to nuclear interactions which the primary beam undergoes as it traverses tissue. Nuclear reactions are important considerations in proton therapy as they contribute to the total absorbed dose. The secondary particles produced via such interactions can have high linear energy transfer (LET) which increases the RBE and secondary neutrons can be produced which leads to dose deposited external to the intended target volume [Paganetti 2002].

LET is an approximation of the microdosimetric quantity “dose mean lineal energy”. It describes the energy deposited by the beam in the medium being traversed per unit length. Typically, LET is expressed in units of keV/µm. Approximately 50% of the proton dose is absorbed at LET values of ∼18keV/µm [ICRU 2007].

Variations in the RBE throughout the treatment volume are primarily due to one of two factors. As protons slow down, their LET increases. This is mainly significant at the end of their range, at the distal edge of the Bragg peak. The contribution of high-LET secondary particles produced in nuclear reactions can potentially affect all parts of the proton Bragg curve [Paganetti 2002]. Currently, a generic RBE value of 1.1 is used for protons. This value was obtained by averaging the RBE over the SOBP. It is possible that at different points throughout the SOBP the RBE is higher (or lower) than 1.1.

When estimating the RBE of proton beams, the contributions of secondary protons and α-particles must be taken into account. Proximal to the Bragg peak or SOBP, secondary particles influence the overall RBE. This contribution from secondary particles depends mainly on the total dose, due to their high LET values. Within the Bragg peak or SOBP, the RBE value is almost entirely dominated by primary protons. The RBE increases with depth in the SOBP due to the increase in LET as the protons slow down.

A result of RBE increasing with decreasing dose and increasing LET is the exten-
sion of the biologically effective range of the proton beam by $\sim1\text{mm}$ for initial proton energies of 60-85MeV and $\sim2\text{mm}$ for 160-250MeV beams (ICRU, 2007).

### 1.3.6 Secondary neutrons

There has been concern in the proton therapy community over the effect of secondary neutrons generated during proton treatments (Hall, 2006). When the proton beam interacts with elements in the beamline, neutrons are produced via nuclear interactions. It has been hypothesised that the advantage of the lower integral dose from protons compared to photon techniques may be negated by the production of secondary neutrons.

There are two sources of neutrons during a proton therapy treatment, the nozzle and the patient. Whilst measures can be taken to reduce the neutron component from the nozzle, neutrons which are produced in the patient are obviously unavoidable.

The number of neutrons produced during a double scattering treatment is dependent on a number of geometrical and physical parameters. The material in the beamline is highly important in terms of neutron production, implying that the neutron dose is facility dependent. It is important to note that whilst neutrons can be produced along the whole beamline, many components also act as shielding, stopping neutrons produced further upstream from reaching the patient. The range-modulator wheel is the largest source of neutrons, however these neutrons interact with nozzle components downstream and do not reach the patient. Due to its close proximity to the patient, the patient-specific aperture is the dominant source of secondary neutrons which reach the patient. Most double scattering systems allow only a set number of field sizes, implying that a large proportion of the beam may need to be stopped by the aperture, particularly for small fields, which increases neutron production.

The neutron yield from the nozzle typically decreases with increased field size, as
there are fewer interactions taking place in the brass aperture \cite{Zacharatou2008}. The contribution of secondary neutrons generated in the patient increases with increasing field size. Treatment of deeper tumours require higher energy protons which increases the probability of neutron generation. The neutrons generated in the treatment head are the dominant component of the total neutron dose for the double scattering method of delivery.

As outlined in section 1.3.3.2, PBS requires less material in the beamline. A range modulator wheel is not required, and there is theoretically no need for patient-specific hardware such as apertures and compensators. This markedly reduces the amount of material which the beam interacts with, thereby reducing the number of neutrons produced \cite{Schneider2002}. For beam scanning techniques, the majority of neutrons are produced in the patient. It is possible for some treatment sites that patient-specific hardware, such as apertures and compensators, will be required \cite{Kooy2010} which may increase the neutron dose. Even when using these devices, the neutron dose from PBS will still be lower than that from double scattering since the aperture is not required to stop a large proportion of the beam, simply protons which have scattered through wide angles.

1.4 Geant4 Monte Carlo toolkit

Monte Carlo simulations provide numerical solutions based on the transportation of particles through a simulated geometry. The principal variation between Monte Carlo and other dose calculation algorithms is the consideration of individual particles. Particle interactions are governed by cross section data and models which are accessed during a simulation. A random number generator is instantiated to determine the change in direction of the primary and secondary particle following an interaction.
1.4.1 Geant4

Monte Carlo simulations performed throughout this thesis utilised the Geant4 toolkit. Geant4 is an open source toolkit based on the C++ programming language and was originally orientated towards high energy physics applications. Extensions of the applicable models and processes have led to its widespread adoption in medical physics and radiation protection. It is designed for the simulation of particle interactions in matter.

Geant4 allows detailed modelling of physical geometries, consideration of numerous particle types and specification of physics processes. This opens up a myriad of options to the user for even a single application. Such flexibility can be a “double-edged sword” as each of these aspects of the simulation need to be specified correctly to ensure accurate results from the simulation.

A wide variety of particles and energies may be simulated using Geant4 making it suitable in a number of applications. The energies available typically range from eV to TeV. Incorporation of high precision models means that some particle types, such as neutrons, can be simulated down to thermal energies. This increases simulation time due to the higher accuracy required but can be important in fields such as microdosimetry.

1.4.2 Geometry

The user has the responsibility of specifying all aspects of geometry required in the simulation. In Geant4, the description of geometrical volumes is done in three stages:

- *solid volume*: size and shape are specified
- *logical volume*: various attributes of the solid are specified (material, density etc)
- *physical volume*: volume position and rotation are specified
1.4. Geant4 Monte Carlo toolkit

The material of the solid is expressed via its chemical composition. The material is pre-defined by the user in terms of the constituent elements.

1.4.3 Physics models

Perhaps the most important aspect of any Geant4 Monte Carlo simulation is the specification and choice of physics models. Geant4 possesses numerous physics models which can be invoked by the user, potentially leading to different results. These physics models can be either theoretical or based on data obtained from experimental measurements.

The physics processes used in Geant4 are separated into the categories of electromagnetic, hadronic, transportation, decay, optical, photolepton, hadron and parameterisation. Depending on the individual application being used, it may or may not be necessary to specify physics models for each of the above categories.

1.4.3.1 Physics interactions

Whilst in flight, a particle may undergo one of several competing processes, each with a given probability. In a Monte Carlo simulation, a particle travels in a series of “steps” at the end of which it undergoes a particular interaction or process. The first thing which is to be considered is the distance the particle will travel before being acted upon by a physics process. This is termed the mean free path ($\lambda$) \cite{Agostinelli2003}. The probability of a given particle surviving a distance $l$ is

$$ P(l) = e^{-n\lambda} $$  \hspace{1cm} (1.1)

where

$$ n\lambda = \int_0^l \frac{dl}{\lambda(l)} $$  \hspace{1cm} (1.2)
If the particle undergoes decay, then the mean free path is given by

$$\lambda = \gamma v \tau$$  \hspace{1cm} (1.3)

where $v$ is the particle velocity and $\tau$ is the mean life.

For interactions, consider an isotope $i$ of mass $m_i$ which has a fractional mass $x_i$ in the material of density $\rho$ which is being traversed by the particle. If the interaction cross-section is given by $\sigma$, then the mean free path is given by

$$\lambda = \left( \rho \sum_i x_i \sigma_i / m_i \right)^{-1}$$  \hspace{1cm} (1.4)

The probability distribution of the parameter $n_\lambda$ from equation 1.1 is an exponential function which is material and energy independent.

$$n_\lambda = -\ln \eta$$  \hspace{1cm} (1.5)

where $\eta$ is a random number between 0 and 1. This random number is used for computation of the distance to the point of interaction or decay in the material which is being traversed by the particle.

Other processes can limit the size of the step in a simulation. The transportation process specifies that a single step may not cross a geometrical boundary and continuous energy loss may also limit the size of the step to ensure precision (Agostinelli et al., 2003). It is also possible for the user to specify a maximum allowable step size.

To determine which process will be invoked, the distance to interaction for each of the processes is calculated for the current step of the particle. The process which returns the smallest value is invoked. If the process is an interaction or decay, the particle is killed and secondaries are generated. Otherwise, the particle is transported and the algorithm is recomputed at the end of the next step.
The processes of interest in proton therapy are discussed in further detail in the following sections.

1.4.4 Electromagnetic processes

Electromagnetic processes in Geant4 govern the interactions of all charged particles and photons. The processes which can be modeled in Geant4 are multiple scattering, ionisation, the photoelectric effect, Compton scattering, Rayleigh scattering, bremsstrahlung, positron annihilation, the Cherenkov effect, synchrotron and transition radiation, refraction, reflection, absorption, scintillation, fluorescence and Auger emission.

Depending on the individual application and the particle types involved in the individual simulation, it may or may not be necessary to include all of the above electromagnetic processes.

1.4.4.1 Range cuts

Unless otherwise specified, charged particles are tracked to the end of their range in Geant4 simulations. To improve performance, when generating particles produced in an interaction, the user may specify to ignore particles produced with a range less than a specified value. This specified value is termed the “range cut”.

Whilst the use of a range cut is optional for some processes, it is necessary for others. Typical examples are δ-ray and bremsstrahlung production. For processes such as this, the use of a range cut is necessary to suppress the production of huge numbers of soft electrons and photons. The energy suppressed via the use of a range cut is transferred to the continuous process which acts along the step of the parent particle. This also implies that the interaction length is influenced by the choice of the range cut.
A range cut is used rather than energy as it allows the specification of a single value and ensures uniformity across all particle types and materials.

To implement range cuts, range-energy and absorption length-energy tables are produced for the relevant electromagnetic processes for each material in the simulation. For electrons, positrons, muons, protons and antiprotons, the range is calculated via numerical integration. The range for other charged hadrons is calculated from the proton table using equation 1.6 which gives the scaled kinetic energy \( T_s \).

\[
T_s = T \left( \frac{m_p}{m} \right)
\]  

where \( T \) is the particle kinetic energy, \( m_p \) is the proton mass and \( m \) is the mass of the charged hadron. The scaled kinetic energy \( (T_s) \) is the energy of a proton with the same velocity as the charged hadron being considered. This approach is valid as ionisation depends only on the particle velocity [Agostinelli et al. 2003].

### 1.4.4.2 Energy loss of electrons and positrons

The class \( G4VeEnergyLoss \) is used to calculate the continuous energy loss of electrons and positrons. The processes which contribute to the energy loss are ionisation (\( G4eIonisation \)) and bremsstrahlung (\( G4eBremsstrahlung \)). \( G4eIonisation \) calculates the contribution of the energy loss due to ionisation and simulates \( \delta \)-ray production. The energy loss due to soft bremsstrahlung is calculated by \( G4eBremsstrahlung \). It also simulates the energy loss due to hard bremsstrahlung.

As mentioned in the previous section, energy loss tables are produced for each material in the simulation. The electron and positron energy loss tables are filled by summing the contributions from ionisation and bremsstrahlung. Range tables and inverse range tables are then created for electrons and positrons in each of the materials.

The energy loss process imposes a limit on the step size of a particle and computes
the energy loss during each step travelled by the particle. The calculation of the mean energy loss is based on the inverse range \( T(r) \) table. The mean energy loss is given by equation (1.7)

\[
\Delta T = T(r_0) - T(r_0 - s)
\]  

where \( r_0 \) is the range at the beginning of the current step of length \( s \). If \( s < \kappa r_0 \), where \( \kappa \) is the linear loss limit, then an approximation of the mean energy loss is used.

\[
\Delta T \approx s \left| \frac{dE}{dx} \right|
\]  

After the mean energy loss has been computed, the actual energy loss is calculated. The actual energy loss is defined as the mean energy loss with some fluctuation. The fluctuation is calculated using the GLANDZ model.

### 1.4.4.3 Energy loss of hadrons

Ionisation is the only process which governs the energy loss of hadrons. The ionisation of hadrons is governed by \( G4hIonisation \) which also is responsible for simulation of hard \( \delta \)-ray production.

### 1.4.4.4 Bremsstrahlung

Bremsstrahlung cannot be considered in exactly the same fashion as other processes. For low energies, it can be approximated that the absorption length decreases with energy. When considering bremsstrahlung with a user defined range cut, a cut value for bremsstrahlung is established such that five absorption lengths equals the user defined range cut. This means that 0.7% of photons equal to the cut energy would travel further than the range cut specified by the user. This gives an approximate correlation between the range cuts of \( \delta \)-rays and bremsstrahlung.
The absorption cross-section of a photon is defined as the sum of the cross sections for gamma conversion, the Compton effect and the photoelectric effect. An approximate empirical formula is used to calculate the absorption cross-sections of a photon in a given element. The cross-section for Rayleigh scattering is not considered in the absorption cross-section because Rayleigh scattering only alters the trajectory of the photon whereas the other processes considered either destroy the photon or decrease its energy.

1.4.4.5 Multiple scattering

The multiple scattering of charged particles in a medium is governed by the class G4MultipleScattering. The model uses tables for electrons and positrons of energy between 0.1keV and 20MeV to calculate the scattering of the particle, compute the mean path length correction and the mean lateral displacement. Interpolation or extrapolation in terms of the atomic number or particle velocity is performed if and when required.

1.4.4.6 Low energy extension

Different physics models are only valid for specific energy ranges. A set of physics processes is included in Geant4 to extend the capability of the standard electromagnetic processes to lower energies. The extensions include processes for electrons, positrons, photons, charged hadrons and positive ions. Currently, the low energy limit of these “low-energy” processes is 250eV.

1.4.5 Hadronic processes

Hadronic processes in Geant4 govern elastic and inelastic scattering of hadrons and ions. The category of hadronic processes includes a number of different classes:
(i) *processes* define the possible processes and give connections to the cross-section data and models which are responsible for implementing the process

(ii) *management* contains classes which decide which ensure the correct interaction model is applied

(iii) *cross-sections* which contain all relevant cross-section data and calculation methods for computing processes

(iv) *stopping* processes are a special class of processes which act on particles either stopping or at rest

(v) *models* implement a final state based on a process or set of processes for a particle or set of particles in a finite specified energy range

(vi) *utility* classes provide standardised computational methods for the models

### 1.4.5.1 Modelling final states

There are three classes of models included in Geant4 to describe hadronic elastic and inelastic scattering. There are some models which are based on experimental data, others are based on parameterisations or extrapolation of experimental data under some theoretical assumptions and others are predominantly theoretical. To completely and sufficiently model physics interactions over a wide energy range, it is necessary to include several models. Different models are required to handle elastic and inelastic scattering and each model is only valid for a given energy range.

**Data driven models:** The best scenario for Monte Carlo modelling is when sufficient experimental data is available over the energy range of interest. Models which use such data are termed “data driven”. Limitations in data driven models often are found for projectile particles of high energy. Theoretical approaches are used to calculate missing cross-sections or predict cross-sections outside the range of the experimental
data. The main data driven models in Geant4 deal with isotope production caused by protons and neutrons. They are somewhat limited by the small amount of data available for neutrons of kinetic energy lower than 20MeV. High precision packages are included in the toolkit which allow simulation of neutrons below 20MeV down to thermal energies (Wellisch, 2005).

**Parameterised models:** These models use extrapolation and parameterisation of cross-section and interaction data. They are used in hadronic showers and in a number of different reactions. These models are available for low and high energies and for stopping particles.

**Theoretical models:** Theoretical models are used to describe hadronic interactions primarily in energy ranges where parameterised and data driven models are not available.

### 1.4.5.2 Inelastic scattering

Inelastic scattering of hadrons is simulated via application of the chosen model throughout different phases of the nuclear system in terms of time. Initially, the incident particle interacts with the target. This gives rise to an intra-nuclear cascade which produces secondary hadrons which exit the nucleus. This leaves the nucleus in an excited state. The modelling of the nuclear de-excitation is performed by simulating the emission of nucleons until an equilibrium is reached. The nucleus is then allowed to further de-excite until the simulation of the event is terminated based on a pre-assigned energy cut-off value. Thus, to simulate inelastic scattering of hadrons, there are three distinct processes which must be considered:

(i) the intra-nuclear cascade

(ii) the de-excitation of the nucleus pre-equilibrium

(iii) the de-excitation of the nucleus once it has reached equilibrium
1.4.6 Geant4 physics models for proton therapy applications

Zacharatou Jarlskog & Paganetti (2008a) performed a study which compared the different physics models for use in proton therapy. A judgement was made on which models were most suitable for use in proton therapy applications based on the results of the simulations and comparison with measurements performed using a multi-layer Faraday cup.

The results of this study dictated which physics models were used for all the proton therapy Monte Carlo simulations presented in this thesis.

1.4.6.1 Electromagnetic

To model electromagnetic interactions, the G4EmStandard model was chosen. The standard electromagnetic model is an analytical model which governs the interactions of photons and all charged particles of energy $\geq 1\text{keV}$ (Agostinelli et al., 2003). The standard model is only valid in this range as the effects of the shell structure of atoms are neglected and these effects become significant at lower energies. The binding energy of electrons is neglected, except when the process being modeled is the photoelectric effect. The recoil momentum of the nucleus is also neglected in this model. For energies above $2\text{MeV}$, the energy loss of hadrons is calculated based on the Bethe-Bloch formula, shown in equation 1.9

\[
-\frac{dE}{dx} = \frac{4\pi n z^2}{m_e v^2} \left( \frac{e^2}{4\pi \epsilon_0} \right)^2 \left[ \ln \left( \frac{2m_e v^2}{I} \right) \right]
\]  

(1.9)

where $n$ is the electron density of the target, $z$ is the particle charge, $m_e$ is the electron rest mass, $v$ is the particle velocity, $e$ is the electron charge, $\epsilon_0$ is the vacuum permittivity and $I$ is the mean excitation potential of the target.
Inelastic interactions

Inelastic hadronic interactions were modeled using a binary cascade \( G_4 \text{BinaryCascade} \) \cite{Folger2004}. The binary cascade is valid in the energy range of 100MeV - 10GeV. It models the hadronic interactions as a number of binary inelastic collisions between two nucleons, one of which is the incident particle, if the incident particle is a proton or a neutron, and the other is part of the target nucleus. Any secondary particles created in the interaction are allowed to interact with the remaining nucleons in a one-on-one basis, thereby leading to the intra-nuclear cascade.

**Binary cascade:** The interaction cross-sections used implemented in the binary cascade are parameterisations of experimental data from the Particle Data Group \cite{Hagiwara2002}. The Pauli exclusion principle is modeled by reducing the two-body cross-sections to effective values. This causes an interaction to be negated if the momenta of the nucleons is less than the local Fermi momentum.

\[
p_F = \sqrt{2mE_F} \quad (1.10)
\]

where the Fermi energy \( E_F \) is defined as

\[
E_F = -\alpha(T)kT \quad (1.11)
\]

where \( \alpha(T) \) specifies the number of particles in the system at a temperature \( T \) and \( k \) is Boltzmann’s constant.

A radially isotropic sphere is used to model the nucleus. Nucleons are distributed according to a harmonic-oscillator shell model density distribution (for \( A < 16 \)) or a Woods-Saxon density distribution (for \( A > 16 \)). The Fermi momentum is defined as a function of radius as the nucleus is considered isotropic. The momenta of the
individual nucleons are assigned a value between 0 and $p_F$ depending on their distance from the centre of the nucleus. The nuclear potential is also described based on the Fermi momentum and is thus assumed to be time independent, leading to a static nuclear system. The projectile is modeled as a wave package which is propagated in time and space between collisions.

The collisions of the incident hadrons are modeled by calculating the distances of closest approach to all nucleons in the medium. A target nucleon is considered as a potential collision site if the cross-section of the interaction is smaller than the geometrical cross-section which is defined by the distance of closest approach. These parameters are then used to calculate the time of flight of the incident hadron to all of the potential collision points, and the interactions are ranked from shortest to longest in terms of time. Each possible reaction is processed in order of rank, and the products of the reactions are tested to ensure that all selection and conservation rules are satisfied in order for the simulation to either accept or reject them. If the interaction is accepted, the binary collision is completed and the secondary particles are tracked and processed in the same manner. If the interaction is rejected, the next highest ranking candidate is tested. If there are no suitable interaction candidates or if the mean energy of the system falls below 70MeV, the binary cascade ceases.

If the incident particle is a light ion, the cascade is modeled in the same way by propagating the nucleons comprising the projectile as though they were free particles. When the cascade is terminated, any particles in the projectile ion which have not undergone an interaction are used to form secondary ion fragmentation. The properties of the incident ion and the interacting nucleons are used to calculate the excitation energy of the ion fragments.

Once all aspects of the binary cascade have completed, the final properties of the system are used as the initial properties used for the precompound model.
Precompound model: The precompound model ($G4PreCompoundModel$) is used in Geant4 for particles of energy below 100MeV. It is a theory driven model based on the semi-classical description of composite nucleus decay by Griffin (1966). It can be invoked as a stand alone model, however here it was used to fill the void between the binary cascade model and the equilibrium state of the nucleus.

In the precompound model, the nucleus is considered as a conglomerate of “exciton” states. An “exciton” is simply a particle or hole which is not in the ground state and the final state of the nucleus is defined by the number of excitons. Continuing from where the binary cascade was terminated, the precompound model simulates multiple two-body interactions in succession, leading to a state where the nucleus reaches equilibrium. Once the nucleus reaches equilibrium, the $G4ExcitationHandler$ is instantiated to simulate the transition of the nucleus to its ground state. In addition to interactions occurring between excitons, the model also considers emission of particles from the nucleus. The emission of particles operates in direct competition with exciton-exciton interactions. The particle types considered for emission from the nucleus are protons, neutrons, $^2$H, $^3$H, $^3$He and $^4$He.

Once all transitions in the nucleus have equal probability, the number of excitons is constant. This means that the nucleus has reached statistical equilibrium. The equilibrium models are then called to compute the nuclear de-excitation.

Equilibrium models: Once thermalisation has been completed, the nucleus is defined by its mass, charge and excitation energy. If the separation energy is less than the excitation energy, this implies that additional particles can undergo emission. The equilibrium models are used to describe emission of photons, nucleons and light ions.

The $G4ExcitationHandler$ governs the decay of the system. It is responsible for deciding which fragments of the nucleus are sent to the relevant models which co-ordinate the nuclear break-up. The breaking-up of the nucleus is based on the applicability of
1.5. Calculation of neutron dose equivalent

the models available. There are currently five de-excitation models available in Geant4:

(i) G4VEvaporation

(ii) G4VFission

(iii) G4VFermiBreakUp

(iv) G4VMulitFragmentation

(v) G4VPhotonEvaporation

For the energies of interest in proton therapy, only G4VEvaporation needs to be invoked. This evaporation model is based on the Weisskopf-Ewing model [Weisskopf & Ewing 1940]. This models the de-excitation of the nucleus by emitting nucleons and light ions. The default emission fragments are protons, neutrons, $^2$H, $^3$H, $^3$He, $^4$He, photon emission and internal conversion. Each of these evaporations channels operate in competition.

Elastic interactions

Elastic interactions of hadrons were modeled using the UHElastic model. This model combines the G4UHadronElasticProcess [Ivanchenko 2006] and the G4HadronElastic model. The UHElastic model incorporates the set of data for nucleon scattering off hydrogen.

1.5 Calculation of neutron dose equivalent

Microdosimetry is concerned with dosimetry on the cellular level. Energy deposition from radiation occurs as stochastic events and the measurement of such events may lead to an increased understanding of the biological effect of radiation exposure. This is of interest in radiotherapy applications as well as other areas such as space science.
1.5. Calculation of neutron dose equivalent

The principle quantity of interest in microdosimetry in lineal energy. As outlined in section 1.3.5, LET is an approximation of this quantity. Lineal energy is a measure of the stochastic energy depositions along a given chord length, typically in tissue. If a detector is used which is not tissue equivalent, the average chord length must be scaled such that it represents the chord length which would have been traversed in tissue.

Energy deposition events in microdosimetric studies are typically acquired as energy spectra ($f(E)$ vs. $E$). These spectra can be used to determine the absorbed dose $D$ at the point of measurement using equation 1.12.

$$D = \int_0^\infty \frac{f(E)dE}{\rho V}$$

(1.12)

where $\rho$ is the detector density, and $V$ is the detector volume.

For radiation protection purposes, a common scale is required for all ionising radiation which accounts for the varying effects that different radiation types have on tissue. This led to the introduction of the quality factor ($Q$) which is used in combination with the absorbed dose ($D$) to give what is termed the “dose equivalent” ($H$).

$$H = QD$$

(1.13)

The dose equivalent is expressed in units of Sieverts and is thus defined as the product of the absorbed dose and the lineal-energy dependent quality factor. Recently, the International Commission on Radiation Protection (ICRP) has changed the convention and now uses the radiation weighting factor ($w_R$) to move from absorbed dose to dose equivalent. This approach is used in all dose equivalent calculations in this thesis.

$$H = w_RD$$

(1.14)
1.5. Calculation of neutron dose equivalent

The concept of the radiation weighting factor is primarily designed for radiation protection purposes. It is not intended to be used for risk assessments for radiotherapy applications (ICRP 2003). The values of \( w_R \) are selected by the ICRP based on a review of the available information regarding biology, radiation exposure and calculation methods.

As shown in figure 1.7, there currently exists an incoherence between the values of \( Q \) and \( w_R \) for neutrons.

![Figure 1.7: Neutron radiation weighting factor (\( w_R \) modified) proposed by the International Commission on Radiation Protection (solid line). The broken lines show the previous convention for \( w_R \) and the effective quality factor (\( q_E \)) (ICRP 2003).](image)

The radiation weighting factor was introduced by the ICRP as a simplification of the quality factor. The two quantities were intended to be consistent. Any inconsistency in the two quantities is largely due to a change in definition. Both absorbed dose and quality factor are related to the radiation field which is delivered. The definition of \( w_R \) does not include any equivalent factor which accounts for the LET of the radiation (ICRP 2003).

In the studies performed in this thesis, the radiation weighting factor \( (w_R) \) is used for the calculation of dose equivalent.
Neutrons are assigned an energy dependent weighting factor as shown in figure 1.7. The neutron $w_R$ can be expressed as a function neutron kinetic energy ($E$), shown in equation 1.15.

$$w_R = 2.5 \left[ 2 - e^{-4E} + 6e^{-\frac{\ln(E)^2}{4}} + e^{-\frac{\ln(E)^2}{2}} \right]$$

For proton therapy studies, the ICRP recommends that a radiation weighting factor of 1 be assigned to photons. Protons are assigned a factor of 2. The weighting factors of particles which deposit dose locally, such as charged nuclear fragments and δ-electrons are included in the factor assigned to protons.

