**DEVELOPMENT OF A TECHNIQUE TO SIMULTANEOUSLY
VERIFY LINEAR ENERGY TRANSFER AND ABSORBED DOSE IN
THERAPEUTIC PROTON BEAMS**

by

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Abstract

The biological response resulting from proton radiotherapy depends on both the absorbed dose in the irradiated tissue and the linear energy transfer (LET) of the beam. Currently, the optimization of proton therapy treatment plans is based only on absorbed dose.

However, recent advances in proton therapy delivery have made it possible to vary the LET distribution for a potential therapeutic gain. As a result, researchers and clinicians have investigated the use of LET as an additional parameter in proton therapy treatment optimization. To safely deliver such treatment plans, it would be ideal to have a method in place to measure and verify both absorbed dose and LET as part of a quality assurance program. While absorbed dose is readily measured using a variety of detectors, there is no device available for the routine measurement and verification of LET.

In this thesis, optically stimulated luminescence (OSL) techniques are investigated for simultaneous measurements of absorbed dose and LET. A Monte Carlo infrastructure to simulate LET distributions in a proton therapy beamline is first developed. Using the simulated LET values, the LET dependence of OSL detectors is thoroughly characterized. Two parameters of the OSL signal, representing the OSL curve shape and the ratio of UV to blue emission intensities, are used to generate LET calibration curves. These curves facilitate the measurement of LET using OSL detectors. Additionally, a new OSL technique is developed to measure absorbed dose in therapeutic proton beams of varying LET.

The potential of the OSL techniques is demonstrated by using them to measure LET and absorbed dose under new irradiation conditions, including real patient-specific proton therapy treatment plans. In the beams investigated, OSL techniques are found to

measure dose-weighted LET within 7.9% of the MC simulated values, and absorbed dose within 2.5% of ionization chamber measurements.

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I am incredibly grateful to my supervisor, Dr. Gabriel O. Sawakuchi, for his guidance, expertise, and tireless support over the last four years. Despite moving to Texas, Gabriel remained incredibly dedicated to my success as a student in Ottawa. To put it simply, Gabriel has been an *awesome* supervisor. I am proud to be the first of what I expect to be a long line of successful PhD students to work under his supervision.

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Statement of Originality

This thesis summarizes the most significant portions of the author's research throughout the PhD program at Carleton University. Many of the results presented in this thesis have been published in peer-reviewed journals and presented at both national and international conferences. The details of these publications and presentations are summarized below. The manuscripts and abstracts were all drafted and revised by the author, with input and supervision from Dr. Gabriel Sawakuchi. Unless otherwise noted below, the author performed all computational work, experiments, and analyses that led to their preparation, with input and guidance from Dr. Sawakuchi.

Published Articles

1. **DA Granville**, N Sahoo and GO Sawakuchi, "Calibration of the $\text{Al}_2\text{O}_3\text{:C}$ optically stimulated luminescence (OSL) signal for linear energy transfer (LET) measurements in therapeutic proton beams," *Phys. Med. Biol.*, **59**, 4295-4310 (2014).
 - The results of this paper are not explicitly included in this thesis, because improved results have since been obtained. However, it is cited often because it serves as the basis for new developments presented in Chapter 5. Dr. Narayan Sahoo performed detector irradiations for the work in this paper. The author performed all other experimental work.
 - The results of this paper were presented at the AAPM Annual Meeting in Austin, TX (2014).
2. **DA Granville**, N Sahoo and GO Sawakuchi, "Linear energy transfer dependence of $\text{Al}_2\text{O}_3\text{:C}$ optically stimulated luminescence detectors exposed to therapeutic proton beams," *Rad. Meas.*, **71**, 69-73 (2014).
 - The results of this paper can be found in Chapter 4. This study presents a preliminary investigation upon which remaining chapters are based. Dr. Narayan Sahoo performed detector irradiations. The author performed all other experimental work.

- The results of this paper were presented at the 17th International Conference on Solid State Dosimetry in Recife, Brazil (2013).
3. **DA Granville** and GO Sawakuchi, “Comparison of linear energy transfer scoring techniques in Monte Carlo simulations of proton beams,” *Phys. Med. Biol.*, **60**, N283-N291 (2015).
- The results of this paper can be found in Chapter 2, which discusses various techniques of scoring LET in Monte Carlo simulations.
 - Preliminary results were presented by the author at the COMP Annual Scientific Meeting in Banff, AB (2014). Further results from this work were presented by Dr. Sawakuchi at the Particle Therapy Co-operative Group – North America Meeting in Houston, TX (2014).

Manuscripts in Preparation

1. **DA Granville**, N Sahoo and GO Sawakuchi, “Simultaneous measurements of absorbed dose and linear energy transfer in therapeutic proton beams.”
- The results of this manuscript can be found throughout Chapters 5, 6 and 7, which detail the OSL techniques developed to measure LET and absorbed dose. Dr. Narayan Sahoo provided guidance in the selection of patient-specific treatment plans, and manipulation of the clinical software.
 - The results of this manuscript were presented at the AAPM Annual Meeting in Anaheim, CA (2015).
2. **DA Granville**, and GO Sawakuchi, “Characterization and modeling of the LET response of Al₂O₃:C optically stimulated luminescence detectors.”
- Experimental results from this manuscript can be found throughout Chapters 5 and 6. In the manuscript, these data are also used to form an analytical model of detector response. Due to the preliminary nature of the modeling work, it is not presented in this thesis.
 - The experimental portion of these results was presented at the AAPM Annual Meeting in Anaheim, CA (2015). Some preliminary results related to this study were also presented at the 17th International Conference on Solid State Dosimetry in Recife, Brazil (2013).

Contributions from other individuals that are not listed in the above publications are summarized below. These individuals were undergraduate students who worked with Dr. Sawakuchi and the author.

Matthew H. Chequers worked on the early development of the Monte Carlo model presented in Chapter 2. MH Chequers implemented early models of some geometry components and performed preliminary validation attempts. Additional geometry and source modeling, thorough validation, implementation of all new scoring techniques, modeling of patient-specific components, numerous bug fixes, and maintenance of the model through 14 updates of the TOPAS Monte Carlo code were all performed by the author.

Mark Leibensperger worked with Dr. Sawakuchi and the author on the time-dependence study outlined in Appendix A. The study was designed by the author. M Leibensperger prepared detectors, assisted with irradiations, and performed ~50% of the readouts and analysis. The remainder of the work was performed by the author.

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List of Abbreviations

CW-OSL	Continuous-wave optically stimulated luminescence
DT	Deep trap
DTA	Distance to agreement
IMPT	Intensity modulated proton therapy
LED	Light emitting diode
LET	Linear energy transfer
<i>LET_D</i>	Dose-weighted linear energy transfer
<i>LET_Φ</i>	Fluence-weighted linear energy transfer
MC	Monte Carlo
MDT	Main dosimetric trap
OSL	Optically stimulated luminescence
OSLD	Optically stimulated luminescence detector
P-OSL	Pulsed optically stimulated luminescence
PDD	Percentage depth dose
PMT	Photomultiplier tube
PNTD	Plastic nuclear track detector
PTCH	Proton Therapy Center - Houston
QA	Quality assurance
RBE	Relative biological effectiveness
RC	Recombination centre
RMW	Range modulator wheel
SOBP	Spread-out Bragg peak
ST	Shallow trap
TOPAS	Tool for Particle Simulation
TPS	Treatment planning system
UV	Ultraviolet

Chapter 1

Introduction and Motivation

1.1 Proton Therapy

Along with surgery and chemotherapy, radiotherapy is one of three main treatment options available to cancer patients. Most commonly, radiotherapy is delivered to patients using an external beam of photons. However, the use of heavy charged particles, including protons, is becoming increasingly common. Between the years 2007 and 2014, the number of patients treated with proton therapy nearly doubled, from 53 thousand annually to more than 105 thousand. As of July 2015, there are 48 institutions that offer proton therapy operating worldwide. A further 27 are under construction, and an additional 17 are in the planning stages of development (PTCOG 2015).

1.1.1 Rationale

The goal of most radiotherapy treatments is to deliver a high, uniform dose of radiation to some target volume (e.g. a cancerous tumour) while limiting the dose delivered to healthy tissue. In conventional external beam radiotherapy using electrons or photons, this is challenging because the beam must irradiate tissues that are both proximal and distal to the target volume in order to provide adequate target coverage. The main rationale behind using protons in radiotherapy lies in the shape of their depth-dose distribution. The depth-dose distribution resulting from a monoenergetic proton beam exhibits a broad region of relatively low dose, followed by a sharp increase before a very rapid falloff to near zero dose (Figure 1.1). This narrow region of high dose is commonly referred to as the Bragg

peak. The depth at which the Bragg peak occurs depends on the energy of the proton beam.

Figure 1.1: Percentage depth-dose distribution for a monoenergetic (250 MeV) proton beam incident on a water tank. The region of maximum dose is referred to as the ‘Bragg peak’.

To create more clinically useful depth-dose distributions (i.e. a broader region of high, uniform dose to cover a target volume), the beam energy is typically modulated. By modulating the proton energy appropriately, a number of different Bragg peaks can be combined to create a uniform dose distribution within the target volume. This energy modulation is achieved using different methods, depending on the proton therapy delivery technique. Using the passive scattering technique, in which a broad beam irradiates the entire treatment field, the energy is modulated by passing the proton beam through varying thicknesses of material. This results in the so-called spread-out Bragg peak (SOBP), as shown in Figure 1.2. The main characteristics of the SOBP depth-dose

distribution are a region of high uniform dose followed by a rapid falloff. This is advantageous for radiotherapy purposes, because a target volume can be placed within the SOBP such that a uniform dose is delivered to it. The rapid falloff in dose offers the potential to spare healthy tissue located distally to the target volume.

Figure 1.2: A series of monoenergetic proton beams (blue) combining to result in the clinically useful ‘spread-out Bragg peak’ (SOBP) depth-dose distribution (black). During treatment planning, the range and SOBP width are chosen such that the SOBP region encases the target volume.

A second proton therapy delivery technique, spot scanning, offers the potential for further improvement of absorbed dose distributions. Using the spot scanning technique, a narrow pencil beam of protons is scanned laterally over the target volume, while the proton accelerator (typically a synchrotron or cyclotron) modulates the energy. The scanning technique allows for lateral variations in SOBP width, unlike passive scattering (Lomax 2012), which potentially allows for improved conformality to the proximal edge of the target volume. Intensity modulated proton therapy (IMPT) is one application of the

spot scanning technique that can produce more highly conformal dose distributions than other proton treatment delivery methods (Trofimov *et al* 2012). This is accomplished with a more advanced planning technique that uses multi-field optimization (Lu and Flanz 2012, Trofimov *et al* 2012). With more traditional treatment planning methods, fields are optimized individually in order to achieve a uniform dose distribution within the target volume for each field. Using IMPT's multi-field optimization, however, multiple fields are optimized simultaneously. This leads to the superposition of many non-uniform fields to achieve a uniform dose distribution in the target volume.

The depth-dose distributions of photons and electrons do not offer the same rapid falloff in dose as protons. Thus proton therapy offers the potential of superior dose distributions for patient treatment, and in particular, the potential for a lower integral dose. A typical depth-dose distribution from a megavoltage photon beam used for radiotherapy is shown in Figure 1.3, for comparison.

Figure 1.3: Percentage depth-dose distribution for a 10 MV photon beam incident on a water tank. Depth-dose curves for photon beams show a gradual falloff in dose.

1.1.2 Linear Energy Transfer and Biological Implications

Radiotherapy treatment plans are typically optimized based on absorbed dose distributions. The absorbed dose is defined as the ratio of the mean energy imparted to a medium per unit mass. In simple terms, the absorbed dose is often used to quantify the ‘amount’ of radiation that is delivered during a radiotherapy treatment. The absorbed dose is typically expressed in units of Gray (Gy), with 1 Gy being defined as 1 joule of energy per kilogram of mass. Generally, increasing the absorbed dose increases the damage done to biological tissues. However, different radiotherapy modalities do not necessarily result in equivalent biological damage for the same absorbed dose (Hall and Giaccia 2006). The biological damage incurred per unit absorbed dose is often described by the relative biological effectiveness (RBE) of a beam. The RBE describes the

biological damage per unit dose in a beam of interest relative to a reference beam (typically a ^{60}Co photon beam). For example, if a given beam had an RBE of 2, it would require half the dose of a ^{60}Co beam to achieve the same level of biological damage. This is of no consequence in conventional radiotherapy modalities that use megavoltage photons and electrons, because they have an RBE of unity. However, in radiotherapy with heavy charged particles, including protons, the RBE increases with the linear energy transfer (LET) of the particles (Hall and Giaccia 2006).

LET is defined by the International Commission on Radiation Units as “the quotient of dE_{Δ} by dl , where dE_{Δ} is the mean energy lost by the charged particles due to electronic interactions in traversing a distance dl , minus the mean sum of the kinetic energies in excess of Δ of all the electrons released by the charged particles” (ICRU 2011). LET is typically expressed in units of $\text{keV}/\mu\text{m}$ in radiotherapy applications. Unrestricted LET includes all electrons ($\Delta = \text{infinity}$) and is numerically equivalent to unrestricted electronic stopping power. In simple terms, the LET describes how densely a charged particle deposits energy along its path. RBE generally increases with LET in therapeutic proton beams. The high ionization densities surrounding the track of high LET protons (Figure 1.4) increases the likelihood of irreparable damage to cell DNA, causing the increase in RBE. At very high LET, there is often an overkill effect that causes a reduction in RBE with increasing LET. However, this occurs at LET values higher than those that are relevant for proton therapy applications (Grassberger *et al* 2011, Paganetti 2014).

Figure 1.4: Image of ionization surrounding a relatively low LET (left) and high LET (right) proton beam generated using Monte Carlo simulations. The same number of primary protons (blue) is shown in each image. Considerably more secondary electrons (red) are produced near the path of the high LET beam. For scale, both figures are 10 μm in width.

LET variations can occur within the target volume during proton therapy treatments. When the passive scattering technique is used, for instance, at regions near the beginning of the SOBP, protons are relatively high in energy, and therefore relatively low in LET. Conversely, near the end of the SOBP, protons are low in energy and therefore high in LET. This non-uniformity in LET results in a non-uniform biological effect, despite the uniform absorbed dose distribution (Figure 1.5). Additionally, healthy tissue beyond the SOBP can be exposed to the most biologically effective (highest LET) region of the proton beam (Carabe *et al* 2012, Paganetti 2012b). This is because clinicians include margins surrounding the target volume to account for uncertainties, and ensure that it is entirely covered during treatment.

Figure 1.5: Non-uniformities in LET can result in non-uniform biological damage within the treatment volume. Here, ‘biological dose’ refers to the produce of RBE and absorbed dose. RBE values were calculated using a simple, approximate model described in the literature for in vitro hamster cells (Wilkens and Oelfke 2004). These RBE data are not indicative of typical clinical scenarios, but rather are included here for illustrative purposes.

Current practice in proton therapy treatment planning ignores the variations in LET, and considers the RBE to be a uniform average value of 1.1. However, this is well known to be only an approximation, and numerous recent studies have demonstrated the variable RBE within therapeutic proton beams (Britten *et al* 2013, Chaudhary *et al* 2014, Guan *et al* 2015, Liu *et al* 2015, Matsumoto *et al* 2014). A recent and thorough review of the available proton RBE data demonstrated that, although the data support an average value of ~ 1.1 , considerable deviations from this value occur as a function of LET and cell type (Paganetti 2014).

1.1.3 LET Optimization in Proton Therapy Treatment Plans

New treatment planning procedures have been investigated to account for LET variations in therapeutic proton beams. These have included the optimization of proton therapy treatment plans using variable RBE considerations (Fager *et al* 2015, Frese *et al* 2011, Krämer and Scholz 2000, Wilkens and Oelfke 2005, 2006) or using LET as a surrogate for RBE (Giantsoudi *et al* 2013, Grassberger *et al* 2011). Whether optimization is performed using RBE or LET, the main goal is the same: to limit the absorbed dose and LET in healthy tissue, and deliver high dose and LET to the target volume.

Using traditional methods of proton therapy delivery, little can be done to improve LET distributions for treatment purposes. However, the advent of IMPT has made it possible to achieve similarly acceptable dose distributions with greatly differing LET distributions (Grassberger *et al* 2011). Treatment plans that contain high dose and high LET within the target volume, and low dose and low LET outside of the target volume, offer the potential of improved patient outcome.

1.2 LET Measurements

To safely deliver RBE- or LET-optimized proton therapy treatments, it would be ideal to have a method in place to measure and verify both absorbed dose and LET as part of a quality assurance (QA) program. Similar patient-specific verification of other complex treatment modalities is often recommended (Ezzell *et al* 2003, Galvin *et al* 2004, Pawlicki *et al* 2010). Though it is possible to determine LET and absorbed dose using analytical or Monte Carlo (MC) methods, it is important to have an independent method of measurement to verify accuracy in calculations and beam delivery prior to patient

treatment. Although several detectors are capable of measuring absorbed dose in therapeutic proton beams, there are currently no detectors available for the routine clinical measurement of proton LET.

Several detectors are capable of measuring LET, however, certain impracticalities or limitations may restrict their potential for routine use in proton therapy clinics. Plastic nuclear track detectors (PNTDs) can measure proton LET. However, PNTDs are better-suited for higher LET values (>5 keV/ μm in water) than those that are typically found in therapeutic proton beams, and their readout procedures are laborious (Benton *et al* 2002, Kohno *et al* 2005). Thermoluminescent dosimeters have been studied for LET measurements, however their LET dependent characteristics strongly depend on batch, dose and preparation (Bilski 2006, Bilski *et al* 2014, Horowitz *et al* 2003, Moyers and Nelson 2009, Vana *et al* 1996). Tissue-equivalent proportional counters are capable of measuring LET, but they cannot provide adequate spatial resolution for proton therapy, and lack the simplicity of use that would be ideal for clinical implementation (Bradley *et al* 2001). Polymer gel dosimeters have shown an LET dependence that is promising for LET measurements, but their use for this purpose has not yet been demonstrated or characterized (Lopatiuk-Tirpak *et al* 2012). Lastly, novel semiconductor devices have shown the promising ability to perform microdosimetric measurements of lineal energy, but their use for routine clinical measurements of LET has not yet been demonstrated (Agosteo *et al* 2010, Guardiola *et al* 2015, Wroe *et al* 2009).

1.3 Outline of Thesis

This thesis explores the development of a technique that has potential for simultaneous measurements of LET and absorbed dose in therapeutic proton beams. The optically stimulated luminescence (OSL) technique is studied for this purpose. The OSL technique is a versatile tool that is commonly used in radiation dosimetry. The hypothesis behind this work is that different properties of OSL signals can be calibrated to allow for simultaneous measurements of absorbed dose and LET. Such measurements would be useful in the pre-treatment QA of RBE- or LET- optimized proton therapy treatment plans.

LET Calibration Curves

As the OSL technique has been well-studied for absorbed dose measurements, the bulk of this thesis is dedicated to the development of a technique to measure LET. The goal behind this work was to generate an LET calibration curve that describes a characteristic of the OSL signal as a function of LET, and can be used to perform LET measurements. Two challenges in the development of such a calibration curve were evident, and addressed in this work. The first challenge was the implementation of a reliable method of determining LET under calibration conditions. There is not a readily available ‘gold standard’ device against which detectors can be calibrated for LET measurements. Thus, another method was necessary to determine reference values of LET under calibration conditions. The second challenge was to determine an appropriate parameter of the OSL signal to calibrate for LET measurements. These two challenges led to two distinct branches of research that were necessary to develop an LET calibration curve 1) Monte

Carlo (MC) simulations to provide reference values of LET against which OSL detectors could be calibrated, and 2) experimental irradiations and analysis of OSL detectors to identify and characterize appropriate LET-dependent parameters.

Chapters 2 and 3 are dedicated to the MC branch. In Chapter 2, the development and validation of an MC model of the proton therapy beamline used for later experimental irradiations is detailed. In Chapter 3, several different techniques of scoring LET in MC simulations of proton beams are investigated and compared, in order to identify a reliable method of determining LET.

Chapters 4 and 5 are dedicated to the experimental branch. In Chapter 4, background information about the OSL technique is discussed, and a preliminary investigation to identify LET-dependent characteristics of OSL detectors is summarized. In Chapter 5, LET-dependent characteristics of the OSL signal are parameterized and calibrated against LET values determined using MC simulations, in order to generate LET calibration curves.

Absorbed Dose Calibration Curves

Chapter 6 describes experiments performed to develop a technique to measure absorbed dose in therapeutic proton beams of varying LET. The dose response of several OSL signal parameters is investigated. Absorbed dose calibration curves are generated, and a novel method to correct for the LET-dependent dose response of OSL detectors is presented.

Measurements of LET and Absorbed Dose

Chapter 7 presents the results of LET and absorbed dose measurements performed using the calibration curves developed in Chapters 5 and 6. Measurements of LET are compared against MC reference values, and measurements of dose are compared against those obtained using calibrated ionization chambers. The results are used to assess the potential of the OSL techniques developed.

Note that the OSL technique is used in Chapters 3-7. For clarity, the relevant OSL theory for each chapter is included in its Introduction section, rather than including all OSL theory in one place.

Chapter 2

A Monte Carlo Model of a Passive Scattering Proton Therapy Nozzle

To calibrate OSL detectors for measurements of LET, it was necessary to have a ‘gold standard’ method to determine reference LET values under experimental irradiation conditions. Because there is not a readily available standard device for LET measurements, MC simulations were used in this work to determine reference LET values. This chapter discusses the development and validation of an MC model of the passive scattering proton therapy nozzle at The University of Texas MD Anderson Cancer Center Proton Therapy Center, Houston (PTCH). This nozzle was used for all proton irradiations discussed in later chapters.

RBE- or LET-optimized treatment plans are only feasible with spot scanning nozzles. However, the passive scattering proton therapy nozzle was used for all irradiations and MC simulations presented in this thesis. This decision was based on the extremely limited availability of PTCH’s spot scanning nozzle for experimental purposes. However, this is not expected to greatly affect the methodology presented in this work, because a similar range of proton LET values can be obtained using either nozzle.

2.1 Introduction

2.1.1 Monte Carlo Simulations

Monte Carlo simulations of radiation transport have proven useful in radiotherapy practice and research, and can be used to determine quantities that are relevant to radiotherapy, but not easily determined analytically or experimentally (Paganetti 2012a,

Rogers 2006). These could include distributions of absorbed dose, fluence or LET among others. Using the MC method, particles are explicitly simulated and tracked through geometries of interest. Known probability distributions are sampled to simulate the trajectories of particles and their interactions with media.

2.1.2 The TOPAS Monte Carlo Platform

A number of general-purpose MC codes are capable of simulating proton therapy beams. The most widely used codes are Geant4 (Agostinelli *et al* 2003), MCNPX (Waters 2002) and Fluka (Ferrari *et al* 2005). These codes support a wide range of particle types, energies, and interactions. As a result, it is often challenging to benchmark these general-purpose codes for specific applications that require only a small fraction of the codes' capabilities. Recently, an MC platform called Tool for Particle Simulation (TOPAS), which is based on the Geant4 simulation toolkit, was developed specifically for simulations of therapeutic proton beams (Perl *et al* 2012). The TOPAS platform provides well-benchmarked physics for therapeutic proton beams (Zacharatou Jarlskog and Paganetti 2008), built-in scorers for quantities relevant to proton therapy, and configurable geometry components that are commonly found in proton beamlines. TOPAS has been validated for the modeling and simulation of passive scattering proton therapy systems (Testa *et al* 2013). Due to its specificity for proton therapy and its flexibility, the TOPAS MC platform (version 1.0-b12, based on Geant4 version v4.09.06-p02) was chosen for all simulations presented throughout this thesis.