1.6 Summary

This chapter has introduced the principles of proton therapy. The motivation for the use of protons in cancer treatment and the different beam delivery techniques have been outlined. The differences in biology of proton beams compared to photons and secondary neutrons have also been introduced.

The methodologies employed in Monte Carlo simulations, particularly the Geant4 toolkit, have been outlined, including how interactions and particle decay are modelled in the simulations.

The research questions which are to be investigated in this thesis have also been presented.
Chapter 2

Rationale for the use of protons in cancer treatment

The clinical rationale for proton therapy lies in the ability to deliver higher doses to the tumour. The doses delivered in radiotherapy are typically limited in order to prevent harmful effects on normal tissue. Delivering higher doses to the tumour leads to a higher tumour control probability (TCP) ([Niemierko et al., 1992]. The potential to increase the dose to the tumour is derived from the irradiation of less normal tissue using protons compared to photons.

Due to the high conformality which can be achieved using proton therapy, it can be used to treat tumour volumes situated in close proximity to critical structures.

In radiotherapy treatment planning, the gross tumour volume (GTV) is defined as the extent and location of the malignant volume. The clinical target volume (CTV) is the tissue that contains the GTV and any sub-clinical microscopic malignant disease which needs to be eliminated. Finally, the planning target volume (PTV) takes into account the net effect of all possible geometric variations to ensure that the prescribed dose is delivered to the entire CTV. It is typically the CTV with a margin used to account for movement of tissues ([Metcalfe et al., 2007]).
2.1 Head and neck

This chapter outlines the potential clinical benefit using proton therapy by reviewing previous treatment planning comparisons for a number of different clinical sites. In addition, a planning comparison of IMRT and proton therapy was performed for a prostate tumour.

2.1 Head and neck

A treatment planning comparison was performed by Cozzi et al. (2001) to assess the potential benefits and limitations of 3D conformal therapy, IMRT, double scattered and spot scanned proton therapy. The comparisons were made for 5 patients who presented with stage III-IV squamous cell carcinoma in the head and neck region. When considering target coverage and TCP alone, all techniques can give similar outcomes. Protons gave improved dose homogeneity in the PTV, increasing the equivalent uniform dose. The dose to organs at risk, such as the spinal cord and parotid glands, was also lower using protons. Using protons for the treatment of advanced head and neck tumours has the potential to reduce the possibility of spinal cord toxicity (Cozzi et al., 2001).

IMRT and IMPT were compared in a treatment planning study by Steneker et al. (2006). The ability of each modality to spare organs at risk whilst keeping target dose homogeneous was determined. As with the study performed by Cozzi et al. (2001), treatment plans were generated for 5 patients with stage III-IV squamous cell carcinoma. Treatment plans were generated for IMRT using 5 and 9 fields and using 3, 5 and 9 fields for IMPT. Figure 2.1 shows the dose distributions from 9 field IMRT and IMPT for an example case. The target volume overlapped with the parotid glands and surrounded the spinal cord. The 9 field IMPT plan in Figure 2.1 gave better target conformation than the 9 field IMRT plan.

For IMRT, a significant improvement was observed moving from 5 to 9 fields. The
critical organs were spared best from the 3 field IMPT plan. Little advantage was observed in increasing the number of fields for IMPT. Reducing the spot size in the IMPT plans lowered the homogeneity in the target volume. However, as the dose to the parotids was reduced, the smaller spot size allowed homogeneity in the PTV to be retained. IMPT with 3 fields gave the same dose homogeneity to the PTV as the 9 field IMRT plan whilst reducing the dose in the parotids from 55% of the PTV dose to 35%. The second cancer risk was reported as lower from IMPT compared to IMRT. Reducing the spot size in IMPT further reduced the risk of second cancer induction. The risk of second cancer for the IMPT treatment plans increases by 15% when moving from 3 fields to 9 fields, suggesting that unlike IMRT, it is not beneficial to use a high number of fields in IMPT (Steneker et al. 2006).

The relative merit of IMRT and IMPT for treatment of tumour volumes in the paranasal sinus was investigated by Lomax et al. (2003a). Treatment plans were generated for a single patient using IMRT and IMPT using nominal dose constraints. Additional IMRT plans were then calculated in an effort to reduce the dose to the critical structures such that these matched the dose-volume histograms from the IMPT plan. The dose distributions for the treatment plans at the level of the globes are shown in Figure 2.1.
in Figure 2.2

Figure 2.2: Dose distributions for the IMPT (a) and IMRT (b) treatment plans at the level of the globes. Adapted from Lomax et al. (2003a).

It was observed that using the same nominal dose constraints led to similar target coverage and organ at risk (OAR) sparing from IMRT and IMPT. Lowering the dose constraints in IMPT led to critical organs being completely spared whilst retaining the required level of dose homogeneity in the tumour volume.

2.2 Paediatrics

The sparing of critical structures is paramount for paediatric patients who have the potential to live for long periods after radiotherapy treatment. St Clair et al. (2004) compared the protons to IMRT and 3D conformal radiotherapy for the treatment of a paediatric patient requiring craniospinal axis irradiation with a boost to the posterior fossa. The isodose distributions at the level of the cochlear in the axial projection is shown in Figure 2.3.

The dose distributions in Figure 2.3 demonstrate the ability of both IMRT and protons to spare the hearing apparatus. Protons gave the best sparing of the hearing
Figure 2.3: Isodose distributions in the axial projection at the level of the cochlear showing 3DCRT (upper left), IMRT (lower left) and protons (right). The arrows show the cochlear. (St Clair et al., 2004)

apparatus and the pituitary. For all organs considered external to the target volume, protons gave the best sparing.

Figure 2.4 shows the dose distributions from craniospinal irradiation. The dose distributions shown are mid-line sagittal views through the spinal column. For children who have still a significant amount of growth potential, it is important to intentionally treat the entire vertebral column to prevent growth imbalances. All OARs were better spared using protons in the craniospinal irradiation except for the posterior esophagus. This is a direct result of the planning methodology. The proton plan was designed to encompass the entire spinal column to prevent differences in growth in the anterior and posterior sections of the spine. The close proximity of the esophagus to the spinal column meant that its posterior wall received close to 100% of the prescribed dose to the spinal column. Despite this higher dose to the posterior esophagus wall, the
anterior wall still receives a lower dose using protons.

The 5 year survival rates for medulloblastoma have increased from 25% to higher than 65% (Packer et al., 1991, 1994), implying that secondary effects such as second cancer induction may become more significant given more patients are surviving for longer.

Figure 2.4: Isodose distributions in the sagittal projection along the spinal cord for 3DCRT (upper left), IMRT (lower left) and protons (right). (St Clair et al., 2004)
The treatment of paediatric ependymomas with different techniques was investigated by MacDonald et al. (2008). Ependymomas are brain tumours which typically occur in young children. Structures such as the brain, cochlear, cranial nerves and brainstem can all be situated in close proximity to the tumour, making a highly conformal treatment desirable. MacDonald et al. (2008) performed a retrospective study of 17 patients treated for ependymoma at the Francis H. Burr Proton Therapy Center, Massachusetts General Hospital or at the Harvard Cyclotron. Treatment plans were generated and compared for IMRT, three dimensional conformal proton therapy (3D-CPT) and IMPT. The IMRT plans used 6 beams compared to 4 for 3D-CPT and 3 for the IMPT treatment plans. The higher number of beams in IMRT is required to achieve acceptable dose homogeneity and conformality in the tumour volume. Figure 2.5 shows the dose distributions from the IMRT, 3D-CPT and IMPT plans for one of the considered patients. All plans were normalised such that the prescription dose of 55.8CGE covered 95% of the CTV.

Figure 2.5: Dose distributions from the IMRT (left), 3D conformal proton (centre) and IMPT (right) treatment plans at the level of the cochlear (top) and the temporal lobes and pituitary gland (bottom). The gross tumour volume (GTV) is shown in red and the clinical tumour volume (CTV) is shown in yellow (MacDonald et al. 2008).
2.3. Eye

The tumour coverage was similar for IMPT, 3D-CPT and IMRT. Better sparing of OARs was observed using 3D-CPT compared to IMRT, which further improved using IMPT. Only IMPT was most able to reduce the dose in the hypothalamus to zero. Both proton plans gave lower doses to all non-target tissues considered, particularly the brain and the temporal lobes compared to IMRT. The benefit of protons is not as clear for structures close to or included in the CTV.

2.3 Eye

The most common type of ocular tumour is the uveal melanoma which encompasses iridial, choroidal and ciliary body tumours. A treatment planning comparison of a uveal melanoma patient was performed by Weber et al. (2005). In this study, the uveal melanoma was a metastasis from a previously treated brain tumour. Treatment plans were generated for the uveal melanoma using a fixed horizontal proton beam line, IMPT, static and dynamic photon stereotactic radiotherapy and intensity modulated stereotactic radiotherapy.

The proton plans gave the best homogeneity in the tumour volume. Protons did not lead to improved sparing of homolateral organs at risk for this patient. The homolateral OARs were the homolateral lens, the lacrimal gland and the optic nerve. The contralateral organs considered were the lens, optic chiasm, optic nerve and the pituitary gland. The sparing of the contralateral OARs was significantly improved through the use of protons. Both proton plans completely spared all of the contralateral OARs, which was not possible using the photon techniques. The dose distribution from the IMPT and intensity modulated stereotactic radiotherapy are shown in Figure 2.6.

Despite the similar dose coverage across all the considered techniques, the dose homogeneity in the proton plans was higher. This is critical, as compromising the
tumour coverage may lead to a decrease in the TCP. To achieve the required dose conformity and OAR dose levels, a large number of non-coplanar beams were needed. There was no improvement observed in terms of dose distribution for this patient and tumour moving from the horizontal proton beam line to IMPT. Both proton plans were equally proficient in sparing the contralateral OARs.

Dendale et al. (2006) have reported on the treatment of uveal melanoma at the Curie InstitutOrsay Proton Therapy Center. The study reports on the treatment of 1406 patients over a 10 year period. The 5 year total and metastasis-free survival rates were 79% and 80.6% respectively. Local control at 5 years was 96%. This level of local control is similar to the values reported in other studies which used proton therapy (Egger et al., 2001; Wilson & Hungerford, 1999; Fuss et al., 2001; Munzenrider et al., 1989) demonstrating the suitability of this technique for the treatment of these tumours.

Alternate treatments for uveal melanoma include enucleation or the use of radioactive plaques. These alternative modalities are more invasive than proton therapy and enucleation involves the loss of the patients eye.
2.4 Prostate

2.4.1 Introduction

Proton therapy (PT) is not currently available in Australia. Sections 2.1, 2.2 and 2.3 demonstrate the potential use of proton therapy for different clinical sites. These previous studies can be used to give an indication of which clinical sites will benefit most from bringing proton therapy technology to Australia. Given the relatively low population of Australia compared to other countries, it is possible that the number of patients at a future Australian PT facility which specifically require PT for effective treatment may not fill the yearly workload of the facility. This study aims to determine if prostate cancer is a suitable candidate to fill any spaces in the workload of a potential facility.

Of all cancer cases in Australian men in 2003, greater than 25% were prostate cancer [AIHW 2007]. Comparisons between treatment plans generated for IMRT using different numbers of incident beams and proton therapy will show the relative merits of each modality. If using proton therapy could improve the dose distribution compared to IMRT, a number of patients could potentially benefit, due to the relatively high incidence of prostate cancer.

2.4.2 Treatment Planning

Treatment plans were generated for a prostate cancer patient using 5 and 7 field IMRT, double scattered proton therapy and intensity modulated proton therapy (IMPT) using an Eclipse treatment planning system (TPS) (Varian Medical Systems, version 8.1). All the beam data used to generate the PT treatment plans was supplied by Varian Medical Systems. IMRT plans used beam data for a Varian 21EX (Varian Medical Systems) linear accelerator from the Royal Prince Alfred Hospital, Sydney, Australia.
The prescription dose was 78 cobalt Gray equivalent (CGE) in 2 CGE fractions for all the treatment plans. Cobalt Gray equivalents were used to account for the proton RBE of 1.1.

The dose to the target was deemed satisfactory if at least 98% of the PTV received the prescription dose. A maximum dose objective of 81 CGE was set for the PTV. After the PTV objectives were achieved, the dose to all critical structures and normal tissue was reduced as much as possible without compromising PTV dose coverage.

### 2.4.2.1 Volume definition

The planning target volume (PTV) was defined as the clinical target volume (CTV) with a 7mm margin, including the seminal vesicles. This margin was employed to account for organ motion which could occur during a treatment. The previous investigation of margins for proton therapy by Thomas (2006) suggests that since organ motion cannot be neglected for prostate treatments that at least a 7mm CTV-PTV margin should be used when treating using two opposed proton fields.

The rectum was contoured from the ischial tuberosities to the sigmoid flexure as was done by Vargas et al. (2008). Both femoral heads were considered as a single volume. The whole body within the CT data set except for the PTV was included in an “external” volume. This allowed comparison of the dose delivered to all the normal tissue in the CT data set which was not contoured as a specific structure.

### 2.4.2.2 IMRT treatment plans

IMRT plans which incorporated either 5 or 7 fields were generated. Plans were produced using step and shoot and sliding window techniques of beam delivery. Step and shoot is a static method for the delivery of IMRT. It incorporates a succession of discrete field settings with a small amount of fluence delivered to each. As the leaves of the multi-leaf collimator (MLC) move to the next position, the beam is turned off.
Turning the beam off reduces the total number of monitor units required for treatment, reducing the radiation exposure due to leakage. Unlike step and shoot IMRT, sliding window is a dynamic technique. The basic principles are the same as step and shoot, except that during leaf motion the beam stays on. Sliding window uses relatively small segments with a large number of segments per beam. Thus, compared to step and shoot the number of monitor units and therefore the level of leakage radiation will be higher using sliding window IMRT.

Separate plans which used step and shoot (SSIMRT) and sliding window (SWIMRT) techniques of delivery were generated for both the 5 and 7 field cases. The step and shoot plans used 10 intensity levels per beam. Beam angles of $270^\circ$, $315^\circ$, $0^\circ$, $45^\circ$ and $90^\circ$ were used for the 5 field IMRT plans. For the 7 field plans, beam angles of $240^\circ$, $280^\circ$, $320^\circ$, $0^\circ$, $40^\circ$, $80^\circ$ and $120^\circ$ were used. Intervals of $40^\circ$ were chosen for the 7 field plans in an attempt to minimise exposure to the femoral heads by ensuring no beam passed directly through this structure. Inverse planning was employed for the optimisation of all the IMRT plans.

### 2.4.2.3 Double scattering proton therapy

Two lateral beams of equal weight were used for the double scattering proton therapy plan as is common at active PT centres (Slater et al. 2004). This treatment was forward planned as inverse planning is not available for passive delivery methods of proton therapy. The distance from the block edge to the PTV was $8\text{mm}$ in all directions. This distance gave the best compromise between dose coverage of the PTV and rectal exposure. The compensator thickness was manually modified in an attempt to reduce dose to the normal tissue and critical structures as much as possible whilst maintaining acceptable dose coverage to the PTV. The dose calculation was performed using a three dimensional convolution superposition algorithm.
2.4.2.4 IMPT treatment plans

The IMPT plan also employed two lateral beams. Each beam was initially generated such that it delivered a flat SOBP to the target volume. The individual pencil beams throughout each of the fields were not of equal weight. Initially assigning equal weighting to the individual pencil beams leads to the production of a gradient SOBP which gives higher doses proximal to the target than a flat SOBP (Albertini et al., 2007). Inverse planning was then incorporated for optimisation of the plan. Dose objectives were prescribed for the PTV. At least 98% the volume was required to receive the prescription dose of 78CGE with a maximum dose objective of 80CGE. After the PTV objectives had been achieved, the dose to the rectum, bladder, femoral heads and the external contour was minimised as much as possible without compromising conformity in the PTV. Highest priority was given to the rectum in terms of critical structure sparing. A convolution superposition algorithm was employed to calculate the dose distribution for the IMPT plan. Multifield optimisation was also used for the IMPT plan. This leads to the delivery of two inhomogenous lateral fields which when superimposed give a homogeneous dose distribution in the PTV.

2.4.2.5 Analysis of results

Plan evaluation was principally performed through analysis of dose-volume histograms (DVH). By ensuring the dose delivered to the PTV was as similar as possible across all plans, the relative abilities of each plan to spare normal tissue and critical structures could be more accurately assessed. The ability of each plan to spare all healthy tissue was determined by calculating the dose given to the external contour described previously. Whilst specific plans may be superior in a given structure, examining the dose to the whole external volume in the CT data set will provide a clearer representation of the ability of each plan to spare all normal tissue. The dose to the rectum, bladder
and femoral heads was also analysed to show the ability of each plan to spare these particular structures.

### 2.4.3 Results

The dose distributions for each of the plans are shown in figure 2.7. The dose sparing qualities of protons are immediately obvious. The minimum dose shown in all the figures is 4CGE. From these figures, it is clear that the PT treatment plans predict much lower normal tissue exposure compared to IMRT. This is a direct result of the physical characteristics of protons which allow dose conformality to be achieved from fewer beam angles, lowering the amount of normal tissue which needs to be irradiated.

### 2.4.4 Planning Target Volume

All treatment plans were normalised so that the prescription dose was delivered to 95\% of the PTV. This ensured that the dose-volume statistics, which are shown in figure 2.8 were as close as possible across all plans. All DVH curves are similar up to doses of 78CGE. After this point the different techniques cause the curves to separate slightly. No plan included any dose >110\% of the prescription dose. The minimum, maximum and mean dose for each of the treatment plans is shown in table 2.1. The highest dose encountered in any of the plans was for the 7 field step and shoot IMRT plan, which also had the highest mean dose within the PTV. The IMPT plan achieved a dose distribution in the PTV closest to the objectives.

### 2.4.5 Rectum

It should be noted that the definition of the PTV could have an impact on the rectal sparing capabilities of these treatment plans. By defining the PTV as the CTV with a 7mm margin, part of the rectum is included in the PTV. The principal objective of
Figure 2.7: Dose distributions from each of the intensity modulated radiotherapy and proton therapy treatment plans. The minimum dose shown in each figure is 4 cobalt Gray equivalent.
2.4. Prostate

Figure 2.8: Dose volume histograms for the planning target volume. SSIMRT = step and shoot IMRT, SWIMRT = sliding window IMRT.

Table 2.1: Doses delivered to the PTV from the different treatment plans. All values are in Cobalt Gray Equivalent.

<table>
<thead>
<tr>
<th>Treatment Plan</th>
<th>Min Dose</th>
<th>Max Dose</th>
<th>Mean Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 field SSIMRT</td>
<td>69.97</td>
<td>85.18</td>
<td>81.12</td>
</tr>
<tr>
<td>5 field SWIMRT</td>
<td>70.75</td>
<td>84.55</td>
<td>80.96</td>
</tr>
<tr>
<td>7 field SSIMRT</td>
<td>69.11</td>
<td>86.11</td>
<td>81.43</td>
</tr>
<tr>
<td>7 field SWIMRT</td>
<td>69.34</td>
<td>83.69</td>
<td>80.65</td>
</tr>
<tr>
<td>Double scattering PT</td>
<td>73.71</td>
<td>84.71</td>
<td>80.73</td>
</tr>
<tr>
<td>IMPT</td>
<td>72.07</td>
<td>81.74</td>
<td>79.56</td>
</tr>
</tbody>
</table>

these plans was to attain homogeneous doses in the PTV, which could have increased high dose rectal exposure. Rectal DVHs are shown in figure 2.9. The IMPT plan was the most proficient in sparing the rectum. The 5 field IMRT plans gave the highest mean rectal doses. 7 field IMRT gave lower mean rectal doses than the double scattering proton therapy plan, however only the two proton plans gave minimum doses of 0%. Above 80CGE, the DVHs are similar for all plans, most likely due to the overlap of the PTV and rectum. For doses >50CGE, the IMPT and the 7 field IMRT plans give similar doses to the rectum, but IMPT gives less low dose exposure. The
rectal doses are summarised in table 2.2.

Figure 2.9: Dose volume histograms for the rectum. SSIMRT = step and shoot IMRT, SWIMRT = sliding window IMRT.

Table 2.2: Rectal doses delivered by the different treatment plans. All values are in Cobalt Gray Equivalent.

<table>
<thead>
<tr>
<th>Treatment Plan</th>
<th>Min Dose</th>
<th>Max Dose</th>
<th>Mean Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 field SSIMRT</td>
<td>5.15</td>
<td>81.98</td>
<td>40.64</td>
</tr>
<tr>
<td>5 field SWIMRT</td>
<td>5.30</td>
<td>81.82</td>
<td>41.34</td>
</tr>
<tr>
<td>7 field SSIMRT</td>
<td>4.91</td>
<td>84.40</td>
<td>35.80</td>
</tr>
<tr>
<td>7 field SWIMRT</td>
<td>4.99</td>
<td>82.37</td>
<td>36.27</td>
</tr>
<tr>
<td>Double scattering PT</td>
<td>0.0</td>
<td>84.63</td>
<td>38.06</td>
</tr>
<tr>
<td>IMPT</td>
<td>0.0</td>
<td>81.51</td>
<td>31.67</td>
</tr>
</tbody>
</table>

2.4.6 Bladder

Figure 2.10 shows the DVH statistics for the bladder. Due to the beam arrangement in particular, both proton plans were much better at sparing the bladder as the two lateral beams do not traverse the bulk of this structure. The IMRT plans all had a field passing directly through the bladder which compromised their ability to minimise
2.4. Prostate

dose to this structure. The doses delivered to the bladder are summarised in table 2.3.

Figure 2.10: Dose volume histograms for the bladder. SSIMRT = step and shoot IMRT, SWIMRT = sliding window IMRT.

Table 2.3: Doses delivered to the bladder by the different treatment plans. All values are in Cobalt Gray Equivalent.

<table>
<thead>
<tr>
<th>Treatment Plan</th>
<th>Min Dose</th>
<th>Max Dose</th>
<th>Mean Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 field SSIMRT</td>
<td>0.78</td>
<td>84.40</td>
<td>23.32</td>
</tr>
<tr>
<td>5 field SWIMRT</td>
<td>0.78</td>
<td>83.38</td>
<td>22.62</td>
</tr>
<tr>
<td>7 field SSIMRT</td>
<td>0.86</td>
<td>83.85</td>
<td>22.78</td>
</tr>
<tr>
<td>7 field SWIMRT</td>
<td>0.86</td>
<td>83.07</td>
<td>22.70</td>
</tr>
<tr>
<td>Double scattering PT</td>
<td>0.0</td>
<td>81.98</td>
<td>10.69</td>
</tr>
<tr>
<td>IMPT</td>
<td>0.0</td>
<td>81.12</td>
<td>9.44</td>
</tr>
</tbody>
</table>

2.4.7 Femoral Heads

The doses delivered to the femoral heads are summarised in table 2.4 and DVH curves are shown in figure 2.11. The lowest exposure to the femoral heads was obtained by the IMPT plan, despite the beam passing directly through this structure. The highest mean exposure was obtained from the 5 field IMRT plans. Using 40 degree increments
between the beams for the 7 field IMRT plans meant no beam passed directly through the femoral heads, unlike the 5 field IMRT and the proton plans. Despite the lower mean doses of the 7 field IMRT plans compared to the double scattering proton therapy plan, the maximum dose in the femoral heads was approximately 25CGE higher for both 7 field IMRT plans. Both proton plans gave higher levels of low dose exposure principally attributable to the beam arrangement. Despite this, smaller volumes were exposed to doses above 35CGE by the proton plans.

Table 2.4: Doses delivered to the bladder by the different treatment plans. All values are in Cobalt Gray Equivalent.

<table>
<thead>
<tr>
<th>Treatment Plan</th>
<th>Min Dose</th>
<th>Max Dose</th>
<th>Mean Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 field SSIMRT</td>
<td>1.25</td>
<td>74.49</td>
<td>30.50</td>
</tr>
<tr>
<td>5 field SWIMRT</td>
<td>1.25</td>
<td>61.46</td>
<td>31.36</td>
</tr>
<tr>
<td>7 field SSIMRT</td>
<td>1.25</td>
<td>63.18</td>
<td>24.02</td>
</tr>
<tr>
<td>7 field SWIMRT</td>
<td>1.25</td>
<td>63.96</td>
<td>23.87</td>
</tr>
<tr>
<td>Double scattering PT</td>
<td>0.0</td>
<td>38.61</td>
<td>28.47</td>
</tr>
<tr>
<td>IMPT</td>
<td>0.0</td>
<td>34.16</td>
<td>23.63</td>
</tr>
</tbody>
</table>

Figure 2.11: Dose volume histograms for the heads of femur. SSIMRT = step and shoot IMRT, SWIMRT = sliding window IMRT.
2.4.8 External Tissue

As discussed previously, external tissue was defined to be any tissue in the CT data set which lied outside the PTV. This contour includes the other critical structures previously analysed. As shown in figure 2.12 both proton plans are superior to the IMRT plans in terms of normal tissue sparing. The doses shown in table 2.5 demonstrate that IMPT is slightly more proficient than double scattering proton therapy at sparing normal tissue. Both proton plans are significantly better at sparing normal tissue than the IMRT plans. The 5 field IMRT plans gave better normal tissue sparing than the 7 field plans which both irradiated the entire “external” volume to some non-zero dose.

![Dose volume histograms](image)

Figure 2.12: Dose volume histograms for all tissue in the CT data set except for the planning target volume. SSIMRT = step and shoot IMRT, SWIMRT = sliding window IMRT.

2.4.9 Discussion

Using 7 field IMRT slightly improved dose coverage in the PTV and better sparing of critical structures was observed, particularly for the rectum. The 5 field step and shoot and sliding window IMRT plans gave mean rectum doses approximately 5CGE
Table 2.5: Doses delivered to the “external” volume by the different treatment plans. All values are in Cobalt Gray Equivalent.

<table>
<thead>
<tr>
<th>Treatment Plan</th>
<th>Min Dose</th>
<th>Max Dose</th>
<th>Mean Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 field SSIMRT</td>
<td>0.0</td>
<td>85.18</td>
<td>9.75</td>
</tr>
<tr>
<td>5 field SWIMRT</td>
<td>0.0</td>
<td>84.55</td>
<td>9.91</td>
</tr>
<tr>
<td>7 field SSIMRT</td>
<td>0.08</td>
<td>86.11</td>
<td>10.37</td>
</tr>
<tr>
<td>7 field SWIMRT</td>
<td>0.08</td>
<td>83.69</td>
<td>10.37</td>
</tr>
<tr>
<td>Double scattering PT</td>
<td>0.0</td>
<td>84.71</td>
<td>5.62</td>
</tr>
<tr>
<td>IMPT</td>
<td>0.0</td>
<td>81.74</td>
<td>4.60</td>
</tr>
</tbody>
</table>

higher than the 7 field plans. Vargas et al. (2008) performed a dose-volume comparison between PT and IMRT for prostate cancer. This involved examination of treatment plans generated for 10 prostate cancer patients. The IMRT plans generated in the report by Vargas et al. (2008) used 5 fields. They found that the proton therapy gave better whole volume dose than IMRT in the PTV and achieved values closer to the prescribed dose. In contrast to the results shown here, the rectal DVH curve for proton therapy was significantly lower than the IMRT curve for all dose values up to >80Gy. In difference to the work presented here, Vargas et al. (2008) also performed optimisation on the beam angles which affected the dose delivered to both the bladder and rectum by their plans. Vargas et al. (2008) defined the PTV as the CTV with a 5mm margin in the axial direction and 8mm margin in the craniocaudal dimension. A greater margin in the superior and inferior directions was used to combat the uncertainty in identifying the apex and base of the prostate. Reducing the dimensions of the margins decreases the amount of rectal volume included in the PTV. The different definitions of the PTV used between the previous work of Vargas et al and the work presented here imply that different levels of rectal volume are included in the PTV. This could greatly impact the level of rectal exposure. In the report by Vargas et al. (2008), a significant reduction in bladder dose was also observed when using proton therapy.
Better low dose rectal sparing using PT was also observed by Zhang et al. (2007). Their target definition incorporated the seminal vesicles into the CTV, unlike Vargas et al. (2008), which could have resulted in different dose distributions in the bladder and rectum. For doses less than 50% of the target dose, proton therapy gave better rectal sparing, but above this value, IMRT using 8 coplanar beams was superior. Different margins were used for the different modalities in the study of Zhang et al. (2007). Their IMRT plans used a 3mm margin between the PTV and CTV, whilst for the proton plans a 12mm CTV-PTV margin was used. No reason for the variation in the margins between the modalities is given in the manuscript. The dose falloff in proton therapy is sharper compared to IMRT implying that any tissue outside the PTV will be under-dosed in proton therapy, possibly compromising the treatment quality. Increasing the PTV size in the proton plan ensures that the CTV receives the required dose. It also reduces the susceptibility of the proton plan to organ motion.

The different margins used for IMRT and proton therapy infer that a larger rectal volume would be included in the PTV for the proton therapy plans, explaining the higher rectal doses observed for this modality in this work. While larger margins have been employed by Zhang et al. (2007) than the other cases here, the work of Thomas (2006) suggests that it may be necessary in some cases to employ such a margin.

Three dimensional conformal proton radiotherapy (3D-CPT) treatment plans were compared to IMRT plans for prostate cancer for 10 patients by Trofimov et al. (2007). They observed better dose conformity to the target using IMRT. To improve conformity for the 3D-CPT plans, the authors used a technique known as compensator smearing. After the 98% isodose is matched to the PTV, a smearing algorithm is implemented. This involves editing the compensator generated by the TPS to ensure adequate PTV coverage despite the uncertainties in patient alignment. Trofimov et al. (2007) employed the smearing algorithm to a radius of 10mm from the PTV. When us-
ing the standard lateral beam configuration, higher doses in the rectum were observed for 3D-CPT compared to IMRT using seven equally spaced coplanar fields. Altering the angle of proton beam delivery was seen to have a large effect on rectal dose. Using small-angle lateral-oblique fields compared to the lateral field configuration reduced rectal exposure by up to 35% with an increase in bladder dose of less than 10%.

Particular care must be taken when comparing proton therapy and IMRT to note the number of beams used, particularly for IMRT. Whilst proton therapy can achieve acceptable conformality for prostate treatment with 1 or 2 lateral beams, IMRT requires more. The use of two lateral beams is primarily done for sparing of the femoral heads. Increasing the number of beams in IMRT usually gives better conformality but at the expense of normal tissue exposure and an increased risk of secondary malignancy (Hall 2006). The results presented here also show that step and shoot IMRT gives slightly different dose distributions to the sliding window method of delivery. For the patient examined here, using IMPT gives a mean rectal dose 13% lower than 7 field sliding window IMRT. Benefits of using proton therapy were also observed in other critical structures. The mean doses to the bladder and femoral heads from both proton plans is far lower than that possible using 7 field IMRT. Tissue outside the PTV is exposed to approximately 50% less dose using either method of proton therapy.

Estimation of the secondary cancer risk from proton therapy is also uncertain due to the effect of secondary neutrons, which are not typically accounted for by the treatment planning system. A complete model for radiocarcinogenesis does not currently exist (Ruben et al. 2008). Most current models are based on the data from the atomic bomb survivors. This data is limited as they relate to a specific population who were exposed to radiation once. Modifications have to be made to this data to account for fractionated treatments. The unwanted secondary particles produced during proton treatments have the potential to deposit dose far outside the treatment
2.4. Prostate

Field \cite{Wroe2007}. Secondary charged particles with high linear energy transfer values produced by neutrons generated in proton treatments have the potential to induce malignancies \cite{Schneider2002}. Since the level of neutron production is highly dependent on the material placed in the beamline, it has been hypothesised that using a spot scanning beam could significantly lower the neutron dose delivered to the patient \cite{Schneider2002}. \cite{Schneider2006b} used the concept of organ equivalent dose to evaluate the secondary cancer risk for prostate radiotherapy patients. Their calculations were based on linear-exponential and plateau-dose response curves. The IMRT plans in the study by \cite{Schneider2006b} used 5 fields. From their calculations, it was calculated that 5 field IMRT treatments increased the risk of secondary cancer by 15% compared to 4 field conventional radiotherapy. The spot-scanning proton therapy plans used in their study reduced the risk of secondary cancer incidence by as much as 50% compared to the conventional treatments and 65% compared to IMRT \cite{Schneider2006b}.

The clinical significance of secondary neutrons generated in proton therapy is still a source of debate \cite{Brenner2008}. Until their effect can be confidently ascertained, generating a complete model for the risk of induction of secondary malignancies from proton therapy treatments is not possible.

2.4.10 Conclusions

The results of this study show that using proton therapy, particularly IMPT, to treat prostate cancer patient may be beneficial compared to IMRT. For the considered patient, homogeneity in the PTV is better using IMPT. Protons also gave better sparing of the bladder and femoral heads. Rectal sparing was similar for all plans at high doses, although IMPT gave better sparing at low dose levels. Using protons has the potential to greatly reduce the dose delivered to healthy tissue outside the PTV,
possibly reducing second malignancies. Whilst there is no clinical evidence to support
the hypothesis that the additional dose delivered external to the PTV from IMRT
increases the risk of second malignancies, no harm can come from lowering the dose
to critical structures, assuming PTV coverage is not compromised.

Given these results, radiotherapy using protons, particularly IMPT, represents
a worthwhile treatment option for the considered patient and could be a suitable
candidate for filling any gaps in the workload of a future Australian proton therapy
facility.

2.5 Clinical trials

The issue of clinical trials comparing proton therapy and other treatment modalities
has generated considerable discussion in the proton therapy community. There are few
randomised clinical trials comparing proton therapy to x-ray external beam therapy
(3D conformal or IMRT) (Goitein & Cox 2008). The lack of level III randomised
clinical trials is not unique to proton therapy. For example, despite its widespread use
in radiotherapy, IMRT only has 3 phase III clinical trials reported in the literature
(Veldeman et al. 2008). Low-dose-rate brachytherapy has never been randomised
against external beam radiotherapy. Most randomised trials test the efficacy of a new
drug with radiotherapy included in both arms of the trial.

The main reasoning for the use of protons in radiation therapy are:

(i) depth dose characteristics

(ii) similarity in tissue response per unit dose

(iii) normal tissue sparing

The depth dose characteristics of protons allow less dose to be delivered proximal
and distal to the target volume compared to photons. The dose distributions have
been compared for photons and protons with and without intensity modulation in a number of treatment planning studies, some of which were introduced in sections 2.1, 2.2, and 2.3. In almost all cases in the literature, the dose distribution from protons is superior to that achievable with photons.

The value used for the proton RBE is 1.1 (Paganetti 2002), which implies the effect of irradiating tissue to a given dose using protons will be similar to the effect from photon irradiation. Thus, the most important differences in the dose distributions are physical, not biological.

There is no benefit in delivering radiation to normal tissue during a treatment. The ability of protons to improve sparing of normal tissue compared to photon techniques without compromising target coverage has been demonstrated in the previous planning studies.

Concerns have been raised by Brada et al. (2007) that there is insufficient evidence-based medicine to warrant the use of proton therapy in radiotherapy. The question is whether or not conclusive results from a randomised clinical trial are required before the adoption of new technology. Such trials were not required for the introduction of IMRT into the clinic and the question asked by some members of the proton community is why should they be required for protons (Goitein & Cox 2008; Suit et al. 2008)?

Quantification of any clinical gain from proton therapy is more difficult to ascertain than the reduction in physical and biologically effective dose compared to photons (Suit et al. 2008). There is also the argument that the high cost and effort required to conduct phase III clinical trials would be better spent on the advancement of the radiotherapy techniques in question.

Assuming both IMRT and proton therapy can deliver sufficient dose to the tumour volume, Suit et al. (2008) have also raised the question of whether it is ethical to
request patients to receive a radiotherapy treatment (photon) whose only known and predicted difference from a newer method (proton) is an increased probability of radiation induced injury with no increase in TCP. This raises concern that in a randomised clinical trial between proton therapy and IMRT there would not be equipoise in the two arms of the trial.

2.6 Second cancer risk

The issue of second cancer induction in proton therapy has been an area of significant investigation and discussion. The generation of secondary neutrons has the potential to cause second cancer induction \cite{Hall2006}. The calculations of \cite{Hall2006} showed that the risk of second cancer induction from protons was higher than IMRT. The values obtained from these calculations have since been questioned and shown to significantly overestimate the risks from proton therapy \cite{Macklis2006, Paganetti2006b, Paganetti2006a}.

The risk of second cancer induction is of particular importance for paediatric patients who can live long after the conclusion of treatment. Factors leading to an increased risk of second cancer induction are both genetic and related to the treatment modality. The paediatric patients with highest risk of second cancer induction are those with retinoblastoma, Hodgkin’s disease, leukemia, neuroblastoma, sarcoma and central nervous system tumours \cite{Meadows1992}.

\cite{Miralbell2002} investigated the potential ability of proton therapy to reduce the incidence of second cancers in two paediatric patients. The first patient presented with a parameningeal rhabdomyosarcoma and the second with a medulloblastoma. Treatment plans were generated for the rhabdomyosarcoma patient using conventional x-ray, IMRT and proton therapy. For the medulloblastoma patient, an IMPT was also generated in addition to the other modalities. The risk of second cancer induction was determined based on a model which is outlined in a paper by \cite{Schneider2006}.
This model allows estimation of the second cancer risk based on the dose-volume statistics in the non-target organs. For the rhabdomyosarcoma patient, using proton therapy reduced the risk of second cancer incidence by more than a factor of two compared to the conventional x-ray and IMRT plans. For the medulloblastoma patient, the proton beams reduced second cancer incidence by 8 to 15 times compared to the photon techniques. The results of the study by Miralbell et al. (2002) demonstrate the potential to significantly reduce the incidence of second cancer in paediatric patients by using proton therapy.

Schneider et al. (2006b) used the concept of organ equivalent dose (OED) to calculate the risk of second cancer for patients treated for prostate cancer treated using spot scanned protons and IMRT with 6MV, 15MV and 18MV photons. It is important to note, that due to the known neutron production when using high photon energies, 15MV and 18MV photons are typically only used for larger patients. A dose distribution in an organ is said to be equivalent, thus corresponding to the same OED, if it leads to the same induction of radiation-induced second cancer (Schneider et al. 2005). A linear-exponential and a plateau dose-response curve was applied to each of the treatment plans. The effect of scattered x-ray and neutron doses were included in the risk estimates. Increasing the photon energy leads to an increased risk of second cancer incidence, because of the neutron production which occurs at these energies. Using protons instead of photon techniques has the potential to reduce the risk of second cancer induction by more than 50%.
2.7 Challenges and future improvements in proton therapy

2.7.1 Uncertainties and organ motion

The majority of the treatment planning performed in clinical proton facilities uses pencil beam algorithms due to their computational efficiency \cite{Petti1992, Hong1996}. This methodology convolves a pencil beam dose deposition model which is based on experimental or simulated depth-dose curves in water with a 3D map of proton stopping power relative to water. These relative proton stopping powers are currently obtained through conversion of x-ray CT Hounsfield numbers using a calibration curve \cite{Schneider2006a}. Using such a conversion introduces errors of approximately 3\% of the maximum proton range \cite{Schaffner1998}. The errors in the conversion should be applied in combination with any errors inherent in the acquisition of the x-ray CT scan. This uncertainty in the range inhibits the ability of clinicians to place the proton Bragg peak directly on the distal edge of the tumour volume, which negates some of the advantages of proton therapy.

Proton CT (pCT) offers the possibility of directly obtaining the proton stopping power for use in treatment planning applications. This would remove the errors associated with x-ray CT and the conversion to stopping power. The methodology outlined for pCT is to track individual protons as they traverse the treatment volume and obtain information about their position and direction pre and post-patient \cite{Schulte2004}. The effects of multiple Coulomb scattering in the patient can be accounted for using a most likely path formalism \cite{Schulte2008}. The energy lost whilst traversing the patient can also be measured which allows calculation of the path integral of relative electron density of a water equivalent object or the integral of relative stopping power along each proton path \cite{Schulte2004}. Proton CT
2.7. Challenges and future improvements in proton therapy

is an imaging modality which is potentially capable of providing all the necessary information for proton therapy treatment planning in a more direct method with fewer uncertainties than the current x-ray CT based approach.

The combination of the finite range and multiple Coulomb scattering can make proton therapy treatments sensitive to density heterogeneities \cite{Lomax2008a}. The high conformality and sharp distal falloff of protons makes this modality more susceptible to uncertainties in the calculated and delivered treatment than photon techniques. The heterogeneities in the patient introduce inaccuracies in the proton planning process.

Density heterogeneities effect both the shape of the depth-dose curve and the proton range \cite{Lomax2008a}. When traversing homogeneous materials, individual protons may take different paths, leading to “range-straggling”. When a density heterogeneity is introduced, the effect can be much more significant. The range of the proton beam may be smeared, leading to an increase in the modulation width of an SOBP or an entire area of the tumour volume may receive no dose. The use of multiple beam angles in intensity modulated proton therapy (IMPT) \cite{Lomax1999} makes this method of delivery and optimisation even more susceptible to heterogeneities. This may indicate the need for Monte Carlo treatment planning \cite{Paganetti2008} which has the potential to handle heterogeneities better than pencil beam calculations by modelling individual proton trajectories through the patient medium. The uncertainties in the calculation of the proton range and dose distributions imply that what is planned in the treatment planning system can potentially be different to what is actually delivered to the patient.

Patient and organ motion can also be significant in proton therapy, particularly for IMPT. \cite{Lomax2008b} investigated the effect of inter-fraction motion and inter-field motion in IMPT. Inter-fraction motion is defined as the movement of the patient or internal organs which occurs between the delivery of treatment fractions. This includes
patient positioning relative to the CT and anatomy changes over the course of the treatment period. Inter-field motions are defined as the movement of the patient or an organ between the delivery of fields during a single fraction. Whilst the concept of a PTV was introduced to combat intra-field motion, that is motion occurring during the delivery of a single field, it may not be sufficient for the other types of motion (Lomax, 2008b). The highly conformal dose distributions which can be generated during treatment planning for IMPT may not be what is delivered due to these types of motion. All types of organ motion cannot be fully negated, but strategies need to be developed to either minimise or manage motion to fully realise the potential of proton therapy.

2.7.2 Cost

The sophisticated technology and apparatus required for proton therapy imply that proton therapy will continue to be more expensive than photon treatments. The question should be whether the proposed improvements from proton therapy justify the increased cost of these treatments. Goitein & Jermann (2003) performed an analysis and determined that the relative cost of proton therapy is approximately 2.4 times that of x-ray therapies. This relative cost is expected to reduce as proton technology becomes more widely available. A similar analysis by Lievens & Van den Bogaert (2005) determined that the cost of proton therapy is not unrealistic and should not be the reason for denying patients access to this technology.

The cost of proton treatments is dependent on the number of patients which can be treated at a given facility. Theoretically, capital costs should remain the same, implying that treating more patients allows the cost per patient to be reduced. Optimising the treatment process in proton therapy may in turn lead to a decrease in the cost of treatment. The cyclotron or synchrotron used in proton therapy will likely last
more than 40 years (Suit et al., 2008) whilst photon linear accelerators in Australia lose their federal government billing after 10 years of operation. The longer working lifetime of proton equipment should also be factored into any relative cost estimates.

Despite the currently increased cost of proton therapy compared to IMRT and other photon techniques, it should be noted that radiotherapy as a whole, including protons, is still a relatively inexpensive method of cancer treatment compared to other modalities.

2.7.3 New technology

The efficiency of beam extraction and power consumption from cyclotrons has improved over the past years. Additionally, superconducting technology has been used to develop smaller cyclotrons still capable of generating high energy protons (Klein et al., 2005). The management of patient transport, positioning, treatment apparatus and imaging systems has improved through the introduction of robotics (Mazal et al., 1997; Allgower et al., 2007).

Several vendors are currently developing single-room proton therapy systems. Such systems have the advantage of providing an less expensive initial capital cost option compared to current proton therapy systems. The majority of the components required for such systems can be placed on or near a rotating gantry, reducing the size of the system as a whole. For large clinical facilities using several treatment rooms, a single cyclotron or synchrotron is used, meaning the beam can only be delivered to a single room at one point in time. Using a single-room system, the competition for beam is removed, as each room becomes self-sufficient. Additionally, should a problem be encountered in a system, it only forces the closure of that particular room rather than the entire facility. However, using multiple single-room systems may somewhat negate any capital cost advantage from this type of system. The cost of maintenance will
likely increase due to the presence of multiple accelerators compared to one in the traditional system.

Advances in accelerator technology may further improve the potential of proton therapy. The development of superconducting cyclotrons and synchrocyclotrons has resulted in higher proton energies being achieved from smaller systems. If the accelerators become small enough so that they can be installed on rotating gantries, the cost of a complex beam transport system will largely be negated. Dielectric wall accelerators (DWA), which are currently under development (Caporaso et al. 2008; Mackie et al. 2007), have the potential to accelerate protons to therapeutic energies over a relatively small distance. Compared to current accelerators which have an accelerating gradient of approximately 1-2MeV/m, a DWA can possess a gradient potentially as high as 100MeV/m. This implies that a DWA of length $\sim$2m will potentially be able to produce protons of high enough energy to treat any clinical site.

There is interest in using positron emission tomography (PET) for range verification in proton therapy (Parodi et al. 2007, 2008). Nuclear fragmentation reactions which occur during a routine proton treatment produce small amounts of $^{11}$C, $^{15}$O and $^{10}$C which are $\beta^+$ emitters that produce $\gamma$-rays when the decay. By comparing the measured activity pattern with a predicted pattern generated by either Monte Carlo simulations or treatment planning, the treatment delivery can be verified.

The realisation of these future developments and introduction of new technology has the potential to reduce the uncertainties in proton therapy, whilst also improving the overall quality of the treatments being delivered.
Chapter 3

Tissue equivalency of phantom materials for neutron dosimetry

3.1 Introduction

Secondary neutrons are produced in proton therapy through interactions of the primary beam with both the beam transport system and the patient (Paganetti, 2002). Neutrons deliver dose via charged secondary particles which have a high linear energy transfer (LET) (Moyers et al., 2008). This causes an increased risk of second cancer compared to other particle types with lower LET (Hall, 2006). Patients requiring radiotherapy for paediatric and intracranial cases are expected to gain additional benefits compared to photon treatments by using protons (St Clair et al., 2004; Miralbell et al., 2002; Lee et al., 2005; MacDonald et al., 2008; Baumert et al., 2004; Bolsi et al., 2003; Feuvret et al., 2007). The dose delivered by secondary neutrons in proton treatments has been measured previously using a number of different techniques (Schneider et al., 2002; Trompier et al., 2007; Wroe et al., 2007, 2009; Yan et al., 2002). In this study, the suitability of the tissue substitutes used for the measurement of the secondary neutron dose delivered during a proton therapy treatment is assessed, with a
particular emphasis on paediatric and intracranial treatments.

The dose from secondary neutrons has been experimentally measured previously for passive (Trompier et al., 2007; Wroe et al., 2007, 2009; Yan et al., 2002) and active (Schneider et al., 2002) beam delivery techniques, with lower doses reported using active delivery methods. Wroe et al. (2009) performed an investigation into the dose equivalent delivered outside the treatment field for a number of clinical field configurations using passive delivery methods. The results of their study showed that the dose equivalent outside the treatment field varies with the field size, beam energy and target site with clinically significant differences observed for different treatment configurations.

Monte Carlo simulations have also been employed to determine the dose from secondary particles (Fontenot et al., 2008; Moyers et al., 2008; Polf et al., 2005). Zacharatou Jarlskog et al. (2008) used Monte Carlo to investigate the organ specific neutron dose delivered throughout pediatric and adult phantoms undergoing proton treatments for brain lesions. The tissue compositions and densities used were those defined by the ICRP (1975).

Monte Carlo simulations allow the properties of the phantom material to be easily specified to match the characteristics of tissue. This is not a straightforward exercise for experimental studies which rely on the use of tissue substitutes. The question of the suitability of these tissue substitutes for neutron studies in proton therapy has not been previously addressed. To determine their suitability, the absorbed dose and dose equivalent from internally generated neutrons in common tissue substitutes and various ICRP tissues was compared.
3.2 Geant4 simulations

Monte Carlo simulations were performed using the Geant4 toolkit (version 4.9.2) \cite{Agostinelli:2003}. The simulations incorporated monoenergetic proton beams with an energy of 150 MeV and a lateral field size of 5 cm x 5 cm. The beams were normally incident upon targets of different chemical composition. Higher energy beams can be delivered at most proton facilities, but such energies are not commonly used in paediatric or intracranial cases. Whilst monoenergetic beams are not often used in a clinical setting, they were employed in this work as the bulk of the primary dose for a treatment incorporating a spread out Bragg peak is still delivered by the individual Bragg peak with highest energy \cite{Kooy:2003}. The primary objective of this study did not require the precise conditions observed in a clinical setting. Since the focus of the study was the investigation of the secondary particle production in the phantom material, a treatment nozzle was not modeled. As long as the same field was incident upon all target volumes, the conclusions of the study should be the same.

The tissue substitutes considered were Lucite, liquid water, solid water and A150 tissue equivalent plastic. The absorbed dose and dose equivalent from internally generated neutrons were compared in these substitutes and ICRP brain, muscle and adipose tissues. The physical properties of the phantoms and tissues used are shown in Table 3.1. Any interactions in a treatment nozzle or resulting from secondary particles generated outside the phantom materials were not considered. New accelerator technology such as the dielectric wall accelerator \cite{Caporaso:2008} will not require beam modification devices, reducing the fluence of secondary particles generated in the treatment nozzle. Each of the phantoms used were 30 cm x 42 cm x 10 cm. This phantom size was chosen to allow sufficiently large out-of-field distances to be simulated whilst retaining the possibility of reproduction in future experiments.

The measurement positions were separated into 5 different series (S1-S5). In se-
Table 3.1: Chemical composition of the phantoms used for the simulations. The composition of the tissue phantoms was taken from [ICRP (1975)]. The range of 150MeV protons in each of the materials is also included.

<table>
<thead>
<tr>
<th></th>
<th>H</th>
<th>C</th>
<th>N</th>
<th>O</th>
<th>P</th>
<th>Na</th>
<th>S</th>
<th>Cl</th>
<th>K</th>
<th>Ca</th>
<th>F</th>
<th>Density (g/cm³)</th>
<th>150MeV proton range (cm)</th>
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<tr>
<td>Adipose</td>
<td>11.4</td>
<td>59.8</td>
<td>0.7</td>
<td>27.8</td>
<td>0.1</td>
<td>0.1</td>
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<td></td>
<td>16.4</td>
<td></td>
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<td>14.5</td>
<td>2.2</td>
<td>71.2</td>
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<td>0.2</td>
<td>0.2</td>
<td>0.3</td>
<td>0.3</td>
<td>1.04</td>
<td>15.0</td>
<td>1.05</td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
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<td>14.3</td>
<td>3.4</td>
<td>71.0</td>
<td>0.2</td>
<td>0.1</td>
<td>0.3</td>
<td>0.1</td>
<td>0.4</td>
<td>1.05</td>
<td>15.2</td>
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<tr>
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<td>31.96</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>1.19</td>
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<tr>
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<td>2.4</td>
<td>19.84</td>
<td>0.13</td>
<td>2.32</td>
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<td></td>
<td></td>
<td>1.01</td>
<td>15.6</td>
<td></td>
</tr>
<tr>
<td>Liquid Water</td>
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<td>33.3</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td>A150</td>
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<td></td>
<td></td>
<td>0.17</td>
<td>1.12</td>
<td>14.0</td>
</tr>
</tbody>
</table>
3.2. Geant4 simulations

series S1, the neutron absorbed dose, average quality factor and dose equivalent were determined as a function of depth inside the primary field along the central axis. S1 measurements were taken every 4cm from 4-28cm depth. S2 gave these quantities at the same depths, but at a lateral distance of 5cm from the edge of the primary field. Measurement series S3, S4 and S5 gave the neutron absorbed dose, average quality factor and dose equivalent as a function of lateral distance from the field edge at depths of 4cm, 8cm and 12cm respectively. Measurements in series S3-5 were taken at 5cm intervals from 5-30cm lateral distance from the primary field edge. The sensitive volumes were of dimensions 2.5mm x 25.0mm x 0.5mm. The positioning and orientation of the sensitive volumes within each of the phantoms is shown in Figure 3.1. Each of the sensitive volumes had the same composition as the phantom being simulated.