The TOPAS platform provides a number of adjustable simulation parameters that can be altered to serve the needs of a particular application. The most commonly adjusted simulation parameters are summarized here:

Secondary Particle Range Production Thresholds: Geant4, which TOPAS is based on, uses range production thresholds to determine whether or not to explicitly generate and track a secondary particle, or deposit its energy locally. For example, if a proton undergoes an interaction that would generate a secondary electron, the code checks to see if this electron is expected to travel further than some user-defined range. If so, the secondary electron is explicitly generated, and tracked through the medium. If not, then the kinetic energy that the secondary electron would have possessed is instead deposited locally. The use of range production thresholds prevents wasted CPU time in the tracking of low energy particles, whose motion does not affect the scored quantity of interest within a particular voxel.

Maximum Step Size: In MC simulations, the continuous motion of a charged particle is typically approximated by a series of discrete steps using the condensed history technique (Berger 1963). In a particular step, the average effect of a large number of soft interactions (i.e. interactions that do not produce secondary particles with an expected range exceeding the production threshold) is accounted for using a single change in energy and direction. Generally, the step length is determined by physics processes, or the distance to the nearest geometrical boundary. Due to the approximate nature of the condensed history technique, it is sometimes necessary to limit the maximum step size allowed. For the simulations presented in this thesis, it was not necessary to limit the step

size. The TOPAS default maximum step size of 100 mm was used for all simulations, such that the user did not artificially limit the calculated step sizes during simulation.

Physics List: The physics list specifies the processes and interactions that can occur for each simulated particle, as well as the models that are used to determine the results of these processes. Many different models and approximations are available in Geant4 and TOPAS. It is up to users to ensure that they choose the physics lists that are relevant for their particular interests. TOPAS provides pre-packaged physics lists that have been validated for use in proton therapy simulations (Testa *et al* 2013, Zacharatou Jarlskog and Paganetti 2008). For all simulations presented in this thesis, the default TOPAS physics list was used. This physics list consisted of the following 6 modules: g4em-standard_opt3, g4h-phy_QGSP_BIC_HP, g4decay, g4ion-binarycascade, g4h-elastic_HP, and g4q-stopping.

2.1.3 Geometry of the PTCH Passive Scattering Proton Therapy Nozzle

To accurately simulate the beams from a proton therapy nozzle, it is necessary to implement the physical components of the beamline within the MC simulations. At PTCH, a synchrotron accelerates primary protons to energies of up to 250 MeV before entering the treatment nozzle. Within the passive scattering nozzle, the near-monoenergetic pencil beam of protons is converted to a clinically useful beam. Using TOPAS, we implemented an MC model of the passive scattering proton therapy nozzle. The model geometry is shown in Figure 2.1.

Figure 2.1: The TOPAS MC model of the passive scattering proton therapy nozzle at the MD Anderson Cancer Center Proton Therapy Center in Houston, TX. All components that the primary proton beam traverses were modeled. Patient-specific components (aperture and range compensator) are not shown in this image.

A brief description of each of the modeled components is given below (Arjomandy *et al* 2009, Smith *et al* 2009). The components are presented in the order that protons traverse them.

Source: The beam source was modeled as a parallel beam of protons, with a Gaussian spread in both energy and profile. The nominal energy of each beam was used as the mean source energy. Due to a lack of certainty in specifications of energy spread and beam size, these were treated as free parameters that could be tuned within reasonable limits. A standard deviation of 0.1% of the mean energy was used to model the energy spread, and a standard deviation of 0.3 cm was used to model the source profile. These

values were found to give sufficient accuracy, over a large range of irradiation conditions.

Unlike the source, the remaining components were modeled based on known geometry specifications, and no adjustments were made.

Vacuum Window: A solid steel cylinder at the entrance of the nozzle. It separates the vacuum of the beam source from the remainder of the nozzle, which is at atmospheric pressure.

Reference Dose Monitor: A segmented, parallel plate ionization chamber that monitors the flatness and symmetry of the beam.

Profile Monitor: A multi-wire ionization chamber that is used to measure the beam profile and position.

Range Modulator Wheel (RMW): The range modulator wheel consists of a number of steps of variable thickness. The wheel rotates through the beam during irradiation, such that the beam travels through material of varying thickness as a function of time. This selectively degrades the energy of the beam in order to modulate the range. This modulation results in the SOBP shape within the depth-dose curves. The steps of the RMWs are made of either plastic or tungsten, and a different RMW is used for each nominal beam energy and field size. RMWs have a thin sheet of metal attached upstream, which acts as a first scatterer to spread the proton beam laterally.

Middle Base Plate: A hollow brass cylinder used for beam collimation.

Range Shifter: The range shifter consists of a series of plastic cylinders with varying thicknesses. Cylinders are shifted in or out of the beamline to selectively degrade the

proton energy, and alter the range of the beam. Using the range shifter, water equivalent thicknesses of 0.5 – 63.5 mm can be placed in the beamline, in steps of 0.5 mm.

Second Scatterer: The second part of the double scattering system that is used to spread the proton beam laterally. The second scatterer is designed to create a flat lateral distribution of dose at depths coinciding to the centre of SOBPs. Different second scatterers are used for low (100 and 120 MeV), medium (140, 160 and 180 MeV) and high energies (200, 225 and 250 MeV) and small (up to $10 \times 10 \text{ cm}^2$), medium (up to $18 \times 18 \text{ cm}^2$) and large (up to $25 \times 25 \text{ cm}^2$) field sizes.

Main and Sub Dose Monitors: Segmented, parallel plate ionization chambers used to monitor the output, flatness and symmetry of the beam.

Collimators: Two hollow brass plates used to collimate the beam.

Snout: The snout is the last component that the beam traverses before exiting the nozzle. During treatments, patient-specific components are placed in the snout. These include patient-specific apertures, and range compensators (see section 2.2.2). There are three different snout sizes available at the PTCH for different field sizes; small (up to $10 \times 10 \text{ cm}^2$), medium (up to $18 \times 18 \text{ cm}^2$) and large (up to $25 \times 25 \text{ cm}^2$). For all simulations and experiments presented in this thesis, only the medium snout was used.

2.2 Methods

2.2.1 Validation of the Nozzle Model

To ensure accuracy in the geometry and physics of our model, it was validated by comparing simulated dose distributions to measured (ionization chamber) dose distributions in water. Validation was performed for a variety of beams. Both depth-dose

distributions and lateral profiles were investigated. Absorbed dose to water was scored using the TOPAS built-in scorer ‘DoseToMedium’.

Depth-dose distributions for square fields were validated in both unmodulated beams, which exhibit the pristine Bragg peak, and modulated beams exhibiting the SOBP. The data for all clinical measurements was supplied by PTCH, and acquired using a parallel-plate ionization chamber (PTW 34045, PTW, Freiburg, Germany). The MC simulated depth-dose distributions were obtained by using the same beam geometry (medium $18 \times 18 \text{ cm}^2$ field size, snout at 5 cm from isocentre) used during the ionization chamber measurements. Depth-dose distributions were scored in a voxelized geometry consisting of a cylinder with a 3-cm radius, divided depth-wise into 1-mm thick voxels within a $30 \times 30 \times 30 \text{ cm}^3$ water phantom. The sensitive volume of the ionization chamber was smaller than the scoring volume in the MC simulations. However, negligible differences were found with varying scoring volume radii, provided that the scoring volume was within the ‘flat’ region of the beam (the central $\sim 5 \text{ cm}$). Using the larger scoring volume greatly reduced the time required to achieve low statistical uncertainties ($<0.1\%$) in the simulated values of absorbed dose. The same voxel size has been used to validate depth-dose distributions in other passive scattering proton therapy nozzles (Testa *et al* 2013).

Lateral profiles for square fields were validated in a similar manner to depth-dose distributions. Ionization chamber (PTW 31016) measurements were compared to simulated values. The scoring volume in the MC simulations was, again, larger than the ionization chamber’s sensitive volume in order to reduce the required computation time

to achieve low statistical uncertainties ($\sim 0.2\%$). Voxelized geometries spanning the width of the beam were used, with a size of $0.1 \times 5 \times 0.1 \text{ cm}^3$ in the inplane, crossplane and depth directions. These three directions (inplane, crossplane and depth) are defined in Figure 2.2. Negligible differences in simulated lateral profiles were seen with variations in the crossplane voxel size within the flat region of the beam.

Figure 2.2: Coordinate system used to describe scoring volumes in the validation of MC simulations of lateral profiles and patient-specific treatment fields.

The default TOPAS secondary particle production threshold of 0.05 mm was used for all particles, with the exception of secondary electrons. The threshold for electrons was set to 100 mm (such that secondary electrons were essentially not tracked). The maximum proton energy in the PTCH passive scattering nozzle is 250 MeV. For 250-MeV protons, the maximum possible range of secondary electrons is ~ 2.5 mm, but most have a range much smaller than 1 mm in water (Paganetti 2012a). As a result, they can

often be ignored for simulations of typical clinical scenarios (Jabbari and Seuntjens 2014, Paganetti *et al* 2004, Paganetti 2012a, Seco and Verhaegen 2013, Xun *et al* 2012). This was tested for the scoring geometries used, and the high production threshold reduced simulation time by a factor of ~ 2 -3, while having only negligible effects on the resulting dose distributions.

2.2.2 Patient-Specific Components

The components of the passive scattering nozzle described in section 2.1.3 provide a broad, flat proton beam. To contour the dose distribution for individual patients, it is necessary to include two additional patient-specific components in the beamline. An aperture and a range compensator are both used for each patient treatment field. At PTCH, apertures are milled from slabs of brass to selectively block portions of the beam that are not directed at the target volume. Range compensators are created by selectively drilling out blocks of Lucite to vary the thickness of material traversed by different regions of the beam. This selectively reduces the range in order to meet the distal edges of the target volume. Examples of a TOPAS implementation of an aperture and a range compensator are shown in Figure 2.3.

Figure 2.3: MC models of a patient-specific aperture (left) and range compensator (right) implemented in TOPAS.

For each patient-specific field investigated in this thesis, the aperture and range compensator were modeled in TOPAS. The geometric data required to define the shapes of the aperture and range compensator were exported from the clinical treatment planning system (TPS), Eclipse (Varian Medical Systems Inc, Palo Alto, CA). This data was then converted to a format required by TOPAS using a Matlab (The MathWorks, Inc, Natick, MA) code developed by the author. In addition to the patient-specific geometries, all field-specific parameters (beam energy, SOBP width, range shift) were supplied by the TPS.

Accuracy in the modeling of each aperture and compensator pair was assessed by comparing simulated dose distributions to those calculated by the TPS. Dose calculations from the TPS do not represent a gold standard, and have their own associated uncertainties and limitations. However, TPS calculations are based on well-validated inputs. Thus, comparisons with the TPS were deemed sufficient to ensure that the MC results of relative dose distributions were close to reality. For each patient-specific field,

three orthogonal 2D dose distributions were studied. These were defined by the planes of 1) the depth and crossplane axes, 2) the depth and inplane axes, and 3) the crossplane and inplane axes. In both the TPS and MC dose distributions, voxels with side lengths of 2 mm were used. Quantitative comparisons between the two were performed, and the pass/fail criteria for each voxel were set as follows: 1) for distributions that included the depth axis, better than 3% agreement in absorbed dose or less than 3 mm distance to agreement (DTA) resulted in a pass, and 2) for the crossplane-inplane distributions (cross section through beam's eye view) better than 3% agreement in absorbed dose resulted in a pass. For a point in the TPS distribution, the DTA is determined by searching the MC distribution for the nearest point with the same dose. Note that the DTA criterion was added for distributions that included the depth axis. This was done to make the test less sensitive to small differences in the TPS and MC proton range. A similar method is often used when comparing calculated and measured dose distributions, to reduce sensitivity to small geometrical errors in setup (Low *et al* 1998, VanDyk *et al* 1993).

2.3 Results and Discussion

2.3.1 Validation of the Nozzle Model

Figure 2.4 shows three examples of comparisons between simulated and measured depth-dose distributions in unmodulated proton beams. Beams with nominal energies of 160, 200 and 250 MeV are shown. Good agreement between the simulated and measured depth-dose curves can be seen. Although the measured dose was systematically higher in the plateau region, agreement was within 2% of the maximum dose. The location of the

Bragg peak as well as the range (defined by the 90% falloff in dose distal to the Bragg peak) agreed within 2 mm.

Figure 2.4: Comparison between simulated and measured (ionization chamber) depth-dose curves for pristine Bragg peaks with nominal energies of 160, 200 and 250 MeV.

Figure 2.5 shows a similar comparison between simulated and measured depth-dose curves for modulated beams. Four beams are shown: 1) a 140-MeV beam with a 4-cm SOBP, 2) a 180-MeV beam with an 8-cm SOBP, 3) a 200-MeV beam with a 10-cm SOBP, and 4) a 250-MeV beam with a 14-cm SOBP.

Figure 2.5: Comparison between simulated and measured (ionization chamber) depth-dose curves for four beams: a 140-MeV beam with a 4-cm SOBP, a 180-MeV beam with an 8-cm SOBP, a 200-MeV beam with a 10-cm SOBP, and a 250-MeV beam with a 14-cm SOBP.

In Figure 2.5, agreement was very good between the simulated and measured depth-dose distributions. Dose in the buildup and SOBP regions agreed within 2.5% of the maximum dose, and the range agreed within a maximum of 3 mm. In the regions proximal to the SOBP, small but distinct differences in shapes of the simulated and measured distributions were seen. The measured values started out higher, then became

lower than the simulated values approaching the SOBP region. Although this effect is small, it has been seen previously in comparisons between measurements and MC simulations (Titt *et al* 2008) and analytical calculations (Li *et al* 2008). It is generally attributed to delays in the beam gating at specified steps of the modulator wheel, which are difficult to model in MC simulations.

Figure 2.6 shows examples of comparisons between simulated and measured lateral profile dose distributions. Comparisons are shown at three different depths in water (6, 8 and 9.8 cm) within a 140-MeV beam with a 4-cm SOBP. These depths correspond approximately to the beginning, middle and end of the SOBP region. Dose agreement within the flat region of the lateral profiles was within 2.5% of the maximum dose, and agreement in the full-width at half maximum was within 2 mm.

These results are typical of those obtained using the TOPAS model, and comparable to previously published results from a model that used a different MC code (Titt *et al* 2008). Further improvement could potentially be achieved by more fine-tuning of the source parameters (e.g. source energy spread, profile size, and angular spread) for individual beam energies. However, the accuracy achieved using generic values for all conditions was deemed to be sufficient for this work.

Figure 2.6: Comparison between simulated and measured (ionization chamber) lateral profiles at three different depths (6, 8 and 9.8 cm) within a 140-MeV beam with a 4-cm SOBP.

2.3.2 Patient-Specific Components

Examples of comparisons between 2D dose distributions obtained from the TPS and MC for a patient-specific treatment field are shown in Figure 2.7. Dose distributions in three cross sections of the same field are shown, as discussed in section 2.2.2. The MC model reproduced the expected dose distribution with pass rates of 94%, 99% and 89% for the three cross sections in this example. For all fields investigated in this thesis, the overall pass rates were greater than 90%.

Figure 2.7: Comparison between 2D dose distributions generated using MC simulations (middle) and the Eclipse clinical treatment planning system (left). The regions that passed and failed the comparison test are shown in the right-hand column, represented by green and red, respectively. Three dose distributions from the same treatment field are shown, representing orthogonal cross sections in planes defined by the depth-inplane axes (top), depth-crossplane axes (middle) and inplane-crossplane axes (bottom). Pass rates for these fields were 94%, 99% and 89%, respectively.

2.4 Conclusion

A model of the PTCH passive scattering proton therapy nozzle was implemented in TOPAS, and validated. This model is capable of simulating simple, square fields and more complex patient-specific treatment fields. This model was necessary to determine reference values of LET, against which OSL detectors could be calibrated for LET measurements (presented in later chapters). Note that the model validation was based on absorbed dose distributions. An implicit assumption of the methodology presented in this thesis is that accuracy in the MC predicted dose distributions translates to accuracy in the LET distributions. This assumption is a potential limitation.

The next challenge in the MC portion of this thesis was to determine an appropriate method to score LET in MC simulations of therapeutic proton beams. Different methods of scoring LET are investigated and compared in Chapter 3.

Chapter 3

Comparison of LET Scoring Methods in Monte Carlo Simulations of Therapeutic Proton Beams

In this chapter, different techniques used to determine LET in MC simulations are studied, in order to determine a reliable and robust method. The techniques outlined in this chapter can be combined with the nozzle model presented in Chapter 2 to determine LET values under experimental irradiation conditions. The results of this chapter have been published in the journal *Physics in Medicine and Biology* (Granville and Sawakuchi 2015).

3.1 Introduction

Because LET is not a readily measurable quantity, MC simulations are often relied upon to quantitatively determine LET distributions. In monoenergetic particle beams, LET is simple to determine based on the particle energy. In reality, a spectrum of energies, and therefore LET values, is present in therapeutic beams. As a result, an average LET value is typically calculated to represent the spectrum. These averages are often calculated in one of two ways: using a fluence-weighted average (LET_ϕ) or using a dose-weighted average (LET_D). To calculate LET_ϕ , the LET of each proton is summed, and the result is then divided by the total number of protons. When calculating LET_D , the LET of each proton is weighted by the absorbed dose delivered by that proton. The dose-weighted LET of each proton is summed, and the result is divided by the total dose delivered. For proton therapy applications, LET_D is thought to better correlate with biological damage

than LET_ϕ , and is more commonly used. However, after reviewing the literature, no clear or rigorous demonstration of the superiority of LET_D over LET_ϕ for describing biological effects was found. Because of this, both quantities are studied in this chapter, and throughout the remainder of this thesis.

A number of studies have used MC simulations to determine LET distributions of particle therapy beams using a variety of platforms, including Geant4 (Chen and Ahmad 2012, Cirrone *et al* 2011, Cortés-Giraldo and Carabe 2015, Grassberger and Paganetti 2011, Grassberger *et al* 2011, Romano *et al* 2014), MCNPX (Johansson *et al* 2013, Perles *et al* 2013, Robertson *et al* 2013, Sawakuchi *et al* 2010, Wang *et al* 2012), FLUKA (Kantemiris *et al* 2011), and TOPAS (Carabe *et al* 2012, Giantsoudi *et al* 2013, Granville *et al* 2014a, Perl *et al* 2012, Sethi *et al* 2014, Zeng *et al* 2013). Both LET_ϕ and LET_D distributions have been scored using a variety of techniques and simulation parameters. A number of investigators have used a technique in which LET is directly scored on a step-by-step basis using the ratio of energy deposition to step-length after each particle step (Chen and Ahmad 2012, Grassberger and Paganetti 2011, Grassberger *et al* 2011). A second step-by-step approach to score LET uses the pre-step proton kinetic energy to calculate the theoretical LET at each step (Cortés-Giraldo and Carabe 2015, Granville and Sawakuchi 2014). A third approach involves scoring the proton energy spectrum inside a voxel of interest and converting to an LET spectrum after the simulation. From the spectrum, average LET values can be calculated (Cirrone *et al* 2011, Granville *et al* 2014a, Perles *et al* 2013, Sawakuchi *et al* 2010). Finally, a fourth approach uses the relationship between absorbed dose, fluence, and LET to calculate LET_ϕ by dividing the

absorbed dose within a voxel by the fluence within the same voxel (Robertson *et al* 2013, Wang *et al* 2012).

Cortés-Giraldo and Carabe 2015 recently reported results comparing primary proton LET_D distributions obtained using the ratio of energy deposition to step-length, and the computation of LET from pre-step kinetic energy. They found that computing theoretical LET using pre-step kinetic energies resulted in LET_D distributions that were insensitive to variations in simulation parameters such as voxel thickness and secondary electron production thresholds, and better agreed with microdosimetric simulations of dose-mean lineal energy. Grassberger and Paganetti 2011 demonstrated the sizable effects of including secondary protons on LET_D distributions obtained during simulations of therapeutic proton beams.

The goal of this chapter is to determine the most consistent way to score LET. The sensitivities of different LET scoring techniques to variations in commonly adjusted simulation parameters, namely the secondary electron and proton production thresholds, are investigated. Additionally, LET distributions obtained using different scoring techniques are compared. These studies expand on that performed by Cortés-Giraldo and Carabe 2015 by including secondary protons in the LET scoring, investigating LET_ϕ distributions, studying an additional LET scoring technique (energy spectrum technique), and investigating the dependence of LET distributions on secondary proton production thresholds.

3.2 Methods

3.2.1 Simulation Details

Two different beams were simulated: 1) a 150-MeV monoenergetic proton beam; and 2) a clinically realistic, modulated 200-MeV beam with a 10-cm SOBP. The modulated beam was produced using the model of the passive scattering proton therapy nozzle described in Chapter 2. All beams were incident on a cylindrical water tank that was 32-cm long with a 10-cm radius. The tank was divided into 1-mm voxels depth-wise.

In this study, various range production thresholds between 0.01 mm and 100 mm for electrons and between 0.001 and 1 mm for protons were used. All protons (primary and secondary) were included in the LET scoring. Other secondary particles were transported (with the TOPAS default production threshold of 0.05 mm) but were not included in the LET scoring. Statistical uncertainties in LET_ϕ and LET_D were better than 0.05% and 0.5%, respectively, for all conditions in which the LET scoring techniques were found to provide reliable results.

TOPAS provides a number of built-in scorers relevant to proton therapy simulations. In addition, TOPAS provides users with the ability to link their own user-written scoring extensions into the TOPAS code. Both built-in scorers and custom user-written extensions were used to score LET using a variety of techniques, as discussed in the following sections.

3.2.2 LET Scoring Techniques

Technique 1: Energy Deposition

Technique 1 is perhaps the most intuitive of the techniques used, because it directly applies the formal definition of LET. With technique 1, LET was scored in a step-by-step manner by summing the energy deposited locally by the proton with the kinetic energies of secondary electrons generated. The resulting energy was then divided by the step-length to determine the LET for each step (LET_i). The proton local energy loss, which included energy loss to secondary particles below the production threshold, was determined using the Geant4 `GetTotalEnergyDeposit()` method.

By using appropriate weighting factors, both LET_ϕ and LET_D were calculated using this technique. Fluence can be scored in MC simulations by dividing the sum of track lengths within a voxel by the volume of that voxel (Chilton 1978, 1979, Papiez and Battista 1994). Thus, the sum of step lengths in a voxel is directly proportional to the fluence within that voxel. To obtain LET_ϕ , LET for each step (i) was multiplied by the length of that step (dx_i). After simulation, the sum of these dx -weighted LET values was divided by the sum of dx_i for all steps:

$$LET_\phi = \frac{\sum_i^N dx_i \times LET_i}{\sum_i^N dx_i}. \quad (3.1)$$

Note that when weighting by fluence (or, equivalently, dx_i), this technique is equivalent to scoring absorbed dose (or energy deposited) within a volume and dividing that by the fluence within the volume, because $dx_i \times LET_i = dx_i \times E_{dep}/dx_i = E_{dep}$.

To obtain LET_D , LET for each step i was multiplied by $E_{dep,i}$, the energy deposited during that step (`GetTotalEnergyDeposit()` + sum of secondary electron kinetic energies).

The sum of these E_{dep} -weighted LET values was then divided by the total energy deposited for each voxel, after simulation:

$$LET_D = \frac{\sum_i^N E_{dep,i} \times LET_i}{\sum_i^N E_{dep,i}}. \quad (3.2)$$

Note that the LET_D scoring technique was built in to TOPAS, whereas the LET_ϕ scorer was created with a custom user-written extension.

Technique 2: dE/dx Computation

With this technique, LET was determined on the basis of proton kinetic energy at the beginning of each proton step. This was accomplished using the Geant4 ComputeElectronicDEDX() method, which computes the unrestricted electronic stopping power (numerically equivalent to the unrestricted LET). This technique was used to score both LET_ϕ and LET_D by weighting the LET values in the same manner as described for technique 1. Note that this technique was implemented in TOPAS with a custom user-written extension.

Technique 3: Energy Spectrum

For this technique, the proton fluence was scored as a function of kinetic energy. After simulation, the resulting energy spectrum was converted to an LET spectrum using a lookup table (Berger *et al* 1998). The LET spectrum was then used to calculate both LET_ϕ and LET_D according to the following formulae:

$$LET_\phi = \frac{\sum_j^N \Phi_j \times LET_j}{\sum_j^N \Phi_j}, \quad (3.3)$$

and

$$LET_D = \frac{\sum_j^N \Phi_j \times LET_j \times LET_j}{\sum_j^N \Phi_j \times LET_j}, \quad (3.4)$$

where N is the number of bins in the LET spectrum, j is the j^{th} LET bin, Φ_j is the proton fluence in the j^{th} bin, and LET_j is the value of the j^{th} bin. This technique was implemented with a user-written TOPAS extension. Fluence was scored in the same manner as discussed for technique 1 (sum of track lengths divided by volume).