Figure 3.1: The five series (S1-S5) of positions where absorbed dose, average quality factor and dose equivalent were calculated from internally generated neutrons. The arrow placed outside the phantom indicates the direction of the 5cm x 5cm 150MeV proton beam. Each of the sensitive volumes was 2.5mm x 25.0mm x 0.5mm in size.
3.2. Geant4 simulations

3.2.1 Determination of neutron dose equivalent

The ICRP suggests the use of a radiation weighting factor ($w_R$) to convert absorbed dose to dose equivalent [ICRP 2003]. Use of this weighting factor in radiotherapy applications can be considered as valid since the particle types, energies and dose rates being discussed out of field in radiation therapy are similar to those used in radiation protection. The ICRP weighting factor is a continuous distribution as a function of neutron kinetic energy. This is in contrast to the quality factor which is based on lineal energy [ICRU 1983]. The energy dependence of $w_R$ makes it a relatively easy quantity to implement in Monte Carlo simulations. Figure 1.7 shows $w_R$ as a function of energy in addition to the previous convention and the effective quality factor (denoted as qE).

The radiation weighting factor was calculated for each neutron passing through one of the sensitive volumes based on the definition given in [ICRP 2003]. This was then used to convert the neutron absorbed dose to dose equivalent using the following relationship

$$H = w_R \times D$$  \hspace{1cm} (3.1)

where $H$ is the neutron dose equivalent, $w_R$ is the average radiation weighting factor and $D$ is the neutron absorbed dose. The neutron absorbed dose was obtained through summation of the energy deposition resulting from neutrons in each of the sensitive volumes. As previously mentioned, neutrons deposit dose via charged secondary particles, often of high LET. Monte Carlo simulations allow separation of the charged secondary particles produced by neutrons from other particles which are otherwise identical. This separation is not easily achievable in experiments, making specific consideration of internally generated neutrons in an experimental setting difficult.
3.3. Results

3.2.2 Physics models

The electromagnetic standard package ($G4EmStandard$) \cite{Agostinelli2003} was employed to describe all electromagnetic interactions. The $G4BinaryCascade$ model \cite{Folger2004} was adopted to describe the hadronic interactions in the energy range of interest for proton therapy treatments. The $G4UHadronElasticProcess$ \cite{Ivanchenko2006} model was adopted to describe the elastic scattering of all long lived hadrons and ions. More information on the physics models used can be found in section 1.4.6. The Monte Carlo code was validated by comparing the range of 150MeV protons in Lucite using our Geant4 code and the NIST pStar database which gives the range of protons based on ICRU (1993). Agreement between the two sources was within 0.01mm.

3.3 Results

3.3.1 Neutron dose as a function of depth

Figure 3.2 shows the neutron absorbed dose and dose equivalent as a function of physical depth along the central axis of the primary field (S1). The highest levels of neutron absorbed dose and dose equivalent are found near the middle of the primary beam range. All the absorbed dose and dose equivalent values are below 0.125mGy/Gy and 1.417mSv/Gy respectively. Both A150 plastic and Lucite over estimate the neutron absorbed dose at proximal depths along the central axis compared to the tissues. The variation in the neutron dose equivalent along the central axis, shown in Figure 3.2b, is similar to the difference in absorbed dose. This suggests the difference in $w_R$ is relatively small. The mean percentage variation of $w_R$ for data series S1 and S2 are shown in Table 3.2.

Figure 3.3 shows the same quantities as Figure 3.2, but at 5cm lateral distance from
3.3. Results

Figure 3.2: Neutron absorbed dose (a) and dose equivalent (b) as a function of depth along the central axis of the primary proton field (series S1). The error bars represent one standard error.

the edge of the primary beam (S2) instead of along the central axis. The principal difference between series S1 and S2 is the decreased magnitude of the absorbed dose and hence dose equivalent in S2. In similarity to the S1, the neutron absorbed dose and dose equivalent is overestimated at proximal depths by A150 plastic and Lucite.
Table 3.2: Mean variation (%) in $w_R$ in data series S1 and S2. The uncertainties, shown in parentheses, are 1 standard deviation.

<table>
<thead>
<tr>
<th></th>
<th>Lucite</th>
<th>Liquid Water</th>
<th>Solid Water</th>
<th>A150</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICRP brain</td>
<td>-1.76(0.48)</td>
<td>1.24(0.20)</td>
<td>-8.12(2.32)</td>
<td>-4.38(1.44)</td>
</tr>
<tr>
<td>ICRP muscle</td>
<td>-1.34(0.39)</td>
<td>1.64(0.29)</td>
<td>-7.76(2.09)</td>
<td>-3.96(1.29)</td>
</tr>
<tr>
<td>ICRP adipose</td>
<td>-0.66(0.97)</td>
<td>2.30(0.93)</td>
<td>-7.01(1.31)</td>
<td>-3.24(0.81)</td>
</tr>
</tbody>
</table>

The percentage differences in neutron absorbed dose and dose equivalent between the phantom materials and ICRP tissues for data series S1 and S2 are shown in Table 3.3. The uncertainty at each of the data points used in these comparisons is less than 2%. The standard deviations of the mean values shown in Table 3.3 demonstrate that the magnitude of the variation between the phantoms and tissues changes moving to different positions within each of the data series. No clear trend was evident in the change in variation of the neutron absorbed dose and dose equivalent with respect to the position of measurement within the phantoms. Of the phantom materials considered, liquid water gives the best representation of the absorbed dose and dose equivalent in each of the tissues along the central axis. A150 plastic shows the worst agreement with each of the tissues at all the points considered.

### 3.3.2 Lateral to the primary field

The neutron absorbed dose and neutron dose equivalent as a function of lateral distance from the primary field edge at depths of 4cm, 8cm and 12cm (series S3-5) are shown in Figures 3.4, 3.5 and 3.6 respectively. The neutron absorbed dose decreases with increased lateral distance at each of the depths considered due to both the attenuation of the neutrons produced in the proton field and decreased level of neutron production occurring outside the primary radiation field. Whilst the magnitude of the doses observed out of field are smaller than those along the central axis, the variations
observed between the tissues and phantoms are generally larger. This is despite the smaller observed variations in $w_R$ out of field, shown in Table 3.4. Larger differences in $w_R$ were observed closer to the primary field, with all the phantom materials giving better approximations of the tissues further out of field. This improved correlation
### 3.3. Results

Table 3.3: Mean percentage differences in the neutron absorbed dose and dose equivalent in the phantom materials and ICRP tissues along the central axis (S1) and as a function of depth at 5cm lateral distance from the field edge (S2). The values in parentheses represent 1 standard deviation.

<table>
<thead>
<tr>
<th>Series</th>
<th>Lucite</th>
<th>Liquid Water</th>
<th>Solid Water</th>
<th>A150</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Absorbed dose</strong>:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICRP brain</td>
<td>17.94(14.12)</td>
<td>-1.18(4.24)</td>
<td>4.84(6.91)</td>
<td>27.65(6.71)</td>
</tr>
<tr>
<td>ICRP muscle</td>
<td>16.93(13.27)</td>
<td>-1.97(4.00)</td>
<td>4.10(6.89)</td>
<td>27.17(5.50)</td>
</tr>
<tr>
<td>ICRP adipose</td>
<td>18.91(29.54)</td>
<td>-2.67(10.31)</td>
<td>3.80(6.68)</td>
<td>25.82(14.72)</td>
</tr>
<tr>
<td><strong>Dose equivalent</strong>:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICRP brain</td>
<td>12.68(9.98)</td>
<td>0.28(4.62)</td>
<td>-3.40(9.09)</td>
<td>32.49(10.51)</td>
</tr>
<tr>
<td>ICRP muscle</td>
<td>12.49(9.21)</td>
<td>-0.03(3.94)</td>
<td>-3.71(8.59)</td>
<td>31.97(8.40)</td>
</tr>
<tr>
<td>ICRP adipose</td>
<td>18.98(30.37)</td>
<td>1.30(11.23)</td>
<td>-3.04(6.09)</td>
<td>35.21(27.42)</td>
</tr>
<tr>
<td><strong>S2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Absorbed dose</strong>:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICRP brain</td>
<td>11.14(13.30)</td>
<td>-1.28(6.78)</td>
<td>12.19(19.73)</td>
<td>24.25(15.92)</td>
</tr>
<tr>
<td>ICRP muscle</td>
<td>13.64(8.19)</td>
<td>1.61(10.87)</td>
<td>15.28(18.76)</td>
<td>26.98(14.40)</td>
</tr>
<tr>
<td>ICRP adipose</td>
<td>19.31(23.08)</td>
<td>5.04(8.43)</td>
<td>15.66(18.25)</td>
<td>26.73(18.75)</td>
</tr>
<tr>
<td><strong>Dose equivalent</strong>:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICRP brain</td>
<td>9.26(13.17)</td>
<td>-0.09(6.93)</td>
<td>-3.04(6.80)</td>
<td>18.67(10.58)</td>
</tr>
<tr>
<td>ICRP muscle</td>
<td>12.08(8.43)</td>
<td>3.15(10.96)</td>
<td>0.10(10.47)</td>
<td>22.05(9.06)</td>
</tr>
<tr>
<td>ICRP adipose</td>
<td>17.98(23.56)</td>
<td>6.86(8.72)</td>
<td>3.42(3.84)</td>
<td>27.85(20.81)</td>
</tr>
</tbody>
</table>

Further out of field may be due to a larger proportion of high energy neutrons present at these locations. The relationship of $w_R$ with neutron energy is such that if a high energy neutron incurs a small energy change $w_R$ undergoes remains relatively unchanged. This is in contrast to low energy neutrons, where a slight change in energy can lead to a large variation in $w_R$.

Table 3.5 shows the mean percentage differences between the phantom materials and ICRP tissues for the out of field data series (S3-5). The variation between the phantoms and tissues generally increased with increasing distance from the field edge. The uncertainty in the comparisons is less than 10% for lateral distances up to 20cm.
3.3. Results

Figure 3.4: Neutron absorbed dose (a) and dose equivalent (b) as a function of lateral distance from the field edge at 4cm depth (S3). The error bars represent one standard error.

For larger distances the uncertainty is higher, mainly due to the low number of neutrons observed at such distances. External to the primary field, the majority of dose observed was due to neutrons rather than other secondary particles or scattered primary protons, particularly at lateral distances greater than 15cm. In similarity to series S1 and S2,
3.3. Results

Figure 3.5: Neutron absorbed dose (a) and dose equivalent (b) as a function of lateral distance from the field edge at 8cm depth (S4). The error bars represent one standard error.

the A150 plastic phantom again shows the worst agreement with each of the tissues at all the points considered, except for ICRP muscle tissue in series S4, where liquid water showed a larger mean variation. Based on the percentage variation in each of the out-of-field data series, solid water shows the best agreement with ICRP brain
Figure 3.6: Neutron absorbed dose (a) and dose equivalent (b) as a function of lateral distance from the field edge at 12cm depth (S5). The error bars represent one standard error.

and muscle tissues whilst liquid water gives the best approximation of ICRP adipose tissue.
3.4 Discussion

This study determined the tissue equivalency of phantom materials used for dosimetry of secondary neutrons in proton therapy. This was achieved by comparing the absorbed dose and dose equivalent delivered by secondary neutrons generated within the various phantoms and tissues. These results also allow estimation of the contribution of internally generated neutrons to the total dose equivalent in homogeneous phantoms for proton energies related to pediatric treatments. Since the dose delivered by secondary particles generated internally cannot be avoided during a treatment, it is imperative that the magnitude of this dose is established. This study only considers homogeneous phantoms, but the total dose equivalent delivered during a treatment may be sensitive to the tissue types traversed by the primary beam.

The amount of neutron production within a medium is dictated by the reaction cross sections, which are in turn based on the chemical composition. The overestimation of the neutron absorbed dose in the tissues by Lucite and A150 plastic at proximal depths within the primary field is likely due to the higher carbon content in these materials compared to the ICRP tissues. The majority of the secondary neutrons observed in the simulations were produced from either carbon or oxygen. Solid water has higher carbon content than the tissues, but a lower percentage of oxygen counteracts this. As liquid water does not contain any carbon, this leads to large underestimation of the neutron doses in the tissues far out of field. A150 gives the

<table>
<thead>
<tr>
<th></th>
<th>Lucite</th>
<th>Liquid Water</th>
<th>Solid Water</th>
<th>A150</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICRP brain</td>
<td>0.18(0.85)</td>
<td>0.78(0.56)</td>
<td>-4.28(1.65)</td>
<td>-2.05(0.92)</td>
</tr>
<tr>
<td>ICRP muscle</td>
<td>0.47(1.02)</td>
<td>1.07(0.80)</td>
<td>-3.97(1.63)</td>
<td>-1.75(1.01)</td>
</tr>
<tr>
<td>ICRP adipose</td>
<td>0.44(0.86)</td>
<td>1.03(0.87)</td>
<td>-4.01(1.60)</td>
<td>-1.78(0.70)</td>
</tr>
</tbody>
</table>

Table 3.4: Mean variation (%) in $w_R$ out of field (series S3, S4 and S5). The values in parentheses are 1 standard deviation.
Table 3.5: Percentage differences in the neutron absorbed dose and dose equivalent in the phantom materials and ICRP tissues as a function of lateral distance from the field edge at 4cm (S3), 8cm (S4) and 12cm depth (S5).

<table>
<thead>
<tr>
<th></th>
<th>Lucite</th>
<th>Liquid Water</th>
<th>Solid Water</th>
<th>A150</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Series S3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absorbed dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICRP brain</td>
<td>34.63(80.82)</td>
<td>28.96(76.29)</td>
<td>21.98(54.11)</td>
<td>31.42(16.99)</td>
</tr>
<tr>
<td>ICRP muscle</td>
<td>8.20(21.54)</td>
<td>8.48(18.87)</td>
<td>6.34(16.24)</td>
<td>54.93(82.07)</td>
</tr>
<tr>
<td>ICRP adipose</td>
<td>11.65(31.83)</td>
<td>11.34(27.13)</td>
<td>10.05(27.24)</td>
<td>35.08(28.05)</td>
</tr>
<tr>
<td>Dose equivalent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICRP brain</td>
<td>-2.08(70.26)</td>
<td>29.77(75.88)</td>
<td>17.73(53.15)</td>
<td>53.01(82.05)</td>
</tr>
<tr>
<td>ICRP muscle</td>
<td>4.63(21.92)</td>
<td>9.63(19.26)</td>
<td>2.82(16.74)</td>
<td>29.89(16.97)</td>
</tr>
<tr>
<td>ICRP adipose</td>
<td>22.82(29.53)</td>
<td>12.31(27.83)</td>
<td>6.11(27.02)</td>
<td>33.17(27.92)</td>
</tr>
<tr>
<td><strong>Series S4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absorbed dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICRP brain</td>
<td>12.07(29.88)</td>
<td>-18.55(28.94)</td>
<td>3.75(19.95)</td>
<td>18.71(36.89)</td>
</tr>
<tr>
<td>ICRP muscle</td>
<td>4.45(23.58)</td>
<td>-21.65(28.14)</td>
<td>-1.04(21.01)</td>
<td>15.03(38.54)</td>
</tr>
<tr>
<td>ICRP adipose</td>
<td>22.27(29.62)</td>
<td>-6.41(35.28)</td>
<td>18.46(35.41)</td>
<td>37.82(49.10)</td>
</tr>
<tr>
<td>Dose equivalent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICRP brain</td>
<td>2.83(37.18)</td>
<td>-17.85(29.54)</td>
<td>-0.64(18.96)</td>
<td>16.19(36.46)</td>
</tr>
<tr>
<td>ICRP muscle</td>
<td>-0.11(29.49)</td>
<td>-20.85(28.69)</td>
<td>-5.14(19.93)</td>
<td>12.84(38.10)</td>
</tr>
<tr>
<td>ICRP adipose</td>
<td>22.82(29.53)</td>
<td>-5.33(35.77)</td>
<td>13.82(34.09)</td>
<td>35.45(48.48)</td>
</tr>
<tr>
<td><strong>Series S5</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absorbed dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICRP brain</td>
<td>27.86(16.61)</td>
<td>-12.58(18.76)</td>
<td>10.87(24.77)</td>
<td>37.15(12.83)</td>
</tr>
<tr>
<td>ICRP muscle</td>
<td>14.71(9.72)</td>
<td>-17.95(27.52)</td>
<td>-1.02(13.58)</td>
<td>23.98(16.20)</td>
</tr>
<tr>
<td>ICRP adipose</td>
<td>32.57(35.82)</td>
<td>-11.26(20.34)</td>
<td>17.62(48.97)</td>
<td>42.67(37.04)</td>
</tr>
<tr>
<td>Dose equivalent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICRP brain</td>
<td>20.66(10.18)</td>
<td>-11.82(19.02)</td>
<td>5.84(24.67)</td>
<td>33.88(12.69)</td>
</tr>
<tr>
<td>ICRP muscle</td>
<td>12.82(6.69)</td>
<td>-16.83(27.88)</td>
<td>-5.10(13.15)</td>
<td>21.63(15.14)</td>
</tr>
<tr>
<td>ICRP adipose</td>
<td>33.34(37.27)</td>
<td>-10.03(20.85)</td>
<td>13.03(48.93)</td>
<td>39.99(36.90)</td>
</tr>
</tbody>
</table>

The dose equivalents reported in this work are all less than approximately 1.5mSv/Gy, which is smaller than the doses reported in previous studies [Schneider et al., 2002; Trompier et al., 2007; Wroe et al., 2007; Yan et al., 2002; Fontenot et al., 2008; Moyers].
3.4. Discussion

particularly those which used passive methods of beam delivery. This is because the major contributor to the total neutron dose experienced in proton therapy is the treatment head, which can produce up to 99% of the total number of neutrons for small fields (Zacharatou Jarlskog et al., 2008). For conversion of neutron absorbed dose to neutron dose equivalent, $w_R$ was used rather than the quality factor. The radiation weighting factor was introduced by the ICRP as a simplification of the quality factor which is based on requires convolution with microdosimetric spectra to obtain dose equivalent. The average neutron radiation weighting factor can be derived directly from neutron energy spectra which are relatively simple to obtain in Monte Carlo simulations. While both methods of determining the dose equivalent are based on derivation of $w_R$ and $Q$ from biological experiments, the values reported here for internally generated neutrons may not correspond to those present in experimental studies obtained with microdosimetry techniques.

Resonance of the neutron cross sections in some energy ranges imply that in reality, $w_R$ as a function of energy is not completely smooth. Additionally, the numerical conversion of the quality factor into $w_R$ is not precise. However, this is not significant due to the inherent uncertainty in the interpolation between the quality factor data of Mares et al. (1997) and Pelliccioni (1998) in the energy range of 20-50MeV. Within this energy range, there is a region where the value of $Q$ remains close to constant which is not reflected in the definition of $w_R$. This could lead to a slight discrepancy between results obtained using the two quantities for radiation fields with a large high energy neutron component (ICRP 2003). In these simulations, the majority of neutrons produced in the phantoms were of energy less than 10MeV, implying that this potential uncertainty in the relationship between $w_R$ and quality factor will not be significant here.

There is potentially some additional uncertainty introduced into Monte Carlo sim-
3.5 Conclusion

The aim of this study was to determine the most suitable phantom material for secondary neutron dosimetry studies in proton therapy. To fully comprehend the significance of the phantom material for neutron dosimetry, actual detectors need to be simulated or used experimentally in different phantom materials. This work has evaluated the dose in different materials and tissues, not the dose obtained in tissue equivalent detectors in the different materials.

The results of this study show that the dose due to secondary neutrons gen-
3.5. Conclusion

ated internally will vary based on the tissues traversed by the primary proton beam. Compared to previous studies, the neutron dose equivalents reported here are small, suggesting that internally generated neutrons are not the primary contributor to the total dose equivalent in proton therapy. The differences observed suggest that using different phantom materials could potentially impact on the final values of neutron absorbed dose and dose equivalent measured in experimental studies. The magnitude of the observed variations between the phantoms and tissues may alter when neutrons generated in the treatment head are also taken into account. Of the phantom materials simulated, solid water gives the smallest mean variation with each of the tissues considered in the positions where the neutrons are the primary contributor to the total dose. Thus, it is recommended that secondary neutron dosimetry in proton therapy, particularly out of field, be performed using solid water phantoms.
Chapter 4

Monte Carlo simulations of pencil beam scanning proton therapy

4.1 Introduction

Previous work by Paganetti et al. (2004) has demonstrated the ability of simulating double scattering proton therapy treatments using the Geant4 Monte Carlo toolkit (Agostinelli et al., 2003). They showed that modelling the treatment nozzle with sub-millimetre accuracy allows the simulation of dose distributions from SOBP fields with an accuracy, in terms of range and modulation, of less than a millimetre. The excellent agreement in the previous work by Paganetti et al. (2004) demonstrates the potential use of Monte Carlo simulations to generate beam data for use in the commissioning of treatment planning systems.

The aim of the current work is to implement the treatment nozzle for pencil beam scanning (PBS) into a Geant4 Monte Carlo code (Agostinelli et al., 2003) which will allow accurate simulations of clinical PBS fields. This work will allow simulation of the dose delivered to patients undergoing a PBS treatment and to determine changes in dose distributions when perturbations are introduced into the PBS hardware.
4.2 Method

4.2.1 Modeling of the PBS nozzle

The various components of the PBS nozzle were modeled in the Geant4 code (version 4.9.0.p01) based on the specifications provided by the manufacturer (Ion Beam Applications, Louvain La Neuve, Belgium). Figure 4.1 shows the geometry implemented in the Monte Carlo code.

The beam initially passes through a vacuum chamber before entering the quadrupole magnets. The quadrupoles do not steer the pencil beam, rather they are used to focus the beam at isocentre, decreasing the spot size. The geometry of the quadrupole magnets is currently implemented in the Monte Carlo code with the magnetic field turned off. The field is not turned on as the quadrupoles are not currently commissioned for clinical use on the actual PBS nozzle. Once this is achieved on the clinical nozzle, the field can be initialised in the Monte Carlo with minimal difficulty.

After the quadrupoles, the beam passes through the first and second scanning
magnets which scan the pencil beam in the x and y directions respectively. The Monte Carlo code reads in the spot positions via an input file which is directly generated by Astroid, the treatment planning system used for PBS at MGH (Kooy et al. 2010).

After passing through the scanning magnets, the beam then passes through the ionisation chambers which are used in the clinical nozzle to monitor spot position and dose and finally passes through the snout. Each of the different snout sizes available in the clinic had been previously modeled in the Monte Carlo for the double scattering system (Paganetti et al. 2004) and the same models are adopted here. Since there may be clinical cases in which apertures or compensators are required (Kooy et al. 2010), the Monte Carlo code also has the capability of including these patient specific devices in the simulations.

4.2.2 Monte Carlo specifications

Figure 4.2 shows the flow of information from the treatment planning system (TPS) to the proton therapy system and/or scanning Monte Carlo.

The treatment plan is initially generated using the TPS. This then is input into the TRAjectory Manipulation Program (TRAMP) which orders the spots and generates the PBS Layer Definition (PLD) file. This PLD file is then used by “Convalgo” to generate equipment layer files (equiplayer files) that include all the properties of the beam which will be delivered by the proton therapy system. The PLD file is also read into the scanning Monte Carlo, allowing simulation of any clinical field which can be delivered by the proton therapy system. The scanning Monte Carlo can either be used to simulate detectors in a phantom material for comparison with measurements or upon importing patient CT data, can be used to simulate the dose delivered to the patient.
4.2. Method

Figure 4.2: Full capabilities of the scanning Monte Carlo and the information flow from the treatment planning system and hardware.

4.2.2.1 PBS layer definition file

The PLD file from TRAMP is the input to the Monte Carlo. This file has the complete trajectory of the beam including the beam position as a function of time. The PLD file is converted to an intermediate “scanfile”, via a MATLAB script. The scanfile is then directly read into the Monte Carlo code. The hardware at MGH is capable of scanning in the general sense and the Monte Carlo has this capability also. Continuous scanning is simulated by moving the beam between two specified positions with current delivered while the beam is moving. Spot scanning is a subset of generalised scanning and is performed by delivering zero current whilst the beam is moving and inserting time at
the required spot position with zero charge before and after any spot to guarantee the centroid of the beam is stationary during the spot.

An example PLD file is shown in Figure 4.3

Figure 4.3: Example PLD file

4.2. Method

4.2.2.2 Nozzle variables

A secondary input file is used to specify all variables in the Monte Carlo simulation which do not vary with time. These include:

(i) gantry number

(ii) snout size and extension

(iii) physics settings

(iv) total number of particles to simulate

(v) flag to insert or remove IC1

(vi) flag to insert or remove quadrupole magnets
Components of the simulation which vary with time are all specified in the PLD file.

### 4.2.2.3 Generation of protons

The simplest way of generating a proton field in Monte Carlo simulations is to have a parallel beam at the top of the nozzle and adjust its width to match the measured width at isocentre. A more realistic solution is to use Twiss parameters. Twiss parameters \((\alpha, \beta, \gamma)\) are used to express an ellipse in mathematical space which governs the generation of protons. Figure 4.4 shows the representation of the Twiss parameters.

![Diagram of Twiss parameters](image.png)

**Figure 4.4:** Diagram of Twiss parameters implemented to express the generation of protons in the scanning Monte Carlo simulations.

The Twiss parameters specify the generation of the protons at the nozzle entrance. The position of the proton is determined based on a Gaussian distribution. Once the position of the proton is determined, the initial angle of the proton trajectory is specified based on another Gaussian distribution. This gives a proton beam which is more realistic than generating a beam from a single point or area.