This scoring method is expected to have some sensitivity to the width of energy bins. Sufficient energy resolution is obviously required for the binned data to accurately represent the proton spectrum present in the simulations. Two bin widths were tested: 0.1 MeV and 0.01 MeV. A maximum discrepancy of 0.12% was found between the resulting LET_D values for depths in water up to the 10% distal falloff in the 150-MeV monoenergetic beam. The maximum discrepancy in the 200-MeV, 10-cm SOBP was 0.62%. LET_ϕ values were even less sensitive to the change in bin width. The results shown in the following sections for technique 3 were acquired using a bin width of 0.1 MeV.

3.3 Results

3.3.1 Dependence on Secondary Electron Production Threshold

Figure 3.1 shows depth- LET distributions obtained using techniques 1, 2, and 3 in the 150-MeV monoenergetic proton beam. In each plot, the results of five different simulations are shown, each with a different secondary electron production threshold: 0.01, 0.05, 0.1, 1, or 100 mm. The depth- LET_D distributions obtained using technique 1 (Figure 3.1a) were heavily dependent on the secondary electron production threshold.

Figure 3.1: Depth- LET_D and depth- LET_ϕ distributions for a 150-MeV monoenergetic proton beam in water, scored using (a) technique 1, (b) technique 2, and (c) technique 3. Dotted lines represent LET_ϕ and solid lines represent LET_D . Secondary electron production thresholds of 0.01, 0.05, 0.1, 1, and 100 mm were used, and are labeled where the results are distinguishable from one another. The depth-dose curve (PDD) is included as a guide.

As the threshold was lowered, the MC-determined LET_D values increased. For thresholds of 0.1 mm and lower, the depth- LET_D curves were not smooth, exhibiting a number of spikes. For thresholds greater than 1 mm, however, the curves were smooth and consistent with one another. Unlike with technique 1, the depth- LET_D curves obtained with techniques 2 and 3 (Figure 3.1b and c) showed only a small dependence on the secondary electron production threshold. With these techniques, reduction of the electron production threshold from 100 mm to 0.01 mm resulted in maximum LET_D increases of 0.8% and 1.0% for techniques 2 and 3, respectively, at depths shallower than the 10% distal falloff. The depth- LET_ϕ distributions for all scoring techniques showed even smaller dependence on the secondary electron production threshold. These results were obtained using a secondary proton production threshold of 0.05 mm.

Similar comparisons for the 200-MeV modulated beam with a 10-cm SOBP are shown in Figure 3.2. For clarity, only the largest and smallest secondary electron production thresholds are shown (0.01 mm and 100 mm). Results from these simulations were qualitatively similar to those obtained with the monoenergetic beam. The LET_D values obtained using technique 1 increased and were less consistent as the secondary electron production thresholds decreased. However, with techniques 2 and 3, the LET_D values showed small dependence (maximum discrepancy of 1.0% and 1.2%) on the secondary electron production threshold. Depth- LET_ϕ distributions showed no strong dependence on the secondary electron production threshold for any of the three scoring techniques.

Figure 3.2: Depth- LET_D and depth- LET_ϕ distributions for a 200-MeV proton beam with a 10-cm SOBP in water, scored using (a) technique 1, (b) technique 2, and (c) technique 3. Dotted lines represent LET_ϕ and solid lines represent LET_D . Results for secondary electron production thresholds of 0.01 mm and 100 mm are shown, and labeled where the results are distinguishable from one another.

3.3.2 Dependence on Secondary Proton Production Threshold

Figure 3.3 shows depth- LET_D and depth- LET_ϕ distributions obtained using techniques 1, 2, and 3 in the 150-MeV monoenergetic beam with varying secondary proton production thresholds. LET_D values obtained using all techniques showed no strong dependence on the secondary proton production threshold. LET_D and LET_ϕ values obtained using the highest (1 mm) and lowest (0.001 mm) secondary proton production thresholds generally agreed within statistical uncertainty.

Figure 3.4 shows similar depth-LET distribution comparisons to those shown in Figure 3.3, for the clinically realistic beam (200 MeV, 10-cm SOBP) using the highest and lowest (0.001 mm and 1 mm) secondary proton production thresholds investigated. Again, LET_D and LET_ϕ showed no dependence outside of statistical uncertainties on the secondary proton production threshold. Note that the secondary electron production threshold was set to 100 mm for these simulations, to eliminate the problems associated with scoring LET_D with technique 1.

Figure 3.3: Depth- LET_D and depth- LET_{ϕ} distributions for a 150-MeV monoenergetic proton beam, scored using (a) technique 1, (b) technique 2, and (c) technique 3. Dotted lines represent LET_{ϕ} and solid lines represent LET_D . Results for secondary proton production thresholds of 0.001, 0.01, 0.1 and 1 mm are shown. The secondary electron production threshold was 100 mm.

Figure 3.4: Depth- LET_D and depth- LET_ϕ distributions for a 200-MeV proton beam with a 10-cm SOBP, scored using (a) technique 1, (b) technique 2, and (c) technique 3. Dotted lines represent LET_ϕ and solid lines represent LET_D . Results for secondary proton production thresholds of 0.001 and 1 mm are shown. The secondary electron production threshold was 100 mm.

3.3.3 Scoring Technique Comparison

Figure 3.5 summarizes a comparison between depth-LET distributions obtained using each of the three scoring techniques in the 150 MeV monoenergetic beam.

Figure 3.5: (a) Comparison among depth- LET_D (solid lines) and depth- LET_ϕ (dotted lines) distributions in a 150-MeV monoenergetic proton beam obtained using technique 1 (green), 2 (red), or 3 (blue). (b) Percentage differences among LET_D and LET_ϕ values obtained using different techniques at each depth in water. Differences between techniques 1 and 2 with respect to technique 3 are shown.

In Figure 3.5a, depth- LET_D distributions are compared. At depths shallower than the Bragg peak, LET_D values obtained using technique 1 were consistently higher than those obtained using technique 2, and those obtained using technique 3 were lower still. LET_ϕ values, however, showed little difference between the three techniques.

Figure 3.5b shows the differences, as a percentage, between LET_D and LET_ϕ results from techniques 1 and 2 and those from technique 3. Differences of up to about 17.5% occurred in LET_D values in the plateau region between techniques 1 and 3, and differences of up to about 7% occurred between techniques 2 and 3. Even larger differences occurred near the Bragg peak. Differences in LET_ϕ values were much smaller, remaining below 5% until depths beyond the Bragg peak in the comparison between techniques 1 and 3. Differences between LET_ϕ values using techniques 2 and 3 were smaller than about 2%.

The data shown in Figure 3.5 were generated in simulations that used a secondary electron production threshold of 100 mm because technique 1 was shown previously to be unreliable for low secondary electron production threshold values (Figure 3.1a). The secondary proton production threshold was 0.05 mm (TOPAS default).

Figure 3.6 shows similar comparisons among the depth-LET distributions for the more clinically realistic 200-MeV beam with a 10-cm SOBP. Discrepancies among values obtained using the 3 different scoring techniques were generally larger in the SOBP beam than in the monoenergetic beam shown in Figure 3.5. The highest LET values were obtained from technique 1, followed by techniques 2 and 3. Discrepancies among LET_D values were highest (about 25%) in the entrance region and near the end of

the SOBP. Discrepancies among LET_ϕ values were smaller than 5% until the end of the SOBP, where they rose to about 15%.

Figure 3.6: (a) Comparison among depth- LET_D (solid lines) and depth- LET_ϕ (dotted lines) distributions in a 200-MeV proton beam with a 10-cm SOBP obtained using technique 1 (green), 2 (red), or 3 (blue). (b) Percentage differences among LET_D and LET_ϕ values obtained using different techniques at each depth in water. Differences between techniques 1 and 2 with respect to technique 3 are shown.

3.4 Discussion

3.4.1 Dependence on Secondary Electron Production Threshold

Ideally, the production and tracking of secondary electrons should have no effect on the resulting proton LET distributions in MC simulations. The energy that would be lost to a secondary electron for low production thresholds is considered a local energy loss to the proton for high production thresholds. Either way, the energy is deposited locally and taken into account in the unrestricted LET.

Cortés-Giraldo and Carabe demonstrated that primary proton depth- LET_D curves calculated using technique 1 showed strong dependence on the secondary electron production threshold and provided spurious results for thresholds of 2.0 mm and below, while results obtained using technique 2 were smooth and consistent (Cortés-Giraldo and Carabe 2015). The results of this chapter's work, which scored total proton LET_D (including secondaries), qualitatively agree with those found by Cortés-Giraldo and Carabe for techniques 1 and 2. In addition, the results of this work demonstrated that the problems associated with technique 1 can be eliminated by using a high secondary electron production threshold. Further, the results of this work demonstrated that technique 3, similarly to technique 2, shows minimal dependence on secondary electron production thresholds.

The basis of technique 1's dependence on secondary electron production threshold has recently been explained in the literature (Cortés-Giraldo and Carabe 2015). In short, high LET for an individual step can occur when a secondary electron is produced during a step that has its length greatly shortened due to a voxel boundary. A

large energy deposition is then divided by a very small step size, providing an unphysical large LET value. Increasing the secondary electron production threshold eliminates this effect by drastically reducing the number of electrons explicitly produced and tracked. Generally, for simulations relevant to proton therapy, eliminating the explicit production and tracking of secondary electrons has only small effects on the resulting dose distributions and greatly reduces computation time. Thus, increasing the secondary electron production threshold can be a useful approach to the problems associated with technique 1.

Cortés-Giraldo and Carabe proposed an approach to the spurious results obtained with technique 1 by considering the entire energy deposition and step length per voxel for each proton, rather than doing a step-by-step calculation. This resulted in smoother depth- LET_D distributions, but showed a strong dependence on voxel thickness (Cortés-Giraldo and Carabe 2015). In the present work, a second approach was considered, which involved instituting a high-LET cutoff value to discriminate against large, unphysical LET values during a given step. The downside of this approach is that the cutoff value is somewhat arbitrary, and the results were found to be highly dependent on the cutoff value chosen (Figure 3.7). High LET cutoffs of 83 keV/ μm (corresponding approximately to the maximum theoretical proton LET), 50 keV/ μm and 20 keV/ μm were used.

No scoring techniques showed strong dependence on secondary electron production thresholds for LET_ϕ distributions. The problems associated with technique 1 for scoring of LET_D are not present when scoring LET_ϕ . This is because the step length value is cancelled out in the fluence weighting, as discussed in section 3.2.2.

Figure 3.7: Comparison between depth- LET_D curves obtained using technique 1 and three different high-LET cutoff values of 83, 50 and 20 keV/ μm . For comparison, the depth- LET_D curve obtained using technique 2 for the same simulation conditions is shown. Results are shown using the default TOPAS secondary electron and proton production thresholds of 0.05 mm. The inset represents the same plotted data in magnified y-axis scale.

3.4.2 Dependence on Secondary Proton Production Threshold

The LET distributions showed little dependence of LET on secondary proton production thresholds in the range of 0.001 to 1 mm. Contrary to the results, decreasing secondary proton production thresholds might be expected to increase average proton LET, because this would increase the number of low-energy (high-LET) protons present in the simulation. It is important to note that the secondary proton production threshold in Geant4 (which the TOPAS framework is based on) is not a universal threshold; this threshold applies only to secondary protons resulting from *elastic* processes. Thus, MC codes that institute a universal cutoff for the production and tracking of secondary protons may exhibit greater dependence on the secondary proton production threshold.

Note that results for secondary proton production thresholds larger than the voxel thickness (1 mm) are not shown. Very high thresholds do result in consistently lower LET values, however such high thresholds make little sense when interested in spatial accuracy on the order of 1 mm. Thus, these results are not presented.

3.4.3 Scoring Technique Comparison

Because there is not a readily available gold standard to compare with, it is not simple to conclude which MC scoring technique provides the most accurate LET distributions. However, it is evident from Figure 3.5 and Figure 3.6 that the choice of scoring technique does affect the resulting LET values. Thus, caution is required when comparing LET values obtained using different MC scoring techniques.

The energy deposition technique (technique 1) provided unreliable values of LET_D when low secondary electron production thresholds were used. The energy spectrum technique (technique 3) provided self-consistent results and was not very sensitive to changes in simulation parameters. However, this technique required on-the-fly binning and storage of more data during the simulation than the other two techniques. In addition, the binning of energy and subsequent conversion to LET could lead to inaccuracies, particularly at low energies where the LET changes rapidly with energy. On the basis of the data presented in this chapter, it is reasonable to conclude that the dE/dx computation technique (technique 2) is the most advantageous choice for scoring LET_D distributions in proton therapy beams. In addition, Cortés-Giraldo and Carabe demonstrated that technique 2 best agrees with microdosimetric simulations of dose-

mean lineal energy (Cortés-Giraldo and Carabe 2015). For simulations of LET_ϕ , however, there is not a clear advantage to choosing either technique 1 or 2.

3.5 Conclusion

The LET_D values obtained from MC simulations of proton beams in the therapeutic energy range can be sensitive to simulation parameters, including secondary particle production thresholds, and scoring techniques. Substantial caution is required when comparing results obtained using different parameters and techniques. The data presented in this chapter indicate that the dE/dx computation method is the most advantageous for scoring LET_D , and that LET_ϕ is less sensitive than LET_D to differing scoring techniques. Throughout the remainder of this thesis, the MC LET values are all scored using technique 2, the dE/dx computation technique.

Chapter 4

LET Dependent Characteristics of Optically Stimulated Luminescence Detectors Exposed to Therapeutic Proton Beams

Chapters 2 and 3 described an MC infrastructure to determine reference LET values under experimental irradiation conditions. The reference MC values provide a means of calibrating detectors for measurements of LET. The next challenge was to determine the appropriate characteristic(s) of the OSL signal to parameterize and calibrate as a function of LET. This chapter describes a preliminary investigation into the LET dependent characteristics of optically stimulated luminescence detectors (OSLDs). The goals were to determine a suitable characteristic to calibrate OSLDs for proton LET measurements and to determine an appropriate readout protocol to evaluate that characteristic. First, general background information about the OSL dosimetry technique and its LET-dependent characteristics is presented. Second, an experiment to investigate the LET dependence of OSLDs is summarized. The results of this study have been published in the journal *Radiation Measurements* (Granville *et al* 2014b).

4.1 Introduction

4.1.1 Optically Stimulated Luminescence

The OSL technique is commonly used for measurements of absorbed dose. Upon optical stimulation, previously irradiated OSLDs emit light. The amount of OSL emission is related to the absorbed dose within the detector's sensitive volume, providing the basis for absorbed dose measurements using OSLDs.

OSL materials are crystalline in structure, and contain defects that result in locally available energy states. These states can act as trapping sites for free charges that result from exposure to ionizing radiation. After irradiation, charges can remain trapped for long periods of time, provided the trap is deep enough (i.e. has a high enough potential barrier) to prevent escape at room temperature. Subsequent illumination with light of an appropriate wavelength provides energy for trapped charges to migrate and potentially recombine with localized charges of the opposite sign. The recombination process can result in emission of photons (the OSL emission).

4.1.2 Optically Stimulated Luminescence of $\text{Al}_2\text{O}_3\text{:C}$

By far, the most commonly used OSL material in radiation dosimetry is aluminum oxide doped with carbon ($\text{Al}_2\text{O}_3\text{:C}$). The OSL emission spectrum of $\text{Al}_2\text{O}_3\text{:C}$ contains two main emission bands; one centered in the blue region of the visible spectrum at ~ 420 nm (Akselrod *et al* 1998) and a second, lower intensity band centered in the UV at ~ 330 nm (Evans and Stapelbroek 1978). The emission spectrum for OSLDs stimulated with green light is shown in Figure 4.1. Note that the relative intensity of the UV and blue emission is heavily dependent on the readout methods used (Denis *et al* 2011b, Gasparian *et al* 2012, Yukihiro and McKeever 2006b). The data in Figure 4.1 were acquired using a technique designed to emphasize the UV emission. This plot is useful to demonstrate the location of the bands within the electromagnetic spectrum, rather than the relative intensity.

Figure 4.1: OSL emission spectrum of $\text{Al}_2\text{O}_3\text{:C}$ stimulated with green light, and transmittance of the Hoya U-340 (Hoya Optics 2015) and Kopp 5113 (GrayGlass 2013) optical filters. OSL emission data provided by Dr. Eduardo G. Yukihiro, Oklahoma State University.

The OSL emission of $\text{Al}_2\text{O}_3\text{:C}$ is explained by the presence of oxygen vacancies with one or two electrons (F^+ and F-centres) and dosimetric traps (believed to be electron traps). The blue OSL emission, specifically, is known to be caused by the relaxation of excited F-centre defects. The electronic transitions between irradiation and readout that result in the emission of blue photons are summarized as follows:

- 1) ionizing radiation creates electron-hole pairs;
- 2) free electrons become trapped in dosimetric traps;
- 3) free holes become trapped in F-centres resulting in F^+ -centres ($\text{F} + \text{h}^+ \rightarrow \text{F}^+$);
- 4) after irradiation, trapped charges remain in metastable states;
- 5) during readout, light stimulation provides electrons in dosimetric traps with

the energy required to escape into the valence band;

- 6) electrons recombine with F^+ -centres resulting in excited F-centres ($F^+ + e^- \rightarrow F^*$);
- 7) relaxation of excited F-centres to ground states results in emission of 420 nm photons ($F^* \rightarrow F + \lambda_{420 \text{ nm}}$).

In addition to the trapping sites mentioned, models used to explain the properties of $\text{Al}_2\text{O}_3:\text{C}$ OSLDs sometimes include shallow (ST) and deep electron traps (DT) that compete for charge with the main dosimetric trap (MDT) (Chen *et al* 2006, Denis *et al* 2011a, Flint and Sawakuchi 2013, Yukihiro and McKeever 2006a, Yukihiro *et al* 2004b). An example of such a model is shown in Figure 4.2.

Figure 4.2: Band model of the $\text{Al}_2\text{O}_3:\text{C}$ OSL process (Flint and Sawakuchi 2013). Three types of electron trapping sites are included: shallow trap (ST), main dosimetric trap (MDT) and deep trap (DT). Two recombination centres (RC) are included: RC1, the recombination centre responsible for UV emission, and RC2, responsible for blue emission. Black arrows represent charge transitions that occur during irradiation (dashed) and OSL readout (solid). Red and blue arrows represent the relaxation of the excited RCs resulting in the emission of a UV and blue photon, respectively.

Generally, STs are thought to have low enough potential barriers that thermal energy is sufficient to allow trapped electrons to escape into the conduction band at room temperature. Electrons in the MDT are trapped at room temperature, but can readily escape with appropriate optical stimulation (usually green is used). In contrast, DTs have high potential barriers, and trapped electrons require stimulation with higher energy optical photons to escape (Umisedo *et al* 2010).

The recombination process that results in UV OSL emission is not as well understood as that of the blue emission. The UV emission is often attributed to F^+ -centres (Evans and Stapelbroek 1978). This fact, however, has not been unequivocally proven.

4.1.3 OSL Readouts

In general, the OSL readout process is simple. During readout, previously irradiated OSLDs are stimulated with a light source (often using light emitting diodes [LEDs] or lasers). This causes the OSL emission, which is collected by a photo-detector (typically a photomultiplier tube [PMT]). Optical filters are often placed in front of the PMT to ensure that only OSL emission is collected, and not light from the stimulation source. A schematic of an OSL reader is shown in Figure 4.3. During OSL readouts, OSL emission intensity as a function of readout time is recorded. The result is a curve that decays approximately exponentially, and is referred to as the ‘OSL curve’ or ‘OSL decay curve’.

Figure 4.3: Simplified schematic diagram of an OSL reader. OSLDs are illuminated with a light source (often LEDs), which causes the OSL emission. The emission is collected using a PMT. Optical filters can be employed in front of the PMT to filter out the stimulation light, and select the range of wavelengths in the OSL emission that is detected.

OSL readouts are often performed using one of two stimulation modes: continuous-wave stimulation (CW-OSL) or pulsed stimulation (P-OSL). CW-OSL is the simplest method, and involves continuous stimulation of the OSLD concurrent with continuous collection of OSL emission. The OSL emission during CW-OSL readouts contains contributions from the entire OSL spectrum, including both the blue and UV emission bands. The range of wavelengths detected can be controlled to an extent through the use of optical filtration. Note that optical filtration can serve two purposes: removing stimulation light from the collected signal, and controlling which portions of the OSL emission spectrum are collected.

P-OSL is a more complicated readout technique that involves repeated cycles of pulsed stimulation and signal collection (Akselrod and McKeever 1999). P-OSL readout schemes can be designed to allow for separate collection of $\text{Al}_2\text{O}_3\text{:C}$'s blue and UV

emission bands (Denis *et al* 2011b, Yukihiro and McKeever 2006b). This is possible because the two bands have considerably different luminescence lifetimes (~35 ms for the blue (Lee and Crawford Jr 1979) and <7 ns for the UV (Evans and Stapelbroek 1978)). During a stimulation pulse, photons from both emission bands are present in the OSL emission. Following a pulse, however, the UV emission quickly decays to zero, and only the longer lifetime blue emission remains. Thus, signal collected during a pulse contains blue and UV, while signal collected shortly after a pulse contains only blue emission. Simple subtraction can provide an estimate of the UV emission alone.

4.1.4 Potential of OSLDs as ‘LET-meters’

OSLDs are manufactured for the purpose of measuring absorbed dose. For absorbed dose measurements, the OSL emission intensity, or ‘amount’ of OSL emission, is the quantity of interest in OSL readouts. However, two characteristics of the OSL emission have shown a strong dependence on LET that could potentially be useful for LET measurements. These two characteristics are:

1) *UV/blue Ratio*: As noted in section 4.1.2, the OSL emission spectrum of $\text{Al}_2\text{O}_3\text{:C}$ contains both a blue and a UV emission band. Previous studies have demonstrated that the relative intensities of these two bands changes as a function of LET when exposed to a broad range of particles (Yukihiro *et al* 2006). Thus, it is potentially possible that the relative intensity could be calibrated as a function of LET, and used for LET measurements. However, from the data in the literature, it is unclear whether the relative intensity is sensitive enough to LET variations in the therapeutic proton range to be used for proton LET

measurements.

2) *OSL Curve Shape*: The OSL curve is a plot of OSL intensity as a function of stimulation time. It has been demonstrated previously that OSL curves, when normalized to their initial intensity, decay more steeply for particles of high LET than low LET (Yasuda *et al* 2002, Yukihiro *et al* 2004a). Sawakuchi *et al* demonstrated through a proof-of-concept experiment that it is feasible to parameterize the OSL curve shape, and calibrate it as a function of LET for the purpose of LET measurements (Sawakuchi *et al* 2010). No studies have been done, however, to investigate which readout protocols provide the most LET-dependent OSL curve shapes following exposure to therapeutic proton beams.

The work presented in this chapter characterizes the LET dependence of OSLDs exposed to therapeutic proton beams. Two main questions are answered: 1) is the relative intensity of the UV and blue emission sensitive to LET variations within the therapeutic proton energy range, and 2) what OSL readout protocol and signal (i.e. CW-OSL or P-OSL, blue or UV emission) provides the most LET-dependent OSL curve shapes?