The equation of the ellipse in mathematical space is given in equation 4.1. This
equation specifies the ellipse at $N\sigma$ of the Gaussian distribution which governs the position of the proton generation.

$$\gamma x^2 + 2\alpha x \theta + \beta \theta^2 = \epsilon$$

(4.1)

$\alpha$ is a unitless quantity which controls the rotation of the ellipse. The spatial spread is controlled by $\beta$, which has units of mm/rad. The parameter $\gamma$ is defined by equation 4.2 and $\epsilon$ is the emittance.

$$\gamma = \frac{1 + \alpha^2}{\beta^2}$$

(4.2)

The Twiss parameters are quadratic functions of range (g/cm$^2$) and also have a gantry angle dependence. Equations 4.3 and 4.4 show how the parameters are expressed in the Monte Carlo.

$$\alpha_x = \alpha_1 R^2 + \alpha_2 R + \alpha_3$$
$$\beta_x = \beta_1 R^2 + \beta_2 R + \beta_3$$
$$\epsilon_x = \epsilon_1 R^2 + \epsilon_2 R + \epsilon_3$$

(4.3)

$$\alpha_y = \alpha_4 R^2 + \alpha_5 R + \alpha_6$$
$$\beta_y = \beta_4 R^2 + \beta_5 R + \beta_6$$
$$\epsilon_y = \epsilon_4 R^2 + \epsilon_5 R + \epsilon_6$$

(4.4)

Fine tuning of the $\beta$ and $N$ parameters was required to match the values obtained from simulation to those obtained from measurements using a Wellhofer MatriXX
detector (IBA Dosimetry) at isocentre in air. This ensured that spot size in the Monte Carlo code matched that of the actual PBS beamline.

The energy spread of the beam at nozzle entrance was determined by minimising the $\chi^2$ of the Monte Carlo results against experimental data. When combined with the Twiss parameters, this allows the specification of all required properties of the proton beam.

The scanning Monte Carlo includes a time dependence. Each proton simulated is assigned a $t$ between 0 and $t_{\text{max}}$, the start and end of the field, respectively. The time taken to deliver each spot is defined directly from the PLD. The dose deposited can then be plotted as a function of time, which is in contrast to having only the total dose deposited in a field, as in other existing Monte Carlo codes. Time is not an important consideration for double scattering, as the entire lateral field is delivered simultaneously (essentially). The methodology used for PBS, or any other scanning technique, means that different areas of the field are delivered at different times. The inclusion of time will be important for studies incorporating motion and interplay effects between individual pencil beams.

### 4.2.3 Magnetic fields

The magnetic fields modeled in the nozzle quadrupole and scanning magnets are modeled as uniform fields filling the magnet volume with zero magnetic field outside the magnets. That is the edges are abrupt and the magnetic field strength drops immediately from 100% to 0%. The field centres are defined based on drawings provided by the manufacturer (Ion Beam Applications). The lengths of the field are defined by the effective lengths of the two scanning magnets. This methodology was also adopted in a previous study by Peterson et al. (2009). As the lateral position of the beam is directly related to the magnetic field strength, the field strength was calibrated in
the Monte Carlo to ensure that the lateral spot position predicted by the simulation
matched that requested by the planning system.

As protons, or other particles, traverse the magnetic fields, their maximum step
size is restricted to 2mm. Monte Carlo simulations typically model particle trajectories
as a series of straight lines. Restricting the maximum step ensures accurate modeling
of the curved trajectory of charged particles through the magnetic fields.

4.3 Calibration and validation

Once all relevant nozzle components and physics models are implemented, it is of
paramount importance that the code is tested to ensure that the results gained from
the simulation are accurate.

4.3.1 Lateral position

The magnetic fields in the two scanning magnets was calibrated to ensure the lateral
spot positions specified in the PLD file were accurately delivered in the Monte Carlo.
This involved scaling the magnitude of the magnetic field until the spots were delivered
in the required position with sufficient accuracy. The amount of deflection required
from the magnetic fields is energy dependent. Higher energies require stronger mag-
netic fields to achieve the same lateral deviation. Figure 4.5 shows an example of the
field irradiated for the calibration of the magnetic fields.

The spots shown are five distinct spots delivered at different lateral positions
and are a superposition of the simulation of beams of range 8.92g/cm², 12.64g/cm²,
15.92g/cm², 21.1g/cm² and 25.15g/cm². These ranges correspond to nominal ener-
gies of 95.69MeV, 112.53MeV, 138.08MeV, 156.67MeV and 174.74MeV respectively.
In Figure 4.5 the beam is traveling into the page. The good overlap of the spots
demonstrates that the magnetic field strength is varying correctly with energy. Com-
4.3. Calibration and validation

Figure 4.5: Calibration of magnetic fields to control lateral position of the proton beam in the Monte Carlo simulations. The units on the colour scale are relative.

pared with the lateral positions specified in the PLD, the accuracy of the Monte Carlo is better than a millimetre. Comparisons were made between the Monte Carlo and the PLD file rather than directly with measurements as day-to-day fluctuations in the experimental system imply that if the Monte Carlo correlates well with a single measurement, it may not for others. Using the PLD gives a “gold standard” to which both Monte Carlo and experimental measurements can be compared.

4.3.2 Depth dose characteristics

Depth dose curves were measured using a Bragg peak chamber (PTW Freiburg GmbH). The Bragg peak chamber is a plane-parallel chamber and has an entrance window of diameter 84mm. The depth dose curves were measured in a water tank for pencil beams at five different ranges, 8.92g/cm$^2$, 12.64g/cm$^2$, 15.92g/cm$^2$, 21.1g/cm$^2$ and 25.15g/cm$^2$. Pencil beams were used to ensure that the majority of the scatter which occurred in the water was still measured by the Bragg peak chamber. The depth
dose curves are shown in Figure 4.6. The dose was scored in the Monte Carlo using cylindrical voxels of radius 4cm and thickness 0.2mm to match the lateral dimension of the Bragg peak chamber. The results shown in the figure are the average of 10 independent simulations. The uncertainty in the depth-dose curves was defined as the standard deviation of the 10 simulations and is less than 1% at all depths for all the ranges considered. The experimental measurement points using the Bragg peak chamber are represented as open squares in the figures. Emphasis was placed on taking measurements close to the Bragg peak and on the distal edge.

The results of the depth dose curves demonstrate good agreement between the measurement and simulation data. The initial energy spread at nozzle entrance ($\Delta E$) was determined by minimising the $\chi^2$ value of a series of Monte Carlo simulations with different $\Delta E$ values against the experimental data. Figure 4.7 shows the results of the calibration of the energy spread and a quadratic fit to the data. The equation of the fit is given in equation (4.5). The data in Figure 4.7 is expressed in terms of energy rather than range, as the properties of the protons generated in the Monte Carlo are defined in terms of energy. Expressing the $\Delta E$ in terms of energy allows the energy spread to be easily implemented in the code without the need for conversion from range. This fit is also embedded in the code and is not altered for different protons or simulations.

$$\frac{\Delta E}{E} (%) = 0.000047 \times E^2 - 0.020925 \times E + 2.600232 \quad (4.5)$$

This equation has been implemented in the Monte Carlo code to specify the energy spread as a percentage in terms of the primary beam energy.

### 4.3.3 Complex irradiation

A complex irradiation was then simulated to test a number of facets of the simulation code. This test pattern was compared to an experimental measurement using the
Figure 4.6: Depth dose curves for five different ranges. The solid line is the Monte Carlo data and the squares represent experimental data points. The Monte Carlo results are averages of 10 independent simulations. The uncertainty in the Monte Carlo is < 1% at all points.
4.3. Calibration and validation

Figure 4.7: Fit of ∆E as a percentage of the proton beam energy. The closed circles represent the five different values optimised and the broken line is a quadratic fit to the data.

Beam Imaging System (BIS) (Ion Beam Applications Dosimetry) at isocentre in air. The BIS uses a 30cm × 30cm scintillator and a CCD camera to capture the image. The energy deposition in the Monte Carlo simulation was obtained at isocentre in air using a 30cm × 30cm × 0.2cm volume of water with the maximum step size restricted to 0.02mm and the front face placed at isocentre. The lateral voxel size used in both the experiment and Monte Carlo simulation was 0.73mm × 0.73mm.

Figure 4.8 shows the results of the Monte Carlo simulation of the test pattern. The test pattern verifies the Monte Carlo (and the beamline) by combining position, stability, spot size and dose delivery checks into a single field. The dose was normalised to the maximum dose observed for both the simulated and experimental data. The two plots were then compared via gamma analysis [Low et al., 1998]. The gamma analysis is a distance-to-agreement comparison which aims to find an agreement in the dose within a prescribed value within a given distance. The equation of the ellipsoid...
used for acceptance criteria is presented in equation (4.6).

\[ \Gamma(R, D) = \sqrt{\frac{r^2}{R^2} + \frac{d^2}{D^2}} \]  

(4.6)

where \( r \) is the distance to agreement, \( R \) is the distance to agreement criteria, \( d \) is the dose difference and \( D \) is the dose difference criteria. If the value of \( \Gamma(R, D) \) is less than 1, the test passes, otherwise it fails.

When comparing the simulation and experimental data in this work, 100% of the points passing the 1mm/1% criteria. The irradiation of the test pattern and comparison via the gamma analysis tests the lateral position, spot size, beam penumbra and the dose delivery. The result of the gamma analysis test confirms that the beamline geometry and physics models have been implemented and calibrated to a high level of accuracy.
4.4 Conclusion

A dedicated Monte Carlo code has been developed for pencil beam scanning simulations based on the beamline at the Francis H. Burr Proton Therapy Center at Massachusetts General Hospital.

Depth-dose curves were compared with experimentally measured data for a number of beam ranges. The energy spread at nozzle entrance was calibrated to ensure the width of pristine Bragg peaks in the simulations match those observed in experiments. A quadratic fit of the energy spread at nozzle entrance in terms of primary proton energy has been implemented in the simulation code.

Good agreement with measurements have been observed for depth-dose curves at a number of different energies. The magnetic fields have been calibrated to ensure that the lateral position of the spots delivered in a simulation match the prescribed positions in the PLD with sub-millimetre accuracy. A complex 2D irradiation was completed to test all aspects of the simulation code apart from the depth-dose characteristics. When compared to a measurement of the same field, 100% of points passed a 1%/1mm gamma index test, confirming the calibration of the magnetic fields.
Chapter 5

Monte Carlo simulations of secondary neutron doses in proton therapy

5.1 Introduction

There is a trend in the proton therapy community to move away from the traditional double scattering method of delivery toward scanning. The energy of the proton beam is altered so conformality can be achieved in three dimensions. In contrast to double scattering, scanning has the ability to conform the dose to both the proximal and distal edges of the target (Lomax et al., 2004). Scanning also reduces the need for patient specific hardware which is required in double scattering (Kooij et al., 2010). Scanning does not require the use of scatterers and collimators to conform the beam to the target leading to a decrease in the number of proton interactions occurring in the nozzle. This leads to a lower neutron dose from scanning techniques (Schneider et al., 2002) which may be clinically significant due to the high radiobiological effectiveness of neutrons. The technique of scanning uses magnetic fields in the nozzle to scan a
narrow proton pencil beam over the target in two dimensions.

Monte Carlo calculations have been used in a number of studies in double scattering proton therapy. Previous studies have employed Monte Carlo for examination of the dose delivered by primary and secondary particles (Paganetti 2002). Given sufficient computing power, there is also potential in the use of Monte Carlo simulations for treatment planning (Paganetti et al. 2008). Paganetti et al. (2004) have previously demonstrated that accurate modeling of a double scattering proton therapy nozzle allows for accurate reproduction of measured dose distributions.

The majority of previous Monte Carlo studies have approximated scanning proton beams by simulating double scattering fields and ignoring the contribution of secondary particles generated in the nozzle. This methodology has been termed the “passive-internal” approximation. These methods may not be satisfactory as the use of patient specific hardware (apertures and compensators) in double scattering gives a sharper penumbra than that typically observed in scanning. Thus, it is expected that the dose distributions obtained using the “passive-internal” dose will differ from that yielded from a realistic scanning nozzle. The primary focus of this work is to generate an accurate Monte Carlo model of the pencil beam scanning (PBS) delivery at the Francis H Burr Proton Therapy Center, Massachusetts General Hospital using the Geant4 Monte Carlo toolkit (Agostinelli et al. 2003).

5.2 Method

5.2.1 Geant4 simulations

A series of Monte Carlo simulations were performed using the Geant4 toolkit (Agostinelli et al. 2003) for a clinical prostate field. The same field properties, see Table 5.1 were used for all the simulations.
5.2. Method

Table 5.1: Properties of the clinical prostate fields used in the Monte Carlo simulations.

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_{90}$</td>
<td>28.8 g/cm$^2$</td>
</tr>
<tr>
<td>$M_{90-90}$</td>
<td>10.4 g/cm$^2$</td>
</tr>
<tr>
<td>FieldSize</td>
<td>45.2 cm$^2$</td>
</tr>
</tbody>
</table>

Simulations were performed for both double scattering and pencil beam scanning methods of delivery. The double scattering simulations used the Monte Carlo code previously described by Paganetti et al. (2004). The full double scattering beamline at the Francis H. Burr Proton Therapy Center, Massachusetts General Hospital (MGH) was included in the simulations. In addition to the full double scattering simulations, the “passive-internal” approximation was simulated. These simulations used the double scattering code, but ignored the contribution of the secondary particles generated in the nozzle. The pencil beam scanning simulations were performed using the code outlined in Chapter 4. As mentioned previously, the use of patient-specific hardware leads to a sharper penumbra for double scattering treatments compared to pencil beam scanning. There are cases where such hardware will be used in pencil beam scanning treatments (Kooy et al., 2010) and thus such simulations were performed. These simulations used the clinical pencil beam scanning field with the patient-specific hardware used for the double scattering fields. A Lucite phantom of size 90cm x 26cm x 37.76cm was used in all the simulations. Figure 5.1 shows the Lucite phantom used in the simulations and the relative size of the primary proton field.

The absorbed dose was scored in sensitive volumes throughout the Lucite phantom. To increase the statistics, larger volumes were used out-of-field where the dose gradient is not as steep. The volume sizes varied based on the lateral distance ($x$) from the field edge. The sizes used were $3.8 \times 3.8 \times 1.1 \text{ mm}^3$ ($x \leq 5 \text{ cm}$), $7.6 \times 7.6 \times 1.1 \text{ mm}^3$ ($5 \text{ cm} < x \leq 20 \text{ cm}$) and $15 \times 15 \times 1.1 \text{ mm}^3$ ($x > 20 \text{ cm}$).

The distances from the lateral field edge simulated were 2.5cm, 5cm, 7.5cm, 10cm,
5.2. Method

Figure 5.1: Schematic showing the 90cm x 26cm x 37.76cm Lucite phantom used in the simulations. The red circle shows the aperture size used in the double scattering simulations and the field size prescribed in the pencil beam scanning simulations.

15cm, 20cm, 30cm, 40cm and 50cm. This allowed the doses to be calculated close to the field edge and further out-of-field.

Figure 5.2: Diagram of the detector positions simulated. The black rectangles show the position, orientation and relative size of the detector volumes. The size of the detector volumes used varied based on the distance from the field edge (x) and were $3.8 \times 3.8 \times 1.1 \text{ mm}^3$ ($x \leq 5\text{cm}$), $7.6 \times 7.6 \times 1.1 \text{ mm}^3$ ($5\text{cm} < x \leq 20\text{cm}$) and $15 \times 15 \times 1.1 \text{ mm}^3$ ($x > 20\text{cm}$). The red section shows the area of the phantom irradiated by the primary field and a depth-dose curve indicates the modulation width of the SOBP.

The results of the simulations were normalised based on the size of the detector
volumes. The absorbed dose was scored in each of the sensitive volumes. As discussed in section 1.3.5, different types of radiation have varying effects on tissue. To account for this, the absorbed dose was scored based on particle type. The absorbed dose due to protons, neutrons and photons was tallied separately. Neutron energy spectra were also collected during the Monte Carlo simulations which allowed calculation of the average radiation weighting factor, $w_R$, based on the definition of the ICRP. The neutron energy spectra were collected in 1MeV bins from 0MeV to the energy of the primary beam. The energy spectra were convolved with the ICRP definition of $w_R$ to obtain the average neutron radiation weighting factor at each measurement point. The average neutron weighting factors were then used in addition with the factors for protons and photons to convert the absorbed dose to dose equivalent. The dose equivalent is calculated at each point using equation 5.1.

$$H = 2D_p + w_RD_n + D_{\gamma}$$

where $D_p$, $D_n$ and $D_{\gamma}$ are the absorbed doses from protons, neutrons and photons respectively. As outlined in section 1.5 the radiation weighting factor assigned to photons is 1 and protons have a factor of 2 which accounts for secondary particles which deposit dose locally such as $\delta$-electrons.

5.2.2 Geant4 physics

The physics used in these simulations was previously outlined in section 1.4.6.

The standard electromagnetic package ($G4EmStandard$) [Agostinelli et al., 2003] was used for the description of electromagnetic interactions. Hadronic interactions were modeled using a binary cascade ($G4BinaryCascade$) [Folger et al., 2004]. The $G4UHadronElasticProcess$ [Ivanchenko, 2006] model was adopted to describe the elastic scattering of all long lived hadrons and ions.
A range cut value of 0.05mm was used for photons, electrons and positrons throughout this study. Protons were tracked to the end of their range. The Geant4 High Precision Package (Wellisch 2005) was employed for the simulation of neutrons of energies below 20MeV down to thermal energies.

To increase the accuracy of the modeling of the curved proton trajectories through the scanning magnets, the maximum step size was restricted to 2mm.

5.3 Results

5.3.1 Proximal to the SOBP

Figures 5.3, 5.4, 5.5 and 5.6 show the absorbed dose (a) and dose equivalent (b) at depths of 0cm, 4.72cm, 9.44cm and 14.16cm respectively.

5.3.1.1 Absorbed dose

The absorbed dose from pencil beam scanning with an aperture is an order of magnitude lower than all other techniques at 2.5cm from the field edge at the phantom entrance. Moving further from the field edge, the different modalities separate. At a depth of 4.72cm, the absorbed dose at 2.5cm out-of-field is \( \sim \)3 times higher for scanning than passive and passive-internal. The absorbed dose in scanning is 5 times higher than double scattering at 2.5cm from the field edge at a depth of 9.44cm. The magnitude of the absorbed doses at 14.16cm depth are approximately double the doses observed at 9.44cm. There is consistency between the passive and passive-internal curves for depths less than 7.5cm from the field edge, suggesting the component of the absorbed dose from the treatment nozzle is diminished compared to shallower depths. For distances greater than 10cm from the field edge, the passive-internal and scanning curves match within the uncertainty levels. Both of these modalities give lower out-of-
field doses than double scattering at all depths proximal to the SOBP. This suggests the secondary particle component from the treatment nozzle is significant at all depths proximal to the SOBP.

For lateral distances less than 10cm from the field edge, the penumbra from the scanning beam dominates the total dose equivalent. At greater distances, the contribution of the penumbra is not significant and the absorbed dose from scanning becomes less than double scattering. Including an aperture at the exit of the treatment nozzle reduces the penumbra width as seen in Figures 5.3(a), 5.4(a), 5.5(a) and 5.6(a). Incorporating an aperture reduces the absorbed dose at 2.5cm lateral field edge at all depths proximal to the SOBP by an order of magnitude. It also reduces the total absorbed dose for lateral distances up to 10cm, where primary particles provide a significant contribution when the aperture is not included. Further out-of-field, where the absorbed dose is dominated by internally produced secondaries, the use of an aperture is not as significant.

5.3.1.2 Dose equivalent

The dose equivalent at the phantom entrance is shown in Figure 5.3(b). These curves include the radiation weighting factors, which leads to greater separation of the different data series. The difference in the dose equivalent for double scattering compared to for passive-internal and scanning is larger than the difference in absorbed dose. This is primarily due to the larger neutron contribution from the treatment nozzle in double scattering which leads to a higher average radiation weighting factor compared to the other techniques. The separation between the double scattering data and the other data series is also increased compared to the absorbed dose data at depths of 4.72cm (Figure 5.4(b)), 9.44cm (Figure 5.5(b)) and 14.16cm (Figure 5.6(b)). Despite the higher radiation weighting factor for double scattering, scanning still gives a higher dose equivalent close to the field edge, due to the wider penumbra. The
scanning penumbra dominates for positions close to the field edge, however for lateral
distances greater than 5cm, the passive-internal and scanning curves correlate within
the uncertainty limits.

Using an aperture for scanning significantly decreases the dose equivalent in scan-
ing for distances less than 15cm from the field edge. For larger values, the values
agree with the simulations which did not incorporate an aperture within $2\sigma$. The
number of neutrons increases using an aperture due to the proton interactions occur-
ing in the brass aperture. The results presented in figures 5.3(b), 5.4(b), 5.5(b) and
5.6(b) demonstrate that any increase in dose equivalent due to the increase in neutron
fluence is more than offset by the large decrease in the dose equivalent from primary
protons.

5.3.2 Within the SOBP

5.3.2.1 Absorbed dose

Figures 5.7(a) and 5.8(a) show the absorbed dose at depths of 18.88cm and 23.60cm.
The absorbed dose close to the field edge is again clearly higher in scanning than the
other techniques. In similarity to the depths proximal to the SOBP, once out of the
penumbra, the scanning data matches well with the passive-internal data. The ab-
sorbed dose from double scattering is significantly higher than scanning at all distances
greater than 10cm from the field edge. The passive-internal and scanning curves match
well for all lateral distances except close to the field edge where the penumbra of the
scanning beam is significant.

Using an aperture significantly reduces the absorbed from scanning for lateral dis-
tances up to 20cm from the field edge at depths within in the SOBP. At 2.5cm from the
field edge, the absorbed dose is reduced by more than an order of magnitude when the
aperture is used. For larger distances, the benefit of an aperture is not as pronounced
5.3. Results

(a) absorbed dose

(b) dose equivalent

Figure 5.3: Absorbed dose and dose equivalent at different lateral distances from the field edge at the phantom entrance. The data shown is for the double scattering (squares), passive-internal approximation (△), pencil beam scanning (circles) and scanning with an aperture (∇). The error bars represent two standard deviations.
Figure 5.4: Absorbed dose and dose equivalent for double scattering (squares), passive-internal approximation (Δ), pencil beam scanning (circles) and scanning with an aperture (∇) at different lateral distances from the field edge at a depth of 4.72cm. The error bars represent two standard deviations.
5.3. Results

(a) absorbed dose

Figure 5.5: Absorbed dose and dose equivalent for double scattering (squares), passive-
internal approximation (△), pencil beam scanning (circles) and scanning with an apen-
ture (▽) at different lateral distances from the field edge at a depth of 9.44cm. The
error bars represent two standard deviations.

(b) dose equivalent
5.3. Results

Figure 5.6: Absorbed dose and dose equivalent for double scattering (squares), passive-internal approximation (△), pencil beam scanning (circles) and scanning with an aperture (▽) at different lateral distances from the field edge at a depth of 14.16cm. The error bars represent two standard deviations.
due to the higher contribution of internally produced secondary particles.

5.3.2.2 Dose equivalent

The dose equivalent curves are essentially indistinguishable for the passive-internal, scanning and scanning with an aperture data for lateral distances greater than 20cm. Between 10cm and 20cm the curves are relatively similar, but for closer distances, the scanning penumbra contributes significantly to the total dose. The higher dose equivalent values observed for the double scattering data again highlights the significant contribution of neutrons generated in the treatment nozzle. The dose equivalent from double scattering is significantly higher than all other techniques for all lateral distances greater than 5cm from the field edge.

As with the other depths and positions considered, using the aperture significantly reduces the dose equivalent for scanning. The difference between scanning and the passive-internal curve is smaller when considering dose equivalent rather than absorbed dose. This is likely due to the contribution of neutrons generated via interactions in the brass aperture.

5.3.3 Distal to the SOBP

The contribution of protons to the total absorbed dose and dose equivalent distal to the SOBP is zero due to their finite range. The doses observed at these positions are due to either secondary neutrons or photons. Interestingly, the absorbed dose and dose equivalent from double scattering is still significantly higher than scanning at both depths and all lateral positions considered distal to the SOBP. As the depth in the phantom increases, the relative contribution from internally generated secondaries increases. The increased neutron fluence from double scattering contributes to a higher neutron absorbed dose and dose equivalent compared to the other techniques. For
5.3. Results

Figure 5.7: Absorbed dose and dose equivalent for double scattering (squares), passive-
internal approximation (\(\Delta\)), pencil beam scanning (circles) and scanning with an aperture
(\(\nabla\)) at different lateral distances from the field edge at a depth of 18.88cm. The
error bars represent two standard deviations.
5.3. Results

(a) absorbed dose

Figure 5.8: Absorbed dose and dose equivalent for double scattering (squares), passive-internal approximation (△), pencil beam scanning (circles) and scanning with an aperture (▽) at different lateral distances from the field edge at a depth of 23.60cm. The error bars represent two standard deviations.

(b) dose equivalent

Figure 5.8: Absorbed dose and dose equivalent for double scattering (squares), passive-internal approximation (△), pencil beam scanning (circles) and scanning with an aperture (▽) at different lateral distances from the field edge at a depth of 23.60cm. The error bars represent two standard deviations.
lateral positions close to the field edge, the neutron absorbed dose for the double scattering and passive-internal data agree within the uncertainty limits. The passive-internal is also in agreement with scanning, but the double scattering is not. These results suggest that the increased number of secondary particles incident upon the phantom in double scattering lead to an increased production of secondary particles within the phantom. This leads to an increased absorbed dose and dose equivalent for the double scattering and passive-internal techniques.

The benefit of incorporating an aperture in the scanning simulations is diminished distal to the SOBP. This is to be expected, as the primary goal of the aperture is to reduce the width of the penumbra from the primary beam. Some benefit can still be observed distal to the SOBP, shown by the reduced absorbed doses and dose equivalents compared to scanning with no aperture. The reduction in penumbra width reduces the proton fluence and dose lateral to the primary field. The reduction in proton fluence leads to a decrease in secondary particle production, the effect of which can still be observed distal to the SOBP.

5.4 Discussion

The increased amount of material in the beamline in double scattering compared to pencil beam scanning leads to a higher amount of neutron production. This increased neutron fluence increases the absorbed dose and particularly the dose equivalent. The methodology for calculation of the neutron radiation weighting factor was to collect neutron energy spectra in each of the sensitive volumes. These neutron spectra were convolved with the ICRP definition of $w_R$ as a function of neutron energy to give the average neutron radiation weighting factor. The ICRP definition of the weighting factor is an energy-dependent relationship with a minimum neutron weighting factor of 5. The higher weighting factors in double scattering suggest that a larger amount
Figure 5.9: Absorbed dose and dose equivalent for double scattering (squares), passive-internal approximation (△), pencil beam scanning (circles) and scanning with an aperture (∇) at different lateral distances from the field edge at a depth of 28.32cm. The error bars represent two standard deviations.
Figure 5.10: Absorbed dose and dose equivalent for double scattering (squares), passive-internal approximation (△), pencil beam scanning (circles) and scanning with an aperture (∇) at different lateral distances from the field edge at a depth of 33.04cm. The error bars represent two standard deviations.
5.4. Discussion

of low-energy neutrons are produced in the treatment nozzle. The passive-internal
approximation has typically lower weighting factors for neutrons because the low-
energy neutrons produced in the treatment nozzle are not included.

The passive-internal approximation used in previous studies includes all secondary
particles produced in the phantom. The main issue with using this approximation
to model delivery of pencil beam scanning fields is the discrepancy in the penumbral
width. Pencil beam scanning has a wider penumbra than double scattering proton
therapy. This is clearly observed at all depths proximal to the distal edge of the
SOBP. If a secondary particle is produced in the nozzle, a flag is set in the simulations
which determines that the energy deposition is counted as originating from the nozzle.
This flag remains active and energy deposition from all subsequent particles will not
be included in the passive-internal approximation. That is, if a secondary neutron is
produced in the nozzle and reaches the phantom, any dose resulting from that particle
or any daughter particles will not be counted in the passive-internal approximation.

It is of paramount importance to ensure that the doses calculated via Monte Carlo
methods is an accurate representation of the doses experienced in the clinical or ex-
perimental environment. The proton therapy Monte Carlo system in use at MGH has
been benchmarked in the past. The code is able to predict absolute doses in water
within an accuracy of 1.5% compared to ionisation chamber measurements [Paganetti
2006]. For in-patient calculations, the accuracy is within 4% [Bednarz & Pagenetti
2010]. The accuracy of these calculations may in fact be better than 4% given they
can only be compared with the radiotherapy TPS doses. The discrepancy may even
be due to the limitations of the pencil beam calculations used in the TPS.

Additionally, the treatment head used for both double scattering and scanning
Monte Carlo simulations are based on original blueprints provided by IBA. It is an-
ticipated that the geometry instantiated in the simulations are within 1-2mm of the
actual treatment heads used in the clinic (Paganetti et al., 2004).

In terms of secondary radiation, extensive validation of the nuclear models used in the Monte Carlo has been previously undertaken through comparisons with Faraday cup measurements (Zacharatou Jarlskog & Paganetti, 2008a). Direct comparison of the Monte Carlo doses with ionisation chamber measurements external to the primary field in proton therapy demonstrated the suitability of the chosen physics models for such applications. Clasie et al. (2009).

The results of this study demonstrate the potential benefits of using an aperture in combination with pencil beam scanning. One reason for moving to scanning methods of delivery is the removal of the dependency on patient-specific hardware which adds to the cost of operating a clinical proton facility. However, one of the issues with scanning is the wider penumbra, which is clearly evident in the results presented here. The use of an aperture may be required to decrease the penumbral width for certain clinical cases (Kooy et al., 2010), but the other advantages of pencil beam scanning compared to double scattering will still be maintained. The results of the simulations in this work show that using an aperture can reduce the absorbed dose and dose equivalent lateral to the primary field by an order of magnitude. In double scattering, the aperture is required to stop a large proportion of the proton beam. When used in combination with pencil beam scanning, the majority of the protons will pass directly through the aperture, with only the outer edge of the penumbra interacting directly with the aperture. This leads to a significantly lower number of neutrons being produced in the aperture for scanning compared to double scattering. It was observed that the neutron dose increased when using the aperture, however the reduction in proton dose lateral to the field was greater, leading to an decrease in the total absorbed dose and dose equivalent out-of-field. This reduction in the particle fluence lateral to the field also reduces the amount of secondary particle production, the effect of which was observed.
at all depths considered, even those distal to the SOBP.

### 5.5 Conclusion

A series of Monte Carlo simulations have been performed using the Geant4 Monte Carlo toolkit. The simulations have incorporated the double scattering and pencil beam scanning treatment nozzles from the Francis H. Burr Proton Therapy Center at Massachusetts General Hospital.

The previous convention of approximating the delivery of scanning fields by disregarding the secondary particles produced in the double scattering nozzle was tested via comparison with results utilising the full pencil beam scanning nozzle. The wider penumbra in pencil beam scanning means that the agreement with the passive-internal approximation is poor for lateral distances from the field edge less than 10cm. The out-of-field doses in scanning are significantly less than double scattering for lateral distances from the field edge greater than 10cm.

Placing a patient-specific aperture at nozzle exit for pencil beam scanning significantly reduces the penumbral width and hence the absorbed dose close to the field edge. At large distances from the field edge the effect of using the aperture is diminished, but still may be significant. Reducing the penumbral width lowers the amount of secondary particle production external to the primary radiation field. The effect of this was still observed distal to the Bragg peak, with lower out-of-field doses encountered using an aperture. One of the main concerns of using an aperture is the increased neutron fluence due to interactions of the primary beam occurring in the brass. An increased neutron dose component was observed close to the field edge, however the reduction in proton dose was larger than the increase in neutron absorbed dose and dose equivalent leading to lower absorbed dose and dose equivalent when an aperture is used.
Chapter 6

Characterisation of the external radiation field in proton therapy

6.1 Introduction

Secondary particles delivered during proton therapy treatments can pose a risk of second cancer induction to the patient (Hall 2006). Due to the varying radiobiological impact of different radiation types, it is desirable to know which particles are present external to the primary radiation field in proton therapy.

The stopping power of a particle of energy $E$, mass $M$ and charge $Z$ is given in equation (6.1).

$$ \frac{dE}{dx} = A \left( \frac{MZ^2}{E} \right) \ln \left( \frac{E}{M} \right) $$

where $A$ is the proportionality coefficient. Equation (6.1) clearly demonstrates that the stopping power of two different particle types with the same energy will be different due to the different masses and/or charge.

The particle type can be detected by using a series of two or more detectors op-
erated in coincidence. This is the methodology used in this work, which utilises a two-stage $\Delta E$-$E$ detector. The first stage is termed the $\Delta E$ stage and has a thickness typically of 1-2$\mu$m. The primary function of the $\Delta E$ stage is to measure the linear energy transfer (LET) of the incident particle. To do this satisfactorily, the $\Delta E$ stage must have a thickness in the micron scale, as is used in this work.

Immediately behind the $\Delta E$ stage is the 500$\mu$m thick $E$ stage, which is used to measure energy deposition. Combining the energy deposition in the $E$ stage with that in the $\Delta E$ stage, the total energy imparted in the detector can be measured. If the range of the incident particle is less than the detector thickness, the particle energy can be ascertained. Otherwise, only the energy imparted on the detector is measured and the total particle energy cannot be determined. The maximum energy deposition of a normally incident proton in 500$\mu$m of silicon is approximately 8MeV. The LET can be determined using the $\Delta E$ stage regardless of the particle range.

The $\Delta E$ stage is produced via high energy implantation of boron to a depth of 1-2$\mu$m in the $E$ stage to produce a p-n junction (Agosteo et al., 2005; Fazzi et al., 2006; Agosteo et al., 2008). Using such technology, a two-stage $\Delta E$-$E$ detector has been developed in collaboration with Politecnico di Milano for use in hadron therapy applications. Operating the two stages of the detector in coincidence allows for identification of the particle type based on the measured LET and energy deposition. A schematic of the detector is shown in figure 6.1. The cross-sectional area of the detector is 1mm$^2$. A single silicon substrate is used for the formation of the two detector stages. High energy boron implantation is used to create the shared p+ anode. Low energy Arsenic implantation is used for the formation of the n+ cathode for the $\Delta E$ stage. The electrical contacts are constructed from a 0.2$\mu$m thick Aluminium/Silicon layer.

Far from the primary field in proton therapy, the majority of the total dose can
be attributed to neutrons (Xu et al., 2008). The \(\Delta E\)-E detector has been previously studied under irradiation from neutron fields (Agosteo et al., 2005) and has been modeled in Monte Carlo simulations. Characterisation of the detectors has also been undertaken previously using Ion Beam Induced Charge Collection Imaging at the Australian Nuclear Science and Technology Organisation (Cornelius et al., 2006). The \(\Delta E\)-E detector does not directly detect neutrons, but is sensitive to the recoil protons produced via \((p,n)\) reactions. Operating the two stages of the detector in coincidence allows identification of the particle type based on the energy deposition in the whole detector volume and the LET detected in the \(\Delta E\) stage. This has been confirmed previously by Agosteo et al. (2008) and is shown in Figure 6.2.

Monte Carlo simulations can be used to determine the particle types and energies out-of-field in proton therapy assuming the physics is correctly specified. An accurate knowledge of the beamline and beam properties must be included in the simulation to ensure accuracy. Additionally, the correct physics models must be instantiated in the simulation to ensure that the physics interactions are modeled correctly. The physics in Monte Carlo simulations, typically rely on either experimental data, which is often incomplete over the energy range of interest, or theoretical models or a combination of the two.

Despite a large proportion of the dose out-of-field resulting from neutron interactions, the \(\Delta E\)-E detector does not directly detect neutrons, but measures the energy
deposition from recoil protons. Using a two-stage detector allows separation of the recoil proton energy deposition from other components such as photons and electrons which are often present in neutron fields (Agosteo et al. 2008).

The ∆E-E detector is used in this work to characterise the radiation field distal and lateral to a clinical proton treatment field. The same field is delivered using the double scattering and pencil beam scanning modalities to determine any differences in the dose external to the target between the techniques. These measurements are the first of their kind external to the primary field for proton therapy.
6.2 Methods

6.2.1 Proton Beam Properties

Both double scattering and pencil beam scanning fields were used to irradiate the detectors in this study. The field properties were matched to ensure the same primary field configuration, allowing accurate determination of the variation in secondary particles from the two modalities. The field used was designed for a patient receiving treatment for a pancreatic tumour. Note, the properties of this field make it similar to those used for other clinical sites such as paediatric medulloblastoma and head and neck tumours. The relevant properties of the primary proton field are given in Table 6.1.

Table 6.1: Properties of the clinical pancreas fields used for the measurements.

<table>
<thead>
<tr>
<th>Field properties:</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_{90}$</td>
</tr>
<tr>
<td>$R_{90}$ (in Lucite)</td>
</tr>
<tr>
<td>$M_{90-90}$</td>
</tr>
<tr>
<td>$M_{90-90}$ (in Lucite)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Double scattering:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field radius</td>
</tr>
<tr>
<td>Isocentre depth</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pencil beam scanning:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field radius</td>
</tr>
<tr>
<td>Isocentre depth</td>
</tr>
</tbody>
</table>

Different field radii and isocentre depths were used for the two modalities in an effort to ensure the primary fields were matched as closely as possible. For the double scattering irradiation, a patient-specific aperture and compensator was used such that the treatment exactly matched that which would be delivered in the clinic. Pencil beam scanning did not use any patient-specific hardware, as it is theoretically not required to conform the beam to the tumour volume [Kooy et al., 2010]. The scanning snout
6.2. Methods

is shown in Figure 6.3.

Figure 6.3: The scanning snout used in the experimental measurements which does not contain any patient-specific hardware.

6.2.2 Experimental setup

The phantom used for all the measurements is shown in Figure 6.4. The phantom is composed of Lucite blocks of dimension 26cm × 26cm × 4.72cm. Smaller blocks were inserted to fill any gaps in the phantom from the insertion of the ∆E-E probe.

A schematic of the ∆E-E probe is shown in Figure 6.5. It shows the dimensions of the probe and the position of the detector in the phantom. The detector was within a perspex rod and was positioned 10.7cm from the top of the phantom. The detector was encased in Aluminium foil, which acted as a Faraday cage. A photo of the device in the perspex probe with the preamplifier box is shown in Figure 6.6.

The measurement positions in the phantom are shown in Figure 6.7. Measurements were made both distal and lateral to the SOBP for double scattering and pencil beam scanning irradiations. The orientation of the detector at each of the positions is also
Figure 6.4: Setup used for the measurements. The Lucite phantom is shown, with the ∆E-E probe inserted. The double scattering snout and patient-specific hardware are in place.

shown in the diagram. For the position at 5cm from the field edge at 14.6cm depth in Lucite, measurements were taken with the detector front face both parallel and perpendicular to the primary field direction. This will show the significance of the detector orientation and the isotropy of the radiation field at this point.

The signal from the detector is passed to a dedicated preamplifier box which was powered by ±15V. This preamplifier is placed as close as possible to the detector to minimise noise. The noise threshold for both the ∆E and E stages was 7keV. The signal is passed from the preamplifier box to a multichannel analyser (MCA) which was positioned outside the treatment room. The MCA was used to collect data in coincidence in the ∆E and E stages of the detector. The readout electronics and software for acquiring the MCA signals was provided by Politecnico di Milano.

The signals read by the MCA are expressed in terms of channel number. To convert channel number to energy deposition, a calibration is required. Such calibrations are typically performed using a pulser, as was the case here. The calibration factors used
6.2. Methods

Figure 6.5: The experimental setup of the $\Delta E$-$E$ probe. The Lucite blocks used were $26\text{cm} \times 26\text{cm} \times 4.72\text{cm}$. The perspex holder (shown in orange) had lateral dimensions of $2\text{cm} \times 2\text{cm}$. The centre of the $\Delta E$-$E$ detector (shown in red) was situated $10.7\text{cm}$ from the top edge of the phantom. The preamplifier box (shown in blue) was placed on top of the phantom to minimise noise and the mechanical load on the preamplifier.

Figure 6.6: Photo of the $\Delta E$-$E$ probe in the perspex probe with the preamplifier box attached. The detector is contained in the Aluminium shielding, approximately $10\text{cm}$ from the end of the perspex probe. When placed in the phantom, the $\Delta E$-$E$ device is $10.7\text{cm}$ from the top edge of the phantom.
6.3. Results

6.3.1 Primary Field

The primary field shape was captured using the MatriXX detector (IBA dosimetry) which was positioned at the field isocentre. This was done to ensure that the primary fields for double scattering and pencil beam scanning were sufficiently similar. The MatriXX detector is a two-dimensional array of ionisation chambers. The results of the
double scattering and pencil beam scanning irradiations are shown in Figures 6.8(a) and 6.8(b) respectively.

![Figure 6.8: Experimental measurement of beam shape using the MatriXX detector (IBA dosimetry). The MatriXX was placed at isocentre for both measurements. The colour scale values are relative and arbitrary.](image)

The images obtained from the MatriXX show the similar distributions between the two considered modalities. The wider penumbra in pencil beam scanning can also be clearly seen. The range and lateral dimensions of the fields were confirmed using
EBT2 Gafchromic film.

To measure the dose delivered during the experiments, a Markus chamber was used to measure the charge deposited in the SOBP. The calibration of the Markus is given in equation 6.4. This converts the charge measured in nano-Coulombs (nC) to dose in centi-Gray (cGy).

\[ D(\text{cGy}) = 55.58 \times Q(\text{nC}) \]  \hspace{1cm} (6.4)

The number of monitor units (MU) on the ionisation chamber (IC) located in the treatment nozzle was also recorded. This allowed the dose delivered to be directly calculated from the MUs on the IC as shown in equation 6.5.

\[ x(\text{cGy/MU}) = \frac{\text{dose (cGy)}}{\# \text{ of MU}} \] \hspace{1cm} (6.5)

The factor \( x \) calculated from equation 6.5 was then multiplied by the number of MUs delivered in each irradiation to give the dose delivered in the SOBP.

### 6.3.2 Out-of-field Measurements

Figure 6.9 shows the ∆E-E spectra on the central axis at a depth of 19.4cm in the Lucite phantom. This position is 1.6cm behind the distal edge of the SOBP. Thus, any counts observed at this position are resultant from secondary neutrons either generated in the treatment nozzle or in the phantom. It is immediately clear from the two figures that there are more counts in the double scattering plot (Figure 6.9(a)) compared to pencil beam scanning (Figure 6.9(b)). Approximately 5000 counts/Gy in the SOBP for double scattering compared to \( \sim 1500 \) counts/Gy for scanning. This is primarily due to the large contribution of neutrons from the treatment nozzle in double scattering proton therapy.
The bulk of the events observed in both double scattering and scanning are high energy protons which incur total energy depositions of 2-4MeV in the detector volume. There are also high LET events which result from low energy protons produced by secondary neutrons.

Figure 6.9: $\Delta E$-$E$ spectra at 19.4cm depth in Lucite on the central axis. The values are normalised to counts/Gy delivered in the SOBP.
Figures 6.10(a) and 6.10(b) show the ∆E-E plots for double scattering and scanning at 24.3 cm depth on the central axis. The plots shown in Figure 6.10 are more similar than those in Figure 6.9. It is generally expected that the secondary particle spectra from double scattering and scanning should become more similar as the depth in the phantom increases, as the relative contribution of secondary particles generated in the phantom increases.

Figure 6.11 shows the ∆E-E spectra at a depth of 14.6 cm in Lucite and 5 cm from the lateral edge of the primary field. The wider penumbra from this implementation of pencil beam scanning is evident in these plots, as a larger number of high energy protons, with LET values of 10-20 keV/µm are present in the scanning spectrum. The total number of counts/Gy observed for the scanning beam was approximately twice as high as that observed for double scattering. The use of a patient-specific aperture in double scattering gives a sharper lateral penumbra which reduces the out-of-field dose contribution from primary protons.

When considering the ∆E-E spectra at 15 cm from the lateral field edge, shown in Figure 6.12, the wider penumbra from the scanning beam is no longer a factor. This leads to a lower number of counts in the scanning plot compared to double scattering. The majority of counts observed in the scanning plot, shown in Figure 6.12(b) are of low LET and deposit little energy, suggesting they are predominantly photon events. A photon contribution can also be seen in the double scattering plot, however the main characteristic of interest in Figure 6.12(a) is the increased events caused by high energy protons compared to that observed for scanning. The position of this measurement means that no primary protons can reach the detector, meaning that all proton events observed, for both double scattering and scanning, are resultant from secondary neutron interactions. The results of these plots demonstrate the higher neutron fluence out-of-field in double scattering compared to scanning.
Figure 6.10: $\Delta E$-$E$ spectra at 24.3cm depth in Lucite on the central axis. The values are normalised to counts/Gy delivered in the SOBP.
Figure 6.11: $\Delta E$-$E$ spectra at a depth of 14.6 cm in Lucite and 5 cm lateral distance from the field edge.

(a) double scattering

(b) scanning
6.3. Results

(a) double scattering

Figure 6.12: $\Delta E$-E spectra at a depth of 14.6cm in Lucite and 15cm lateral distance from the field edge.

(b) scanning

Figure 6.12: $\Delta E$-E spectra at a depth of 14.6cm in Lucite and 15cm lateral distance from the field edge.
6.3. Results

The higher neutron fluence for double scattering is further emphasised when moving to 25cm lateral distance from the field edge. Figure 6.13(a) shows the ∆E-E spectra for double scattering at this lateral distance and a depth of 14.6cm. The scanning plot for the same position is shown in Figure 6.13(b). A contribution from secondary photons can be observed in both double scattering and pencil beam scanning plots at this position. The counts observed for low energy deposition (E + ∆E) and low LET (ΔE) are secondary electrons produced by photons as they traverse the detector volume. The number of neutrons present in the double scattering plot is significantly higher than what is observed in scanning.

The ∆E-E spectra for the two detector orientations are shown in Figure 6.14. Figure 6.14(a) represents the ∆E-E spectra with the front face of the detector parallel to and facing the primary beam axis. The ∆E-E spectra with the front face perpendicular to the primary beam axis is shown in Figure 6.14(b). It is immediately clear that the number of counts/Gy is significantly higher in this position when the detector face is parallel to the primary beam axis.

Facing the detector front face towards the primary field (parallel to beam axis) implies that the bulk of particles passing through the detector will originate from the primary field itself. Figure 6.14(a) shows a high number of high LET events, caused from low-energy protons. A number of low LET events are also present, due to high energy protons, either scattered from the primary field or produced via neutrons.

If the detector is faced upstream (perpendicular to beam axis) then the results are biased towards particles generated in the treatment nozzle or at proximal depths in the phantom. The very thin ∆E layer and operating the device in coincidence implies that a large proportion of events scattered from the primary field which are incident upon the detector will not pass through both stages and thus will not be counted in this configuration. This is confirmed by the significantly lower total counts/Gy in
6.3. Results

(a) double scattering

(b) scanning

Figure 6.13: ΔE-E spectra at a depth of 14.6cm in Lucite and 25cm lateral distance from the field edge.
Figure 6.14(b) compared to Figure 6.14(a). The majority of events observed in this configuration are due to high energy protons produced from secondary neutrons which were generated in the treatment nozzle. There is also a contribution from electrons produced from photons. This detector orientation makes it more unlikely that particles scattered from or generated in the primary field will be detected when the ΔE-E device is operated in coincidence mode due to the thin ΔE stage. The results of these ΔE-E spectra demonstrate the significance which detector orientation can have on the results gained lateral to the primary field. They also show that at 5cm from the field edge, the radiation field is highly anisotropic, which cannot be observed using other detector types.

6.4 Discussion

The maximum amount of energy which can be deposited in 500μm of silicon by a proton is \( \sim 8\text{MeV} \). This implies any events detected which have higher energy depositions are either pile-up events, particles which were not normally incident upon the detector, particles stopping in the detector or particles which undergo nuclear interactions within the detector. This is particularly evident in Figure 6.14(b) which shows a number of events with energy depositions higher than 8MeV. Facing the detector upstream implies that a larger proportion of the particles produced in the treatment nozzle or proximally in the phantom will be detected at the expense of particles scattered or produced at depth in the primary field. The particles which pass through both stages of the detector that were produced in the primary field will likely do so at oblique angles. Traveling through the detector at an oblique angle implies they are traveling through more than 500μm of silicon which allows their energy deposition to be higher than 8MeV.

Altering the detector orientation can markedly change the properties of the ΔE-E
6.4. Discussion

(a) front face parallel to primary beam axis

(b) front face perpendicular to primary beam axis

Figure 6.14: $\Delta E$-$E$ spectra at 5cm from the field edge and a depth of 14.6cm in Lucite with the detector orientated parallel (a) and perpendicular (b) to the primary beam axis.

Figure 6.14: $\Delta E$-$E$ spectra at 5cm from the field edge and a depth of 14.6cm in Lucite with the detector orientated parallel (a) and perpendicular (b) to the primary beam axis.
spectra obtained. Rotating the detector when positioned near the field edge biases the results to either be predominantly particles from the primary field or those produced in the treatment nozzle. The variation in the results obtained through rotating the detector confirm that relatively close to the field edge ($\leq 5$cm) at the depth of the SOBP, the radiation field is anisotropic for double scattering proton therapy with the majority of secondary particles moving orthogonally away from the primary radiation field. Further measurements are required to determine the field isotropy further out-of-field, at different depths and for pencil beam scanning.

At the measurement point on the central axis at 1.6cm distal to the SOBP, significantly more high energy particles are detected in double scattering compared to scanning. This is possibly an effect of the secondary neutrons produced in the treatment nozzle in double scattering. For small fields, the contribution of neutrons generated in the treatment head to the total neutron dose can be higher than 99% \cite{ZacharatouJarlskog2008}.

The majority of the energy deposition from fast neutron beams of energy $<80$MeV occurs in the first 10cm \cite{SoderbergCarlsson2000}. Secondary neutrons in proton therapy can have energies up to the energy of the primary proton beam \cite{Paganetti2002}. The majority of neutrons have low energies. \cite{Paganetti2002} showed that for a downstream of a 160MeV proton beam, approximately half of all the secondary neutrons have energies below 20MeV, approximately one third have an energy less than 10MeV and a quarter have energies less than 5MeV. As shown in the Monte Carlo simulations of \cite{SoderbergCarlsson2000}, 20MeV neutrons can travel at least 30cm in ICRU soft tissue. The finite range of protons implies that all the events observed distal to the Bragg peak are due to secondary particles. The higher neutron fluence from double scattering and the high range of neutrons implies that the number of events observed distal to the Bragg peak should be higher for this modality compared
to scanning. The contribution of neutrons generated in the treatment nozzle in double scattering leads to higher neutron fluence 1.6cm distal to the SOBP compared to scanning. A lower neutron fluence was observed at the point 6.5cm distal to the SOBP. Due to the high proportion of low energy neutrons (< 1MeV), the majority of the secondary neutrons would have small ranges in the phantom. Thus, the higher neutron fluence observed in double scattering compared to scanning at 1.6cm distal to the SOBP is less significant in the spectra at 6.5cm behind the SOBP.

The contribution of photons to the total dose out-of-field is non-negligible. Clasie et al. (2009) observed that using a prostate field, for lateral distances from the field edge greater than 20cm, the contribution of photons to the total dose can be greater than 40% in scanning. For double scattering, the relative contribution of neutrons is approximately 80% up to 60cm from the field edge, whilst photons contribute ~10%. The photon events obtained in the ∆E-E plots are detected via Compton electrons which are produced when the photon passes through the detector volume.

The noise threshold on both ∆E and E stages was 7keV throughout the experiments. This restricts the amount of high-energy, low-LET particles which can be detected by the device. Low energy protons can be detected easily because they have high LET values. Certainly, reducing the noise threshold further is important, especially if the detector is to be further used for out-of-field applications. When used within the primary field, the vast majority of events are obviously resultant from primary protons. The LET of these protons is typically high enough to be detected by the device, except perhaps at very proximal depths, close to the phantom entrance.

6.5 Conclusion

A ∆E-E detector was used to characterise the radiation field external to the target volume for a clinical proton field which was designed for treatment of a pancreatic
tumour. Clinical proton fields were planned for both double scattering and pencil beam scanning proton therapy to show any difference in the radiation field external to the target for the two modalities. Operating the detector in coincidence mode allows the particle types incident upon the device to be identified based on their LET and the energy deposited in the detector volume.

The contribution of neutrons generated in the treatment nozzle in double scattering lead to a significantly higher neutron fluence for small distances distal to the SOBP. The low average energy of the secondary neutrons generated implies that further beyond the SOBP, the variation in neutron contribution between double scattering and pencil beam scanning proton therapy diminishes. The secondary neutrons generated in the treatment nozzle and in the phantom are primarily forward scattered, leading to higher neutron fluences distal to the SOBP compared to the lateral positions considered.