4.2 Methods

4.2.1 OSLD Preparation

All OSLDs used to acquire the data presented in this thesis were prepared from $\text{Al}_2\text{O}_3\text{:C}$ tape supplied by Landauer, Inc (Landauer 2012) (powder lot 0698-196). OSLDs from the same powder lot were used for all studies in this thesis. This is exactly the same material used in commercially available nanoDotTM and LuxelTM OSL dosimeters. Individual

detectors were cut into disks of 7-mm diameter. Each OSLD consisted of a sensitive volume of $\text{Al}_2\text{O}_3:\text{C}$ powder fixed between two thin layers of plastic. The thickness of each detector (including plastic and sensitive volume) was ~ 0.3 mm. Prior to packaging and irradiation, detectors were bleached for ~ 12 hours using filtered (GG-495, Schott AG, Mainz, Germany) 26 W fluorescent light bulbs (General Electric, Fairfield, CT) in a custom-built bleaching unit to remove any residual signal acquired during storage (Omotayo *et al* 2012). After bleaching, the detectors were sealed between layers of cellophane and electrical tape in order to protect them from exposure to light. A photograph of the detector packaging process is shown in Figure 4.4. The total thickness of the packaged OSLDs was ~ 0.6 mm.

Figure 4.4: Packing of OSLDs for irradiation. Individual OSLDs were cut into 7-mm disks, and placed between layers of cellophane tape (left) followed by black, opaque electrical tape (middle) in order to shield them from light exposure. The final product of OSLD packaging is seen in the rightmost image.

4.2.2 OSLD Irradiations

Eight batches of OSLDs were irradiated with an absorbed dose to water of 0.2 Gy (confirmed using a calibrated ionization chamber). Each batch was irradiated in an unmodulated proton beam of differing LET. The LET_ϕ values ranged from 0.47 to 2.28 keV/ μm in water. Irradiations were performed along the beam's central axis either in air or at a specified depth in a solid-water phantom, depending on the condition. The

nominal beam energy, range at the central axis, water equivalent depth, and resulting LET values for each irradiation condition are summarized in Table 4.1. Note that the range is defined as the point at which the percentage absorbed dose to water falls to 90%, distal to the Bragg peak or SOBP. An open, square field of $18 \times 18 \text{ cm}^2$ with the snout set at 5 cm from isocentre was used for all irradiation conditions. All OSLD irradiations were performed using a passive scattering nozzle at PTCH, as described in Chapter 2.

Table 4.1: Proton irradiation conditions. Nominal beam energy, range at the central axis, water equivalent depth, and fluence-averaged LET at the OSLD position in water are summarized.

Nominal energy (MeV)	Range (cm)	Water equivalent depth (cm)	LET_ϕ in H_2O (keV/ μm)
250	28.5	0.0	0.47
160	13.0	0.0	0.62
140	10.0	0.0	0.68
100	4.3	0.0	0.95
100	4.3	2.0	1.19
100	4.3	3.0	1.49
200	19.0	18.0	1.63
160	13.0	12.5	2.28

4.2.3 Monte Carlo Simulations

The LET value for each irradiation condition was determined using the MC model of the proton therapy nozzle discussed in Chapter 1, and the dE/dx computation LET scoring technique presented in Chapter 2. All LET values presented in this chapter are fluence-weighted averages (LET_ϕ). LET_ϕ was scored in water volumes along the central axis of the proton beams. The scoring volumes approximately matched the size of the OSLD

packages ($4 \times 4 \text{ cm}^2$ in surface area, and 0.3 mm in depth). Statistical uncertainties in the LET_ϕ values were better than 0.05%. Note that the LET_ϕ values listed in Table 4.1 differ slightly from those that appear in the published version of this study, because a different LET scoring technique was used (Granville *et al* 2014b).

The secondary electron range production threshold was set to 100 mm for these simulations. The high threshold greatly reduced computation time, while providing only minimal differences in the resulting LET_ϕ values (Chapter 3). Other secondary particles were produced and tracked using the TOPAS default production threshold of 0.05 mm. All protons (primary and secondary) were included in the LET_ϕ scoring, but other secondaries were not.

4.2.4 OSL Readouts

The OSL reader and readout processes presented in this section are also used later in Chapters 5, 6 and 7.

OSL Reader

All OSLD readouts were performed using the in-house OSL reader shown in Figure 4.5. The OSLDs were stimulated using green light-emitting diodes (LXML-PM01-0100; Philips Lumileds Light Company, San Jose, CA) and signal was collected using a PMT (P25PC-02; Sens-Tech Limited, Langley, Berkshire, United Kingdom). The power of the stimulation light was $\sim 50 \text{ mW/cm}^2$ at the OSLD position. In front of the PMT, optical filters were used to remove stimulation light from the collected signal and select the range of wavelengths detected. In this study, two filter sets were employed: Hoya U-340 (7.5 mm thickness, Hoya Corporation, Tokyo, Japan) and Kopp 5113 (12 mm thickness,

Kopp Glass, Inc., Pittsburgh, Pennsylvania). U-340 filters transmit light in the UV and part of the blue region of the OSL emission spectrum, and 5113 filters transmit light primarily in the blue region. The transmission spectra of the two filter sets, as well as the emission spectrum of the OSLDs, are shown in Figure 4.1.

Figure 4.5: In-house OSL reader used to perform all OSLD readouts presented in this thesis. The housings that hold the LEDs, the PMT, and the OSLD tray are labeled.

Relative Intensities of UV and Blue Emission

To investigate the relative intensities of the UV and blue emission bands, P-OSL readouts were used. P-OSL readouts were performed according to a pulsing and signal collection (counting) scheme that was chosen based on the differing lifetimes of the blue and UV OSL emission bands. This scheme is shown graphically in Figure 4.6.

Figure 4.6: Optical stimulation and signal counting scheme used for P-OSL readouts. Counter A was active during stimulation pulses, and counter B was active only following stimulation pulses. Due to the differing lifetimes of the UV and blue emission, counter B contained only blue emission while counter A contained both blue and UV. Red squares represent the activity of counter A, blue dashes represent counter B and the solid green lines represent the LED stimulation.

Two counters (A and B) were used to collect signal in the P-OSL scheme. Counter A collected both the long- and short-lifetime components of the OSL signal (blue and UV), and counter B collected only the long-lifetime (blue) component. This was accomplished by repeating the following 5-ms pulsing and counting cycle: 2-ms stimulation and PMT counting by counter A; 0.5-ms delay in which stimulation and counting were inactive; 2-ms counting by counter B; 0.5-ms delay. Because the UV emission lifetime is much shorter and the blue emission lifetime is much longer than the 0.5-ms post-stimulation delay, counter B collected only blue emission. By subtracting the signal collected by counter B from that collected by counter A, an estimate of the UV signal alone was acquired. The blue signal was defined as the sum of the counter B signal collected over a

10-second readout, and the UV signal was defined as the difference between counters A and B summed over 10 seconds. The time interval of 10 s was chosen because shorter times led to increases in statistical uncertainties, while longer times were found to provide little, if any, improvement in characterization studies of the OSL reader (Flint *et al* 2015). Note that only Hoya U-340 filters were used for P-OSL readouts, because these filters transmit both blue and UV.

OSL Curve Shapes

To investigate the LET dependence of OSL curve shapes, both P-OSL and CW-OSL readouts were used. CW-OSL readouts were performed using both the U-340 and 5113 filters. This allowed for comparison of CW-OSL curve shape variations between readouts containing similar intensities of the blue and UV signals (U-340 filters) and readouts containing primarily the blue signal (5113 filters). P-OSL readouts allowed for comparison between the blue (counter B), UV (counter A – counter B) and combined blue and UV (counter A) curve shapes. The OSL curves were normalized to their initial intensities to demonstrate changes in the shapes.

Readout Timing

The signal intensity of the UV emission band has been shown to increase as a function of time after irradiation. The rate at which this increase occurs, however, decreases with time (Yukihara and McKeever 2006b, 2006a). To minimize the effects of the time dependence, OSL readouts were performed after a period of ~35 days following irradiation. Note that this length of time is not necessary, especially if all readouts are performed within a small range of time. Potentially, a time-dependent correction factor could also be applied (see Appendix A).

Uncertainties

For each readout method and LET value, five OSLDs were evaluated. Error bars represent the 68% confidence interval for the five readouts.

4.3 Results and Discussion

The signal intensities of the blue and UV emission bands as a function of LET are shown in Figure 4.7. Over the range of proton LET values investigated, the signal intensity of the blue emission band (determined using counter B in the P-OSL readout scheme) remained approximately constant. However, as LET increased, the signal intensity of the UV emission band (determined using the difference between counters A and B) steadily increased. These data demonstrate that the relative signal intensities of the UV and blue emission bands show strong dependence on LET within the therapeutic proton range. These data support the suggestion that the ratio of the UV and blue intensities could potentially be used to calibrate $\text{Al}_2\text{O}_3\text{:C}$ OSLDs for LET measurements in therapeutic proton beams.

Figure 4.7: OSL signal intensity as a function of LET for the UV and blue OSL emission bands of $\text{Al}_2\text{O}_3\text{:C}$. Signals were acquired using a P-OSL stimulation scheme and the Hoya U-340 filter set. The signal intensity was defined as the sum of photomultiplier tube counts over a 10-second readout.

The normalized CW-OSL curves acquired using the Kopp 5113 filters (transmission primarily in blue) and the Hoya U-340 filters (transmission in UV and partial transmission in blue) are shown in Figure 4.8a and b, respectively. For both filter sets, irradiation with the highest LET beam resulted in the steepest decay and the lowest LET beam resulted in the most gradual decay. Between these two extremes, however, the distinction was much clearer with the U-340 filters than the 5113 filters. For OSL curves evaluated using the U-340 filters, there was a consistent increase in OSL curve steepness with increasing LET. For those evaluated using the 5113 filters, there was less consistency and a greater overlap between the OSL curves.

Figure 4.8: CW-OSL curves normalized to their initial intensities. Signals were collected using the Kopp 5113 filters (a) or the Hoya U-340 filters (b) in front of the PMT. Each OSL curve was acquired from OSLDs irradiated with proton beams of varying LET and is the average of signals acquired using 5 OSLD readouts. The insets show a magnified view of a small portion of the OSL curves.

Similar curves, obtained using P-OSL readouts, are shown in Figure 4.9. The distinction between P-OSL curves was not as clear as for CW-OSL. This could be a result of the smaller signals, and increased statistical uncertainties that result from P-OSL readouts with the system used. These data suggest that the CW-OSL curve shape collected using Hoya U-340 filters shows the greatest potential for use in LET

measurements. This finding has since been confirmed by another study (Flint *et al* 2015).

Figure 4.9: P-OSL curves normalized to their initial intensities. Signals represent the combined blue and UV emission (a), blue emission (b) and UV emission (c). Each OSL curve was acquired from OSLDs irradiated with proton beams of varying LET and is the average of signals acquired using 5 OSLD readouts. The insets show a magnified view of a small portion of the OSL curves.

These two LET-dependent characteristics, the ratio of UV and blue emission intensities and the OSL curve shape, may be partly due to different manifestations of the same effect. Increases in LET result in increases in the ratio of UV to blue emission intensity (Figure 4.7). The UV and blue emission signals have differing rates of decay. Consequently, changing the relative proportion of these two signals should result in differing shapes of the OSL decay curve. This likely explains why increased variation in the OSL curve shape is seen when both the UV and blue emission bands are present in the collected signal. However, small changes in OSL curve shape are also seen when only one emission band is present. Thus, there is likely another underlying mechanism.

4.4 Conclusion

Two characteristics of the $\text{Al}_2\text{O}_3\text{:C}$ OSL signal show potential for proton LET measurements: the ratio of UV to blue emission intensity, and the shape of the OSL curve. The shape of the OSL curve shows the most LET dependence when both the UV and blue emission bands are present in the collected signal.

In the following chapter, these two characteristics are parameterized and calibrated against LET for a variety of proton irradiation conditions in order to generate LET calibration curves.

Chapter 5

Calibration of OSLDs for Measurements of LET in Therapeutic Proton Beams

This chapter presents the parameterization and calibration of OSL signal characteristics as functions of LET in therapeutic proton beams. First, a review of previous attempts to calibrate OSLDs is presented. Second, LET calibration curves are generated, by parameterizing and calibrating the LET dependent characteristics studied in Chapter 4 against LET values determined using the MC infrastructure described in Chapters 2 and 3. This chapter is heavily based on a study performed by the author during his PhD studies, that was published in the journal *Physics in Medicine and Biology* (Granville *et al* 2014a). However, the work presented in this chapter includes more extensive data and several improvements over the published study. Because of this, the previous study is not explicitly included in this chapter, but is cited as a reference.