The wider penumbra in this implementation of pencil beam scanning leads to a higher contribution of proton dose close to the field edge. Further out-of-field, where only secondary particles are present, the secondary particle fluence is significantly lower in scanning. Neutron events dominate the $\Delta E-E$ spectra at all positions for double scattering, whilst photons make a significant contribution to the scanning spectra at large lateral distances from the field edge.

Close to the field edge in double scattering, the radiation field is highly anisotropic. Further from the field edge, this may be less significant, but this hypothesis needs to be tested through further measurements. The choice of detector orientation can play a crucial role in the results obtained using this apparatus.
Chapter 7

Calculation of pencil beam scanning irradiation times based on the system hardware

7.1 Introduction

Due to their inherent charge, the trajectory of protons can be controlled using magnetic fields (Kooy et al., 2010). This is the basis of pencil beam scanning (PBS) which uses magnetic fields to aim the proton beam at a specific point within the patient (Pedroni et al., 1995). When the ability to change the energy of the proton beam is added to the capability to scan the beam laterally, conformality to a target volume can be achieved in three dimensions. The ability to conform the dose in three dimensions offers improved control over the dose distribution compared to photon techniques such as IMRT which do not have precise energy or depth modulation. The dose proximal to the target is also reduced compared to double scattering proton therapy (Lomax et al., 1999). There is theoretically no need for patient specific hardware, i.e. apertures and compensators, when using pencil beam scanning. However, there may be specific
cases where they are still used as they improve the lateral and distal penumbras \cite{Kooy2010}. Using PBS will also reduce time for planning and delivery and the cost of treatment. The time required to deliver the field is the focus of this study.

The irradiation time for a scanning field has been calculated based on the properties of the system hardware. The calculations are an approximation in that the field is assumed to be rectangular. Optimising the time taken for an irradiation requires consideration of a number of different aspects. Treatment fields in scanning are made up of a series of two-dimensional layers which are combined to give a homogeneous target dose in three dimensions. Within a single layer, a certain time is required to deposit the required dose and to move the beam between spots using the scanning magnets. When moving the beam during scanning, the beam must be stationary for a given time to ensure that the prescribed dose is delivered at the required position. This settling time should also be accounted for in the calculations. Almost all of the parameters of a clinical scanning system are dependent on the proton momentum and thus change within a single three-dimensional irradiation.

There are then various pieces of additional equipment which need to be considered at each spot during the irradiation. There is also time introduced into the system to send and receive electrical signals for various components which need to be considered for each spot during the irradiation. Elements such as the dosimetry system are crucial from a clinical point of view to ensure that the required dose is delivered in each spot. This and other elements introduce additional time on a per spot basis which need to be considered in the time calculations. There are also clinical considerations such as the required flatness in the SOBP which must be considered in the calculations. A smaller tolerance on flatness inherently requires more individual Bragg peaks which will in turn increase the irradiation time. Bragg peaks of differing weights need to be placed within the target volume to create a SOBP with homogeneous dose. The
methodology of placing the individual peaks within the target volume can influence
the number of peaks required to satisfy the prescribed dose tolerance. Altering the
number of Bragg peaks will obviously influence the time required for the irradiation.
Different spacing arrangements are considered in this study.

In this chapter, a series of calculations is presented which will ultimately allow
determination of the total irradiation time for an arbitrary two magnet pencil beam
scanning system for proton therapy. From these calculations, the effect of each pa-
rameter of the scanning system on the time required to complete a given irradiation
can be ascertained.

7.2 Method

7.2.1 Generation of an SOBP

SOBPs are generated using individual Bragg peaks previously generated using Geant4
Monte Carlo simulations. The use of a ridge filter is simulated by smearing the
proton depth dose curves to give different values of ∆E. The considered ∆E values are
0%, 0.5%, 1%, 2% and 3%. Using a ridge filter requires fewer Bragg peaks to generate
the SOBP. The trade-off is that the distal falloff is no longer as sharp when the ∆E is
increased.

The relative weights of the individual Bragg peaks are optimized using single value
decomposition (SVD) (Golub & Reinsch [1970]). The SVD solves the equation:

\[ A \times W = D \]  

(7.1)

Where \( A \) is a matrix containing the depth doses of the individual pencil beams,
\( W \) is the beam weights (in number of protons) and \( D \) is the prescription dose. The
issue with finding the beam weights is that one must find the inverse of the matrix
7.2. Method

$A$ and it is typically not square. The SVD finds the least-squares best solution for this problem by decomposing the matrix $A$. During the process, small beam weights ($< 10^6$ protons) are reset to zero and the SVD optimisation is re-run. Whilst this removes a linear combination of the equations which are trying to be solved, this solution would have been highly corrupted by round off errors. The SVD also has the possibility of generating negative solutions to the problem. Obviously, negative beam weights cannot be delivered, so these solutions are also removed and the optimization is recalculated. Other optimization methods such as the simplex algorithm could also be used as a method of determining the beam weights; however the SVD serves our purpose well and thus is used throughout this study.

7.2.2 Spacing between Bragg peaks

Different spacing arrangements were considered to determine which would give the required flatness in the SOBP with the fewest number of individual Bragg peaks. The considered spacing arrangements between pristine the Bragg peaks which made up the SOBP were constant distance, constant energy and the full width at half maximum (FWHM) of the individual Bragg peaks multiplied by a spacing factor $s$.

For the constant distance spacing, Bragg peaks are initially placed at the maximum and minimum range of the SOBP which is to be generated. A single peak is then placed in the center of the SOBP and the SVD optimisation is computed. If the SOBP flatness is greater than the chosen tolerance, an additional peak is placed in the SOBP. The individual peaks are then repositioned such that they are always equidistant.

The constant energy spacing works in much the same way as the constant distance except energy is the defining quantity. The depth of penetration of a proton beam is non-linear with energy, which implies that this spacing method is non-uniform in depth.
The final spacing arrangement is based upon the FWHM of the individual Bragg peaks. This method initially places a Bragg peak at the required range of the SOBP. The next Bragg peak is then placed at a depth of the previous peak minus its FWHM multiplied by the spacing factor $s$, which is initially 1. This process is repeated until the minimum range of the SOBP is reached. Once the SOBP has been populated with the Bragg peaks, the SVD optimisation is run to find the beam weights and the flatness is checked. If the flatness requirement is not met, the factor $s$ is reduced by 10% and the process repeated. Reducing the magnitude of $s$ decreases the distance between adjacent Bragg peaks, which in turn leads to a flatter SOBP after the weights have been optimised. This type of beam spacing is non-uniform in both depth and energy.

### 7.2.3 Irradiation Time Calculation

To calculate the time for a total scanning irradiation, we must first calculate the time taken for a single layer irradiation. We have separated these into the time taken to deposit the dose ($\tau_{\text{dose}}$), the time taken by the scanning magnets to move the beam ($\tau_{\text{magnet}}$) and the time taken by other equipment used during the course of an irradiation ($\tau_{\text{equip}}$). This leads to the total irradiation time:

$$
\tau_{\text{total}} = \tau_{\text{dose}} + \tau_{\text{magnet}} + \tau_{\text{equip}}
$$

#### 7.2.3.1 Time to deposit dose

The time to deposit dose in an individual spot ($\tau_{\text{dose''}}$) is given by

$$
\tau_{\text{dose''}} = \frac{W \times q}{I}
$$

Where $W$ is the absolute beam weight in number of protons, $q$ is the proton charge
and \( I \) is the beam current in Amps. The total number of spots in the layer (\( N \)) is

\[
N = N_x \times N_y
\]  \quad (7.4)

where

\[
N_x = \frac{\delta_x}{d_x} \quad \text{and} \quad N_y = \frac{\delta_y}{d_y}
\]  \quad (7.5)

Where \( \delta \) is the field size and \( d \) is the spot spacing. Only rectangular fields are considered in this study. Whilst typical clinical fields are not rectangular, using such fields serves the required purpose of this study. The spot spacing is expressed in terms of the spot FWHM. The ICRU recommends that the spacing of pencil beams is less than 80% of the FWHM [ICRU 2007] to prevent ripples in the lateral dose profile. In the implementation of carbon ion therapy at GSI [Haberer et al. 1993], the spacing employed was 20% of the FWHM to make the system more robust against fluctuations in the pencil beam position. Using the total number of spots in the layer, the time to deposit the dose in the layer can be calculated.

\[
\tau_{\text{dose}} = \sum_{i=1}^{N} \tau_{\text{dose}}
\]  \quad (7.6)

If the number of layers in the irradiation is given by \( n \), the total time to deposit the dose throughout the full irradiation is given by:

\[
\tau_{\text{dose}} = \sum_{i=1}^{n} \tau_{\text{dose}}
\]  \quad (7.7)

This gives the time to deposit dose throughout a field in terms of the spot weight, beam current and proton charge.
7.2. Method

7.2.3.2 Time to move the beam

After the required dose has been deposited in a spot, the scanning magnets are used to move the beam to the next spot position. We call this movement of the beam between adjacent spots through changing the scanning magnet settings a “slew”. The time to move the beam throughout an irradiation depends only on the field size, the spot spacing, the time required for the scanning magnets to settle and the scanning speed. The scanning speed can be determined from the fundamental magnet properties. The maximum voltage supplied to the scanning magnets is related to the inductance and the current rate.

\[ V = L \frac{dI}{dt} \] (7.8)

The current rate can be expressed in terms of the magnetic field in the scanning magnets.

\[ \frac{dI}{dt} = \alpha \frac{dB}{dt} \] (7.9)

Where \( \alpha \) is the “field to current” parameter and has units of Amps/Tesla. The rate of change of the magnetic field is expressed as

\[ \frac{dB}{dt} = \frac{d}{dt} \left( \frac{p \times x}{Z_{\text{eff}} \times q \times x_{\text{SAD}}} \right) \] (7.10)

\[ = (B\rho) \frac{1}{Z_{\text{eff}} \times x_{\text{SAD}}} \left( \frac{dx}{dt} \right) \] (7.11)

Where \( p \) is the proton momentum, \( x \) is the distance between adjacent spots, \( q \) is the proton charge, \( Z_{\text{eff}} \) is the effective length of the magnetic field, \( x_{\text{SAD}} \) is the source to axis distance for the x magnet, and \( B\rho \) is the magnetic rigidity. Substituting the results of equation 7.9 and 7.11 into equation 7.8 and rearranging leads to an
expression of the scanning speed in one direction based on the fundamental properties of the given scanning magnet.

\[
\frac{dx}{dt} = \frac{V_x \times Z_{eff} \times x_{SAD}}{L \times \alpha \times (B \rho)} \tag{7.12}
\]

\[
\frac{dy}{dt} = \frac{V_y \times Z_{eff} \times y_{SAD}}{L \times \alpha \times (B \rho)} \tag{7.13}
\]

Equations 7.12 and 7.13 give the scanning speed in the x and y directions respectively. It is important to note that the scanning speed can be different in the x and y directions. The scanning speed calculated using equation 10 is the speed at isocentre. Away from isocentre, the scanning speed varies due to the change in the bending radius. For a 40cm x 40cm field, the variation at the field edge compared to isocentre is \(\sim 2\%\). This field size is larger than an average field and thus any variation in the scanning speed is neglected and the speed at isocentre is assumed throughout the layer. The scanning speed changes during a full three-dimensional irradiation due to the change in the proton momentum moving between layers.

As mentioned previously, the spot spacing is expressed in terms of the spot FWHM. The assumed scanning pattern is shown in Figure 7.1. This was chosen as it gives the fewest number of slews throughout a single layer, thereby minimizing the time. The chosen pattern also means that one magnet will be used to move the beam more often during each layer, the x magnet in our case. If the magnets are able to move the beam at different speeds, the faster of the two will always be used more in this work to minimize the irradiation time.

Assuming the scanning pattern shown in Figure 7.1, the number of slews in the
7.2. Method

Figure 7.1: Scanning pattern used for this study. The irradiation starts at the lower left and finishes at the upper right of the figure. The spots are denoted by “x” and the arrows show the direction that the beam is moved between the spots. The faster of the two magnets is scanned in the x-direction.

y-direction ($S_y$) is given by

$$S_y = \frac{\delta_y}{\sigma_y} - 1 \quad (7.14)$$

Where $\delta_y$ is the field size and $\sigma_y$ is the beam sigma in the y-direction. The number of slews in the x-direction ($S_x$) is then given by

$$S_x = \frac{\delta_x}{\sigma_x} \times N_y \quad (7.15)$$

Where $\delta_x$ is the field size and $\sigma_x$ is the beam sigma in the x-direction and $N_y$ is the number of spots in the y-direction.

We can then calculate the time to move between adjacent spots (τmagnet) using equation 7.16.

$$\tau_{magnet} = \frac{d}{dt} + \tau_{settling} \quad (7.16)$$
7.2. Method

Where $d$ is the distance between adjacent spots, $\frac{dx}{dt}$ is the scanning speed and $\tau_{settling}$ is the settling time of the scanning magnet. From here, we can calculate the time to move the beam during a single layer ($\tau_{magnet}'$).

$$
\tau_{magnet}' = \sum_{i=1}^{S_x} \tau_{magnet}''(x)(i) + \sum_{j=1}^{S_y} \tau_{magnet}''(y)(j) \tag{7.17}
$$

Where $S_x$ is the number of slews in the x-direction (from equation 7.15), $S_y$ is the number of slews in the y-direction (from equation 7.14) and $\tau_{magnet}''(x)$ and $\tau_{magnet}''(y)$ are the times to move between adjacent spots in the x and y directions respectively. Finally, the time taken moving the beam during an irradiation consisting of n layers ($\tau_{magnet}$) can be calculated.

$$
\tau_{magnet} = \sum_{i=1}^{N} \tau_{magnet}'(i) \tag{7.18}
$$

7.2.3.3 Time for other components

Other parameters need to be considered during a typical irradiation. The effect of the different parameters is dependent on the method of irradiation and the beam source.

Typically, scanning fields are delivered using either spot scanning or continuous scanning. The additional time due to other equipment which is to be considered for each spot is then:

$$
\tau_{equip}''(s) = \tau_{on} + \tau_{readout} + \tau_{signal} + \tau_{off} \tag{7.19}
$$

$$
\tau_{equip}''(c) = \tau_{readout} + \tau_{signal} \tag{7.20}
$$

Where $\tau_{on}$ is the time to turn the beam on, $\tau_{readout}$ is the time for the dosimetry system to readout, $\tau_{signal}$ is the time for the signal to decay and $\tau_{off}$ is the time to
turn the beam off. For continuous scanning, \( \tau_{on} \) and \( \tau_{off} \) are only considered at the start and end of each layer. When considering the time required in a single layer, the beam source must be considered. Both a cyclotron and synchrotron will be considered as a possible beam source.

A finite number of protons are available in the ring of the synchrotron at a given time. Once these protons are used, the synchrotron must be repopulated. The time taken for cycling the synchrotron is dependent on the acceleration time (\( \tau_{accel} \)), the deceleration time (\( \tau_{decel} \)) and the amount of charge that can be stored in the synchrotron ring. The acceleration and deceleration times are assumed to be linear with proton momentum. The time taken to cycle the synchrotron (\( \tau_{cycle} \)) in each layer is given by

\[
\tau_{cycle} = \left\lceil \frac{W \times N}{Q} \times (\tau_{accel} + \tau_{decel}) \right\rceil
\]  

(7.21)

Where \( W \) is the spot weight (in number of protons), \( N \) is the number of spots in the layer and \( Q \) is the charge which can be held in the synchrotron ring (in number of protons). Incorporating the cycling time gives us the additional equipment time to be considered within a single layer comprised of \( N \) spots during the irradiation.

\[
\tau_{eqip'}(s, c) = \sum_{i=1}^{N} \tau_{eqip''}(s)(i)
\]  

(7.22)

\[
\tau_{eqip'}(c, c) = \sum_{i=1}^{N} \tau_{eqip''}(c)(i) + \tau_{on} + \tau_{off}
\]  

(7.23)

\[
\tau_{eqip'}(s, s) = \sum_{i=1}^{N} \tau_{eqip''}(s)(i) + \tau_{cycle}
\]  

(7.24)

\[
\tau_{eqip'}(c, s) = \sum_{i=1}^{N} \tau_{eqip''}(c)(i) + \tau_{cycle} + \tau_{on} + \tau_{off}
\]  

(7.25)

Where \( \tau_{eqip'}(s, c) \) is the time per layer for spot scanning using a cyclotron, \( \tau_{eqip'}(c, c) \)
is continuous scanning using a cyclotron, $\tau_{\text{equip}}'(s, s)$ is spot scanning using a synchrotron and $\tau_{\text{equip}}'(c, s)$ is continuous scanning using a synchrotron. The equipment time for the total irradiation ($\tau_{\text{equip}}$) is then given by

$$\tau_{\text{equip}} = \sum_{i=1}^{n} \tau_{\text{equip}}'(i) + (n - 1) \times \tau_{\text{energy}}$$ (7.26)

Where $\tau_{\text{equip}}'$ is the for the given layer depending on the chosen modality, $n$ is the number of layers and $\tau_{\text{energy}}$ is the time required to change the beam energy before irradiation of the next layer can commence. The choice of delivery modality only effects the variable $\tau_{\text{equip}}$. The time to deposit the dose and the time to move the beam are independent of the choice of modality.

### 7.3 Results

#### 7.3.1 Bragg peak spacing

To give the quickest treatment time, one would ideally like to irradiate using the smallest number of layers possible. The number of layers required for different beam spacing arrangements to achieve an SOBP within 2% flatness was ascertained for an irradiation of a 10cm x 10cm x 10cm cube at different ranges. The results are summarised in Table 7.1.

<table>
<thead>
<tr>
<th>Range</th>
<th>Spacing type 20cm</th>
<th>25cm</th>
<th>30cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy</td>
<td>18</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>FWHM</td>
<td>19</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Distance</td>
<td>17</td>
<td>14</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 7.1: Number of layers required to achieve a SOBP with 2% flatness for a 10cm x 10cm x 10cm cube with different beam spacing arrangements at various ranges.
7.3. Results

Using a constant distance between Bragg peaks leads to an irradiation with the fewest number of layers. Employing a constant energy or using a spacing methodology based on the FWHM of the individual Bragg peaks requires more layers to achieve the same flatness in the SOBP.

Utilising beam spacing in the SOBP based on constant distance will lead to the shortest irradiation times and this spacing methodology is therefore used throughout this study.

7.3.2 Effect on irradiation time by varying hardware

To more easily observe the effect that each parameter has on the components of the irradiation time, a set of default parameters was chosen. These are shown in Table 7.2, where $R_{80}$ is the depth of the 80% dose level on the distal edge of the SOBP, $I$ is the beam current, $\sigma_x$ and $\sigma_y$ are the sigma values of the spot in the x and y directions, $V_{\text{max}}$ is the maximum voltage that can be supplied to the x or y scanning magnet, $L$ is the inductance of the scanning magnet, $\alpha$ is the field to current parameter, $Z_{\text{eff}}$ is the effective length of the magnetic field, $x_{\text{SAD}}$ and $y_{\text{SAD}}$ are the source to axis distances for the x and y scanning magnets, $\tau_{\text{settling}}$ is the scanning magnet settling time, $\tau_{\text{off}}$ is the time to turn the beam off, $\tau_{\text{on}}$ is the time to turn the beam on, $\tau_{\text{readout}}$ is the time to readout the signal, $\tau_{\text{signal}}$ is the time for the signal to decay, $\tau_{\text{energy}}$ is the time required to change energy, $\tau_{\text{accel}}(250\text{MeV})$ is the time to accelerate 250MeV protons in the synchrotron and $\tau_{\text{decel}}(250\text{MeV})$ is the time required for deceleration of 250MeV protons in the synchrotron. $\tau_{\text{decel}}$ and $\tau_{\text{decel}}$ are specified for a given energy as both quantities are linear with proton momentum. Choosing the default parameters allowed each individual parameter to be varied in turn.

The time to deposit the dose ($\tau_{\text{dose}}$) increases linearly with the prescription dose. Larger beam currents allow the prescribed dose to be delivered quicker. Theoretically,
Table 7.2: Values used for the example irradiation

<table>
<thead>
<tr>
<th>Field parameters:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescription dose (Gy):</td>
<td>2</td>
</tr>
<tr>
<td>$R_{S0}$ (g/cm$^2$):</td>
<td>20</td>
</tr>
<tr>
<td>Field size X (cm):</td>
<td>10</td>
</tr>
<tr>
<td>Field size Y (cm):</td>
<td>10</td>
</tr>
<tr>
<td>Field size Z (cm):</td>
<td>10</td>
</tr>
<tr>
<td>$I$ (nA):</td>
<td>2</td>
</tr>
<tr>
<td>$\sigma_x$ (cm):</td>
<td>10</td>
</tr>
<tr>
<td>$\sigma_y$ (cm):</td>
<td>10</td>
</tr>
<tr>
<td>Spot spacing (% of FWHM):</td>
<td>42.47</td>
</tr>
<tr>
<td>Dose tolerance (%):</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Magnet parameters:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of paintings:</td>
<td>1</td>
</tr>
<tr>
<td>$V_{max}(x)$ (V):</td>
<td>375</td>
</tr>
<tr>
<td>$V_{max}(y)$ (V):</td>
<td>375</td>
</tr>
<tr>
<td>$L_x$ (H):</td>
<td>0.005</td>
</tr>
<tr>
<td>$L_y$ (H):</td>
<td>0.05</td>
</tr>
<tr>
<td>$\alpha$ (A/T):</td>
<td>1000</td>
</tr>
<tr>
<td>$Z_{eff}$ (m):</td>
<td>0.3</td>
</tr>
<tr>
<td>$x_{SAD}$ (m):</td>
<td>2.5</td>
</tr>
<tr>
<td>$y_{SAD}$ (m):</td>
<td>2</td>
</tr>
<tr>
<td>$\tau_{settling}(x)$ (ms):</td>
<td>5</td>
</tr>
<tr>
<td>$\tau_{settling}(y)$ (ms):</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Equipment parameters:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tau_{off}$ (ms):</td>
<td>0.1</td>
</tr>
<tr>
<td>$\tau_{on}$ (ms):</td>
<td>0.1</td>
</tr>
<tr>
<td>$\tau_{readout}$ (ms):</td>
<td>2</td>
</tr>
<tr>
<td>$\tau_{signal}$ (ms):</td>
<td>0.1</td>
</tr>
<tr>
<td>$\tau_{energy}$ (ms):</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Synchrotron parameters:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tau_{acc}(250,MeV)$ (s):</td>
<td>1</td>
</tr>
<tr>
<td>$\tau_{decel}(250,MeV)$ (s):</td>
<td>0.3</td>
</tr>
<tr>
<td>Charge in ring (x $10^9$ protons):</td>
<td>1</td>
</tr>
</tbody>
</table>

using the highest beam current will give the quickest treatment time. However, one cannot simply state that irradiating the highest possible current is a good idea. For safety considerations, it is recommended that the maximum dose rate of the system is
no more than the inverse of the time required to turn the beam off. This recommendation in turn places an upper restriction on the beam current which should be used in a clinical setting.

As mentioned previously, the time to move the beam is dependent on the field size, the spot spacing, the scanning magnet settling time and the scanning speed. The parameters listed in Table 7.2 lead to a scanning system with scanning speeds of $28\text{m/s}$ in the fast (x) direction and $\sim 2\text{m/s}$ in the slow (y) direction. $\tau_{\text{magnet}}$ is proportional to the lateral field size. There are some fluctuations in magnet when the $R_{80}$ is altered as the number of layers required for the prescribed dose tolerance can change. The dependence on the spot spacing is relatively small. Assuming the field size remains constant, altering the spot spacing only changes the number of spots in each of the layers. Whilst the beam is still scanned through the same total distance, the change in the number of spots alters the number of times the magnets must be allowed to settle ($\tau_{\text{settling}}$) which in turn effects $\tau_{\text{magnet}}$. The effect of altering the magnet settling time itself is demonstrated in Figure 7.2.

Larger $\Delta E$ values lead to fewer layers in the irradiation which reduces the total distance through which the beam must be scanned over the full irradiation, reducing magnet. The differences in the value of magnet when altering the settling time of the fast and slow magnets is due to the different number of slews in each direction and the difference in scanning speeds.

The time to move the beam is proportional to the inductance in the scanning magnets, the field to current parameter and the magnetic rigidity. It is inversely proportional to the maximum voltage which can be supplied to the scanning magnets, the effective length of the magnetic field and the source to axis distance of the scanning magnets.

The plots in Figure 7.3 clearly demonstrate the linear relationship between $\tau_{\text{off}}$ and
7.3. Results

(a) fast (x) magnet

(b) slow (x) magnet

Figure 7.2: Effect on $\tau_{\text{magnet}}$ when altering the settling time of the fast (a) and slow (b) scanning magnets. The different data series show the different values of $\Delta E$ (0% squares, 0.5% circles, 1% $\Delta$, 2% $\nabla$, 3% stars)

$\tau_{\text{equip}}$. The differences between spot scanning and continuous scanning can be observed in these plots. Since the beam remains on for the duration of the layer for continuous
7.3. Results

(a) cyclotron

(b) synchrotron

Figure 7.3: Effect on $\tau_{e\text{quip}}$ when the time to turn the beam off ($\tau_{\text{off}}$) is altered. Figure 7.3(a) is for a cyclotron beam source, whilst Figure 7.3(b) is for a synchrotron. The percentage values represent the different $\Delta E$ values, simulating various ridge filter thicknesses. Open symbols are for spot scanning and the closed symbols are for continuous scanning.
scanning, the $\tau_{\text{off}}$ parameter is only instantiated at the conclusion of the layer, hence the flat curves. The same trends are observed when the $\tau_{\text{on}}$ parameter is considered. Only these two parameters lead to significant (> 1 second) time differences between spot scanning and continuous scanning. Apart from turning the beam on and off at each spot, the two modalities are essentially the same. $\tau_{\text{equip}}$ is proportional to the time for signal decay ($\tau_{\text{signal}}$) and readout ($\tau_{\text{readout}}$). The difference in the magnitude of $\tau_{\text{equip}}$ for the cyclotron and synchrotron in Figure 7.3 is largely due to the time required for repopulating the synchrotron ($\tau_{\text{cycle}}$).

$\tau_{\text{equip}}$ increases linearly with $\tau_{\text{accel}}$ and $\tau_{\text{decel}}$. Using the parameters given in Table 2 and increasing the acceleration time from 1s to 10s causes $\tau_{\text{equip}}$ to increase from 181s to 1119s. Increasing the charge which can be stored in the ring of the synchrotron will reduce the number of times it must be repopulated during each layer. Obviously, the best case scenario is that the synchrotron could store enough charge to deliver the entire layer without having to be repopulated. However it is unlikely that such a large amount of charge can be safely stored in the synchrotron. The effect of increasing the amount of charge which can be stored in the synchrotron ring is shown in Figure 7.4.

Figure 7.4 shows the decrease in $\tau_{\text{equip}}$ which can be achieved when the synchrotron ring can store more charge. As was the case with the maximum recommended beam current, one must take safety into consideration when considering this parameter. For each synchrotron and facility there will exist a limit on the amount of charge which can be stored in the ring. This upper restriction may be due to hardware capabilities, safety or both. Increasing the amount of charge which can be stored in the ring causes the variation in the total irradiation times between cyclotron and synchrotron beam sources to diminish.

Another parameter which needs to be considered is the time to reset all the beamline magnets so a layer of different energy can be irradiated ($\tau_{\text{energy}}$). This additional
7.3. Results

Figure 7.4: Reduction in $\tau_{eqip}$ when the amount of charge which can be stored in the synchrotron ring is increased. Open symbols are for spot scanning and the closed symbols are for continuous scanning.

time is typically not due to the beam source (cyclotron or synchrotron) or any components in the nozzle. A large number of magnets are present between the beam source and the nozzle to ensure the beam is steered correctly and the efficiency is as high as possible. The set points of these magnets are momentum dependent and need to be adjusted when changing layers. Figure 7.5 shows the effect on $\tau_{eqip}$ when $\tau_{energy}$ is altered.

It can be seen from Figure 7.5(a) that for the cyclotron with no ridge filter (0% curve) increasing the time to change energies from 1s to 10s causes the irradiation to take 8 times longer. It is obviously of interest to minimise this quantity as much as possible to speed up the irradiation. For the system considered here, $\tau_{energy}$ is the dominant effect on the total irradiation time assuming a cyclotron beam source. There is also an appreciable effect on $\tau_{eqip}$ for the synchrotron case. The increase in time is not as drastic due to the effect of the cycling time to repopulate the synchrotron. If one could do some repopulating whilst also resetting magnets for irradiation with a
7.3. Results

(a) cyclotron

(b) synchrotron

Figure 7.5: Effect on $\tau_{equip}$ when the time to change energy ($\tau_{energy}$) is altered for a cyclotron (a) and synchrotron (b) beam source. The percentage values show the $\Delta E$ values which represent different thickness ridge filters. Open symbols are for spot scanning and the closed symbols are for continuous scanning.
new energy, some time savings could be achieved.

Clinically, the flatness in the SOBP, or the dose tolerance is one of the most important parameters to consider. Under or over dosing can compromise the quality of the treatment. In terms of the treatment time, smaller tolerances on the SOBP flatness usually require more layers in the irradiation which is shown in Figure 7.6.

![Figure 7.6: The number of layers required to achieve a given dose tolerance in the SOBP. The percentages represent the different ∆E values of ridge filters of various thicknesses (0% squares, 0.5% circles, 1% Δ, 2% ∇, 3% stars).](image)

The method of placing individual Bragg peaks to construct an SOBP can result in slight discrepancies in the curves shown in Figure 7.6 such as for 3% dose tolerance, the 0% ∆E needs 13 layers, whilst the 0.5% filter requires 14 layers to achieve the required tolerance. The overlap in the 0% and 0.5% series is due the similarity of the Bragg peaks for these ∆E values. It can be seen that all the ∆E values follow the same trend, larger dose tolerances require fewer layers. The flat points in the curves are again due to the method of placing Bragg peaks to build the SOBP. It is possible that placing one more peak in the SOBP will take the flatness below the required tolerance, but this flatness may also satisfy a lower tolerance, e.g. 0% ∆E for 3% and
4% dose tolerance.

For the parameters outlined in Table 7.2 with no ridge filter (ΔE = 0%) the different time components and the total irradiation time for the different modalities is given in Table 7.3.

Table 7.3: Total irradiation times for the example irradiation of 2Gy with an $R_{80}$ of 20cm and a modulation of 10cm.

<table>
<thead>
<tr>
<th></th>
<th>Spot scanning</th>
<th>Continuous scanning</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cyclotron</td>
<td>Synchrotron</td>
</tr>
<tr>
<td>$\tau_{\text{dose}}(s)$:</td>
<td>10.62</td>
<td>10.62</td>
</tr>
<tr>
<td>$\tau_{\text{magnet}}(s)$:</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>$\tau_{\text{equip}}(s)$:</td>
<td>35.91</td>
<td>181.91</td>
</tr>
<tr>
<td>$\tau_{\text{total}}(s)$:</td>
<td>46.54</td>
<td>192.54</td>
</tr>
<tr>
<td></td>
<td>Cyclotron</td>
<td>Synchrotron</td>
</tr>
<tr>
<td>$\tau_{\text{dose}}(s)$:</td>
<td>10.62</td>
<td>10.62</td>
</tr>
<tr>
<td>$\tau_{\text{magnet}}(s)$:</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>$\tau_{\text{equip}}(s)$:</td>
<td>35.57</td>
<td>181.57</td>
</tr>
<tr>
<td>$\tau_{\text{total}}(s)$:</td>
<td>46.20</td>
<td>192.20</td>
</tr>
</tbody>
</table>

Table 7.3 shows the small variation in total irradiation time between spot scanning and continuous scanning for the same clinical requirements.

7.4 Discussion

The calculations outlined above cannot be currently applied to an arbitrary, irregularly shaped scanning field. The method of calculating the number of spots in the layer and the amount of slews required assumes a rectangular field. It is also assumed that the lateral field size does not change throughout the irradiation. In a clinical setting, the lateral field size is altered in each layer to conform the dose to the target volume. Fields used throughout the commissioning process are often rectangular for simplicity and as there is no need to conform to an irregularly shaped target. Regardless of the individual field configuration, if the same field is used for all methods of beam delivery, the conclusions regarding the hardware will be the same.

To generate the SOBPs used for the calculations, a database of Bragg peaks generated via Monte Carlo simulations using the Geant4 toolkit have been used. This
serves the purpose of this study, but other members of the scientific community may not have access to such a database, particularly those not based at clinical proton facilities. An additional goal of this study is to provide an outline for people interested in acquiring PBS functionality at a current or future proton facility. There are a number of functions presented in the literature (Bortfeld & Schlegel, 1996; Bortfeld, 1997; Fourkal et al., 2007) which allow for generation of the beam weights for generation of an SOBP. The functions in the literature typically allow calculation of the relative beam weights. Whilst this is no doubt useful for certain applications, relative weights are not sufficient for our method of calculating the time to deposit the dose as we require the absolute number of protons in each spot. Figure 7.7 shows the beam weights for the distal Bragg peaks of a 10cm x 10cm x 10cm cube at different ranges. The data presented in this figure can be used as a guide for members of the community who do not have access to a database of Bragg peaks. One of the several functions in the literature can then be used to generate the weights of the other peaks which are to be used in the SOBP. The plateaus or regions of inconsistency in the curve shown in Figure 7.7 is due to the method of optimisation and the Bragg peak spacing. Constant distances are used between Bragg peaks positioned throughout the SOBP. As seen previously in Table 7.1, the number of Bragg peaks required to give the 2% flatness within the SOBP changes with range. As the number of peaks in the SOBP changes, so does the number of protons delivered in each of the individual Bragg peaks.

The calculations used in this study assume that the scanning system is comprised of two perpendicular scanning magnets. This is the most common type of pencil beam scanning system and is the type used at MGH. Other types of scanning system are in operation such as that at the Paul Scherrer Institut (PSI) (Pedroni et al., 1995) which uses a single scanning magnet and the treatment couch is moved to give additional dimension of movement. The equations presented in this study will need to be altered
Figure 7.7: Beam weight, in number of protons, of the distal Bragg peak of a 10cm x 10cm x 10cm SOBP at various ranges. The range is defined as the distal $R_{80}$ of the SOBP.

to be applicable to systems such as this. For example, to approximate the system at PSI, the time for one of the scanning magnets would be substituted with the time required to move the treatment couch.

Ridge filters can be used to minimise the number of peaks required to deliver a treatment field. We have used different levels of energy smearing to represent the presence of ridge filters of various thicknesses. This gives certain values of $\Delta E/E$ whilst a ridge filter is designed to give constant $\Delta R/R$ where $R$ is the range. The main reasoning for employing the ridge filter in this study is to ascertain the benefit in terms of irradiation time, as the irradiation can be completed using fewer layers. There are a number of clinical questions which also need to be addressed when considering
the use of ridge filters. Increasing the energy spread of the proton beam causes the
distal falloff to be less sharp, which can have clinical implications.

Through investigation of the different Bragg peak spacing arrangements, it was
found that using a constant distance between the Bragg peaks gave the required flat-
ness using the smallest number of layers, leading to the shortest treatment time. This
is the reasoning behind the use of this arrangement throughout this study. However,
it needs to be noted that what is planned in proton therapy is not necessarily what
is delivered. For pencil beam scanning treatments, organ motion can result in dose
fluctuations within the target volume due to interplay effects (Bortfeld et al. 2002).
The sharp falloff in dose at the end of the proton range makes this modality highly
sensitive to uncertainties in both the calculated and delivered position of the Bragg
peak (Lomax 2008a).

It is possible that using fewer layers in the irradiation may in fact make the treat-
ment less robust against delivery uncertainties. In using the chosen spacing arrange-
ment throughout this study, we are not claiming that it should necessarily be employed
in a clinical scenario. That is a question for clinicians and is outside the scope of this
study.

7.5 Conclusion

A series of equations have been presented which allow calculation of the time required
to deliver relatively simple pencil beam scanning proton fields based on the properties
of the system hardware.

An example irradiation of a 1L cube was presented to highlight how altering the
individual components effected the various aspects of the total irradiation time. The
differences in spot scanning and continuous scanning have been highlighted and proton
beams produced by both a cyclotron and synchrotron have been considered.
The calculations presented in this study are facility independent and can be applied to any current or future pencil beam scanning system.
Chapter 8

Summary and future work

Proton therapy is an exciting development in the radiation therapy community and is the number of clinical facilities continues to grow around the world. There are 30 proton therapy facilities currently operating with a further 23 either proposed or under construction (PTCOG, 2009). Previous studies have shown the potential benefit of proton therapy compared to other treatment modalities (Dendale et al., 2006; Lomax et al., 2003b; Cozzi et al., 2001; Steneker et al., 2006; Miralbell et al., 2002; St Clair et al., 2004). Protons have a finite range in tissue which assists in the ability to spare normal tissue without compromising the effectiveness of treatment.

8.1 Potential for proton therapy in the treatment of cancer

In Chapter 2 the potential application of proton therapy to different clinical sites was examined through prospective and retrospective comparative planning studies. The results of these studies showed the potential improvement in the dose distributions using proton therapy compared to IMRT and other photon radiotherapy techniques.

A comparison of treatment plans using IMRT and proton therapy was performed
for a prostate patient. Step-and-shoot and sliding window IMRT plans using 5 and 7 fields were compared to double scattering proton therapy and intensity modulated proton therapy (IMPT).

The best target homogeneity was achievable using IMPT. The inclusion of some of the rectal volume in the PTV led to similar rectal sparing at high dose levels across all treatment plans. For all other critical structures considered, the proton plans gave better dose sparing.

The risk of second cancer from proton treatments has been compared to IMRT treatments. The results of the comparisons show that despite the concern of the effect of secondary neutrons generated during proton interactions in the treatment nozzle and patient that the risk of second cancer is expected to be lower from proton therapy treatments.

The lack of clinical trial data and the relatively high cost has somewhat hindered the widespread adoption of proton therapy. The debate continues regarding phase III randomised clinical trials and the need for conclusive results before proton therapy is accepted as a viable treatment option. Through research and the introduction of new technology, the variation in the cost between IMRT and proton therapy should become smaller.

Assuming that all additional delivery uncertainties such as organ motion and proton range uncertainties can be successfully managed or negated, proton therapy has the potential to deliver dose distributions which are superior to IMRT in terms of peripheral dose, with a lower risk of secondary cancer induction.
8.2 Choice of phantom materials for dosimetry of secondary neutrons

Secondary neutrons are produced in proton therapy via interactions which occur in the treatment nozzle and in the patient. Moving to active methods of beam delivery, such as pencil beam scanning, reduces the neutron component from the nozzle, however neutrons produced in the patient cannot be avoided.

The amount and energy of the neutrons produced is directly related to the proton-neutron interaction cross section, which is determined by the chemical composition of the target material. This implies that using different phantom materials will lead to varying levels of neutron production and hence dose.

Chapter 3 showed the variation in neutron absorbed dose and dose equivalent from neutrons generated in a series of phantom materials. Such phantom materials are routinely used in experimental studies to represent human tissue. The doses in the phantom materials were compared to those in various tissue types to assess their tissue equivalency. The contribution of neutrons from the treatment nozzle was not included.

The values of absorbed dose and dose equivalent observed are lower than those reported in previous studies, especially those which used double scattering proton therapy, suggesting that for this modality the total neutron dose is dominated by neutrons produced in the treatment nozzle. Using different phantom materials leads to variation in the neutron doses observed, which could be potentially clinically significant. Outside the treatment field, where the total dose is dominated by neutrons, solid water gave the best agreement out of the considered phantom materials with the different tissues investigated.
8.3 Geant4 Monte Carlo code for pencil beam scanning proton therapy

Chapter 4 outlines the work done in generating a dedicated code for simulation of pencil beam scanning proton fields. The simulation code was written using the Geant4 Monte Carlo toolkit and incorporated the beamline at the Francis H. Burr Proton Therapy Center at Massachusetts General Hospital.

The strength of the magnetic fields in the scanning magnets were calibrated such that the simulated lateral deflection of the proton beam matched the required positions within 1mm. Good agreement was observed between the depth-dose characteristics and measurements at a number of different ranges. The energy spread at the nozzle entrance was calibrated to ensure the width of the pristine Bragg peaks matched the width measured experimentally. This was achieved by minimising the $\chi^2$ variation between the simulations and experiments and the results were used to compute a fit which was used in all subsequent simulations using this code.

A complex two-dimensional irradiation was simulated to test the simulation code. The results of the simulation were compared to experimental measurements and a gamma index analysis was performed. 100% of the points passed the test using a criteria of 1%/1mm.

8.4 Neutron absorbed dose and dose equivalent in double scattering and pencil beam scanning proton therapy

Chapter 5 outlines the simulation of out-of-field doses using the double scattering Monte Carlo code previously described by Paganetti et al. (2004) and the pencil beam
Previous Monte Carlo studies have approximated the delivery of scanning fields by simulating a double scattering field and disregarding the dose resulting from secondary particles generated in the nozzle. This includes secondary particles generated in the phantom or patient which are daughter particles of secondaries produced in the nozzle. This methodology has been termed the “passive-internal” approximation and its validity was tested via comparison with simulation of a pencil beam scanning field using the full scanning treatment nozzle and beam properties. Scanning has a wider penumbra than double scattering because an aperture is typically not used for this modality. This leads to large discrepancies between the scanning results and the passive-internal data close to the field edge. For lateral distances greater than 10cm from the field edge, the effect of the scanning penumbra is not as significant and the passive-internal approximation largely agrees with scanning within the uncertainty limits.

There may be clinical cases where patient-specific hardware is used for clinical scanning treatments \cite{Kooy2010}. Typically, these will be cases where a sharper penumbra is required than is achievable without such hardware. As such, the aperture was included at nozzle exit in the simulations to ascertain the effect on the lateral penumbra and the out-of-field dose. Using an aperture reduces the absorbed dose and dose equivalent at 2.5cm from the field edge by over an order of magnitude. The increased neutron fluence from the primary beam interactions in the brass aperture do not lead to higher absorbed doses or dose equivalents lateral to the primary field because the proton dose in the same positions is reduced by such a large proportion. By reducing the dose and fluence lateral to the primary field, using an aperture also decreases secondary particle production out-of-field, the effect of which can be observed at all the depths considered, even distal to the SOBP.
Characterisation of the mixed radiation field in proton therapy

Chapter 6 showed how a ∆E-E detector can be used to characterise the radiation field external to the target volume in proton therapy. Operating the detector in coincidence mode allows identification of the particle type incident upon the detector based on the LET and energy deposited in the detector volume.

In proton therapy, the majority of the dose delivered external to the target volume is resultant from secondary neutrons. The secondary neutrons generated in the treatment nozzle in double scattering contribute to a higher neutron fluence distal to the SOBP. The contribution of the neutrons from the treatment nozzle diminishes with increased depth distal to the SOBP due to attenuation and the low average neutron energy.

The wider penumbra in pencil beam scanning leads to a higher contribution of primary protons to the total number of events collected close to (<5cm) the primary field edge. At larger distances lateral to the primary field, the neutron fluence is significantly lower in scanning. At 25cm from the field the photon fluence is significant for pencil beam scanning and should be accounted for in dose and risk estimates for this modality. Neutron events dominate the ∆E-E spectra for double scattering at all positions considered.

The orientation of the detector was found to be highly significant in the results obtained close to the radiation field due to the high anisotropy of the radiation field at such positions. The two orientations considered bias the results towards either scattered particles from the primary radiation field or secondary neutrons generated in the treatment nozzle. This confirms that the majority of secondary neutrons in double scattering proton therapy are forward scattered. Further measurements are required to ascertain if the detector orientation has the same significance further from
the field edge for double scattering and in pencil beam scanning.

8.6 Irradiation times for pencil beam scanning proton therapy

The time required to irradiate a field using pencil beam scanning can be calculated based on the properties of the system hardware. A series of equations have been presented in Chapter 7 which allow calculation of the time to deposit dose, to move the beam and for other equipment considerations which need to be accounted for.

An example irradiation of a 1 Litre cube was presented and the different parameters varied to ascertain their effect on the total irradiation time. The equations presented clearly demonstrate the differences between spot scanning and continuous scanning. For spot scanning treatments, the beam is turned off between individual spots, whilst continuous scanning leaves the beam on while it is moving. The difference in irradiation time between the two modalities arises from the time required to turn the beam on and off. This is included for each spot for a spot scanning irradiation and once per layer for a continuous scanning irradiation.

The differences in irradiation time resulting from different beam sources was also investigated. The equations allow a cyclotron or synchrotron to be the beam source with different parameters used depending on the choice made. A synchrotron can only store a finite number of protons in the ring. Once these are used, the synchrotron needs to be repopulated. This increases the time required to complete the irradiation. The best case when using a synchrotron as the beam source is that an entire layer can be delivered without repopulating the synchrotron. If this is possible, the irradiation times for a cyclotron and synchrotron will be the same, otherwise the irradiation using a synchrotron will take longer.
The calculations presented assume a scanning system composed of two perpendicular scanning magnets. The calculations are facility independent and can be easily applied to any scanning system of this type.

8.7 Future work

8.7.1 The next step

The topics presented in this thesis have a number of areas which warrant investigation in the future. These include:

(i) Perform planning comparisons for prostate radiotherapy using a larger cohort of patients

(ii) Simulate neutron doses in additional materials and tissues and include the effects of neutrons generated in the treatment nozzle

(iii) Assessment of neutron doses for different pencil beam scanning fields

(iv) Measurements using the $\Delta E$-$E$ detectors at more positions and for other field configurations to further understand the effect of secondary neutrons

(v) Test the significance of the $\Delta E$-$E$ orientation in pencil beam scanning and at other measurement positions

(vi) Extend pencil beam irradiation time calculations to other scanning systems and arbitrary field shapes

8.7.2 Proton therapy for prostate cancer

The results presented in Chapter 2 demonstrate the potential benefit of proton therapy for prostate cancer. Whilst IMRT and other photon techniques can deliver the required
dose and conformality to the tumour volume, proton therapy can achieve the required conformality with lower a integral dose. This has potential benefit if the low dose bath delivered in IMRT is shown to increase the risk of second malignancy.

Further investigation requires consideration of a larger patient cohort. Different patients have different tumour histologies and anatomy, implying the potential benefit observed for the considered patient may or may not be realised for other patients. To fully explore the potential usefulness of proton therapy for prostate cancer, a variety of patients must be included in a future study.

What is prescribed in the treatment plan is not always what is delivered in the clinic. The higher conformality of protons makes this modality more susceptible to organ motion. Protons are also more sensitive to inhomogeneities which can alter the proton range. Both organ motion and inhomogeneities need to be accounted for to give a more robust conclusion regarding the potential benefit of protons compared to IMRT.

### 8.7.3 Tissue equivalency of phantom materials

In Chapter 3, the tissue equivalency of a series of phantom materials was determined via Monte Carlo simulations and comparison with the neutron doses in ICRP tissue materials. The neutron production in the phantom or patient is dependent on the proton-neutron cross-section which is in turn determined by the chemical composition of the target material.

The simulation of the neutron absorbed dose, average radiation weighting factor and dose equivalent in additional materials may lead to the finding of a more suitable phantom material for use in secondary neutron experiments in proton therapy. The interaction cross-sections are also energy dependent, implying that to make a definitive conclusion, each material should be simulated at a series of primary beam energies over
the range which can be delivered in a clinical treatment.

8.7.4 Monte Carlo simulations for pencil beam scanning

The Monte Carlo code outlined in Chapter 4 and implemented in Chapter 5 demonstrated the potential application of Monte Carlo simulations in proton radiotherapy. The results of the simulations show that for small lateral distances from the field edge the previously used “passive-internal” approximation does not provide an accurate representation of the doses resulting from pencil beam scanning fields. For larger distances from the primary field, the total dose is dominated by internally produced secondaries which implies that the approximation is valid in such areas.

The out-of-field doses from pencil beam scanning are typically an order of magnitude lower than double scattering for distances larger than 15cm from the primary field. Incorporating a patient-specific aperture at the exit of the scanning treatment nozzle further reduces the absorbed dose and dose equivalent by over an order of magnitude at all positions proximal to and within the SOBP. It is known that for double scattering, the neutron dose is dependent on the field parameters (Zacharatou Jarlskog & Paganetti, 2008b). For smaller fields, the neutron yield from the treatment nozzle is higher because the aperture is required to stop a higher number of protons. In scanning, the neutron yield should not be as dependent on field size because the aperture is only being used to reduce the width of the penumbra. The use of apertures in scanning has already been proposed for certain clinical sites which will require narrower lateral penumbra (Kooy et al. 2010).

To fully understand the consequences and potential applications of apertures in pencil beam scanning, proton fields of different sizes and ranges should be simulated. This will give a clear indication of the potential utilisation of apertures in pencil beam scanning.
8.7.5 Characterisation of the mixed radiation field outside the target volume in proton therapy

The experimental measurements outlined in Chapter 6 show the potential of ∆E-E detectors for use out-of-field in proton therapy. When operated in coincidence mode, the particle types incident upon the detector can be distinguished based on the LET and energy deposited.

The ∆E-E detectors were used to characterise the mixed radiation out-of-field for a clinical pancreatic field for both double scattering and pencil beam scanning methods of delivery. The noise threshold on the device restricts the lower limit on the LET which can be detected in thin ∆E stage of the detector. This could be potentially important for out-of-field applications where the dose is primarily due to secondary neutrons which can travel far in tissue.

The results of the measurements performed show the lower neutron fluence lateral to the primary field in pencil beam scanning compared to double scattering. To fully comprehend the potential benefit of this modality in terms of out-of-field dose, measurements need to be performed for different clinical cases which use beams of both higher and lower energies than what was considered here. Measurements at more positions out-of-field should be performed, particularly close to the proximal surface of the phantom, where the neutrons generated in the double scattering treatment nozzle may have a significant effect.

8.7.6 Calculation of pencil beam scanning treatment times

Chapter 7 outlines how the irradiation time for a scanning field can be calculated based on the properties of the system hardware. This allows the effect of each parameter in the system on the irradiation time to be determined. The potential use of these calculations is to optimise existing scanning facilities through alteration of
various components or for specification of the hardware in a facility which is yet to be constructed.

There are some assumptions made in the calculation which could be removed to make the calculations more general and robust. The assumption of a scanning system which uses two perpendicular magnets was implemented as this is the most common setup. To be more widely applicable, the equations could be adapted such that they can be applied to the setup any current or future scanning system.

The method of scanning the beam in the calculations is used as it requires the beam to be moved the least amount of times during irradiation of a layer. This may not be the method used in all facilities and inclusion of different scanning methods could make the calculations more widely applicable.

The fewest number of layers are used in the calculation to give the required dose tolerance. This could potentially make the treatment less robust to treatment uncertainties such as inhomogeneities and organ motion. A method of determining the robustness of the fields to these uncertainties could be included in the calculation of the number of layers required in the field.

Simple rectangular fields are typically used in commissioning measurements as the complexity of a clinical treatment field is not essential for such applications. As such, only simple fields can be calculated using these equations. The ability to import clinical fields and calculate the time required for irradiation could be included in the equations for direct application in the clinic. Such a calculation could potentially be used as a safety check to ensure the treatment is delivered in the correct amount of time.
8.7. **Future work**

8.7.7 **Summary**

This thesis represents a study into the potential benefits of proton therapy, particularly pencil beam scanning for the treatment of cancer. The main priorities for future work resulting from the studies presented in this thesis are

(i) Quantification of any benefit of proton therapy compared to IMRT and other techniques for different clinical sites

(ii) Perform further measurements and Monte Carlo simulations to fully characterise the field external to the tumour volume for different field configurations

(iii) Determine the risk of second cancer induction from the measured neutron doses in double scattering and pencil beam scanning proton therapy
References


References


Peterson, S. W., Polf, J., Bues, M., Ciangaru, G., Archambault, L., Beddar, S., &


References


References


dose equivalent to proton therapy patients outside of the proton radiation field.


From Neutron Dose in Proton Therapy as Function of Field Characteristics, Organ,

Assessment of organ-specific neutron equivalent doses in proton therapy using com-
putational whole-body age-dependent voxel phantoms. Phys Med Biol, 53(3), 693–
717.

Y., Newhauser, W. D., Gillin, M., & Mohan, R. 2007. Effect of anatomic motion on
proton therapy dose distributions in prostate cancer treatment. Int J Radiat Oncol
Biol Phys, 67(2), 620–9.