5.1 Introduction

5.1.1 LET Measurements with OSLDs – Previous Attempts

Two studies documenting the use of OSLDs for measurements of LET have been published (Granville *et al* 2014a, Sawakuchi *et al* 2010). Sawakuchi *et al* parameterized the CW-OSL curve shape and calibrated it as a function of both LET_{ϕ} and LET_D in unmodulated proton beams. Subsequently, the calibration curves were used to perform measurements of both LET_{ϕ} and LET_D under new irradiation conditions in modulated proton beams. Agreement between measured and MC simulated values of LET_{ϕ} and

LET_D was within 24% and 47%, respectively. In Sawakuchi *et al*'s study, the parameter defined to describe the OSL curve shape was time-consuming and complicated to determine. Calculation of the parameter required that the entire OSL curve be read, which could take between 300 and 600 s, and that OSLDs be exposed to a second reference dose and re-evaluated for normalization. A simpler, less time-consuming, and more accurate approach to LET measurements is desirable for clinical implementation.

Granville *et al* 2014a expanded and improved on Sawakuchi *et al*'s methods by investigating OSL parameters that were faster and simpler to determine and did not require re-irradiation and re-evaluation. In addition to the CW-OSL curve shape, the P-OSL curve shape and UV/blue ratio (as discussed in Chapter 4) were also calibrated for LET measurements. Measured and MC simulated values of LET_ϕ agreed within 34%, 33%, and 26% using the CW-OSL curve shape, P-OSL curve shape, and UV/blue ratio, respectively. For LET_D , agreement was within 11%, 6% and 31%. Although the P-OSL curve shape provided comparable or better accuracy than the other two parameters, it was associated with much larger uncertainties due to detector-to-detector variation and showed poorer correlation in the LET calibration curves.

Both previous attempts to calibrate OSLDs for LET measurements demonstrated their potential as 'LET-meters', but required improvements that could lead to better accuracy and consistency. In both studies, reference LET values were determined using the MC energy spectrum LET scoring technique (see Chapter 3), with a low energy cutoff value that may have resulted in inconsistencies in the scored values. Additionally, the calibration curves were generated using a limited variety of irradiation conditions.

The calibration data were obtained from irradiations in simple unmodulated proton beams exhibiting the Bragg peak depth-dose distribution. High LET values in such beams (greater than $\sim 1.5 \text{ keV}/\mu\text{m}$) occur only in regions of very steep LET gradients that make them more sensitive to errors in setup and small uncertainties in water-equivalent depth. Lastly, the time between irradiation and readout was not precisely controlled, which may have lead to time-dependent uncertainties that were not accounted for.

The work presented in this chapter addresses the necessary improvements in the calibration of OSLDs for LET measurements. In this study, the CW-OSL curve shape and UV/blue ratio are parameterized and calibrated for LET measurements. The OSLDs are calibrated using a more robust method of LET scoring, as well as a broader range and greater number of calibration conditions. Time between irradiation and readout is carefully controlled to nearly eliminate any time-dependent uncertainties. Additionally, a new readout procedure that carefully controls for temperature variations in the OSL readout system is used to potentially improve stability and reproducibility.

In addition to the LET-response of the CW-OSL curve shape and the UV/blue ratio, the dose-response of these two OSL characteristics is investigated in this chapter. Ideally, the LET-dependent characteristics would have little to no dependence on absorbed dose. If this was the case, then a single calibration curve could be used to measure LET regardless of the absorbed dose delivered. However, the OSL curve shape and UV/blue ratio have both been shown to vary with absorbed dose in studies that used other readout protocols (Sawakuchi *et al* 2010, Yukihiro and McKeever 2006a). Thus, an experiment is presented in this chapter that characterizes the dose response of these two

characteristics, to help evaluate their potential for LET measurements.

5.2 Methods

5.2.1 OSLD Preparation

OSLDs were prepared using the same procedure and setup as described in Chapter 4 (section 4.2.1). Four OSLDs were irradiated and evaluated for each condition and OSLD readout protocol.

5.2.2 Proton Irradiations

To study the LET response of the OSL curve shape and the UV/blue ratio (and generate LET calibration curves) OSLDs were irradiated in a series of therapeutic proton beams of varying LET. An absorbed dose to water of 0.2 Gy was delivered to all OSLDs irradiated in proton beams. The absorbed dose for each irradiation was verified individually using a calibrated parallel-plate ionization chamber. A total of 37 different irradiation conditions were used, in a combination of modulated and unmodulated beams. The nominal beam energy, range, SOBP width (if modulated), water-equivalent depth, LET_ϕ , and LET_D for all irradiation conditions are summarized in Table 5.1. All irradiations were performed using the passive scattering proton therapy nozzle at PTCH using the same physical setup as described in Chapter 4, section 4.2.2.

Table 5.1: Proton irradiation conditions. Nominal beam energy, range at central axis, SOBP width (0 if unmodulated), water equivalent depth and LET (both LET_ϕ and LET_D) at the OSLD positions along the central axis are shown for each condition. These irradiation conditions were used to generate the LET calibration curves in Figure 5.2.

Nominal energy (MeV)	Range (cm)	SOBP width (cm)	Depth (cm)	LET_ϕ (keV/ μ m)	LET_D (keV/ μ m)
250	28.5	0	0	0.47	0.99
225	23.6	0	0	0.50	0.97
250	28.5	0	5	0.52	0.95
250	28.5	10	5	0.54	0.96
200	19.0	0	0	0.54	0.97
250	28.5	0	10	0.57	0.98
180	16.1	0	0	0.58	0.97
250	28.5	10	0	0.59	0.99
250	28.5	10	10	0.59	0.99
160	13.0	0	0	0.62	1.00
250	28.5	0	15	0.63	1.01
140	10.0	0	0	0.69	1.04
250	28.5	10	15	0.69	1.06
250	28.5	0	18	0.69	1.05
250	28.5	14	16	0.74	1.18
250	28.5	0	20	0.75	1.09
250	28.5	10	18	0.80	1.24
200	19.0	10	9	0.81	1.23
250	28.5	0	22	0.83	1.14
250	28.5	14	19	0.85	1.43
250	28.5	10	20	0.90	1.47
250	28.5	0	24	0.95	1.24
250	28.5	14	22	0.99	1.65
200	19.0	10	12	0.99	1.65
250	28.5	10	22	1.02	1.69
140	10.0	4	5	1.04	1.34
250	28.5	10	24	1.20	1.96
250	28.5	0	26	1.20	1.44
200	19.0	10	15	1.25	2.04
250	28.5	14	25	1.26	2.04
140	10.0	4	7	1.43	2.27
250	28.5	10	26	1.52	2.43
200	19.0	10	18	2.03	3.12
250	28.5	14	28	2.09	3.26
140	10.0	4	9	2.18	3.31
250	28.5	0	28	2.38	3.33
250	28.5	10	28	2.55	3.90

5.2.3 6 MV Photon Irradiations

To characterize the dose response of the LET-dependent characteristics (CW-OSL curve shape and UV/blue ratio), OSLDs were irradiated with varying doses in a 6 MV photon beam. Photons were used due to limitations in the availability of the proton nozzle. An assumption was made that the relative dependence on dose under photon irradiation would be similar to that under proton irradiation. This assumption was based on preliminary data (Flint 2012), and has since been verified (Flint *et al* 2015).

Absorbed doses to water of 0.1, 0.2, 0.5, 1, 2, 5, 10, 20, 50, 100, 200 and 500 Gy were delivered to OSLDs. These irradiations were performed using a Varian TrueBeam (Varian Medical Systems Inc., Palo Alto, CA) linear accelerator at The University of Texas MD Anderson Cancer Center in Houston, TX. Irradiations were performed at a water-equivalent depth of 1.45 cm in polymethyl methacrylate (PMMA), and absorbed doses were verified using a calibrated ionization chamber.

Note that high doses above 1 or 2 Gy are not normally relevant for proton therapy. However, OSL dose response to low LET radiation can be used to understand and model the LET dependence in high LET radiation (Edmund *et al* 2007a, Sawakuchi and Yukihiro 2012). For this reason, the high dose data are included in this chapter.

5.2.4 Monte Carlo Simulations

MC simulations were used to determine the LET_{ϕ} and LET_D values for each OSLD irradiation condition. Simulations were performed with the same parameter settings as outlined in Chapter 4, using the dE/dx computation scoring technique discussed in Chapter 3.

5.2.5 OSL Readouts

Both CW-OSL and P-OSL readouts were performed using the readout schemes described in Chapter 4, section 4.2.4. However, readouts using Kopp 5113 filters were not included, because these did not show strong dependence on LET (Chapter 4). Thus, all OSL readouts were performed using Hoya U-340 filters. OSL readouts were performed at carefully controlled time intervals after irradiation (12-14 days, depending on readout protocol).

Due to the high number of readouts involved in this experiment, a new effort was undertaken to ensure that the OSL reader stability was not affected by extensive repeated use. With normal, occasional use, the OSL reader remains near room temperature, and this is of little concern. However, when performing very large numbers of readouts with little time between them, there is potential for the reader's temperature to increase. OSLDs have been found to have small or negligible dependence on temperature, up to $\sim 40^{\circ}\text{C}$ (Jursinic 2007, Miller and Murphy 2007, Yukihiro *et al* 2008). This temperature dependence, however, could vary depending on the readout system used. Additionally, the PMT sensitivity may also depend on temperature. To counter such effects, readouts were performed at a rate of one 10-s readout per minute, following an initial warm-up. This protocol was found to maintain a stable temperature within the OSL reader (DB Flint, unpublished data).

5.2.6 OSL Signal Parameterization

Throughout the remainder of this thesis, two distinct groups of OSL signal parameters are investigated. These groups can be broadly classified into “*dose parameters*” and “*LET*

parameters". The *dose parameters* represent OSL signal intensities (i.e. absolute amounts of OSL emission) and are investigated for use in measurements of absorbed dose later on in Chapters 6 and 7. The *LET parameters* represent the two LET-dependent characteristics of the OSL signal identified in Chapter 4 (the CW-OSL curve shape measured using U-340 filters and the P-OSL UV/blue ratio). The *LET parameters* are studied in this chapter. They are defined below, and summarized graphically in Figure 5.1. A parameter describing the OSL curve shape, S_{CW} , was defined as follows:

$$S_{CW} = \frac{\sum_{t=1\text{ s}}^{t=10\text{ s}} I_{CW}(t)}{I_{CW}(1\text{ s})}, \quad (5.1)$$

where $I_{CW}(t)$ is the CW-OSL intensity at readout time t . Physically, the shape parameter represents the area underneath the OSL decay curve after normalization to the initial intensity, where the initial intensity is defined as the signal collected during the first 1 s of readout. Thus, as LET increases and the OSL curves decay more steeply (Chapter 4), the shape parameter is expected to decrease. Other parameters to describe the shape have been investigated, but none matched the reproducibility and simplicity of S_{CW} (Flint *et al* 2015). Note that throughout this thesis, S_{CW} refers strictly to the shape of CW-OSL curves obtained using Hoya U-340 filters during readout, because these show the most LET dependence (Chapter 4).

A parameter describing the ratio of UV to blue emission intensity, $(UV/B)_P$, was calculated by summing the UV signal counts and dividing by the sum of the blue counts for a 10-s P-OSL readout, as follows:

$$(UV/B)_P = \frac{\sum_{t=1\text{ s}}^{t=10\text{ s}} (I_P^{UV+B}(t) - I_P^B(t))}{\sum_{t=1\text{ s}}^{t=10\text{ s}} I_P^B(t)}, \quad (5.2)$$

where $I_P^{UV+B}(t)$ is the P-OSL intensity of the combined UV and blue emission (counter A, as described in Chapter 4 section 4.2.4), and $I_P^B(t)$ is the P-OSL intensity of the blue emission at readout time t (counter B). Time intervals of 10 s were used, because shorter times resulted in greater statistical uncertainty in the OSL signals (i.e. detector-to-detector variation) while longer times provided limited improvement using the in-house OSL reader (Flint 2012). Note that the uncertainties for all OSL parameters represent the 68% confidence interval from four OSLD readouts.

Figure 5.1: Plots of OSL curves showing definitions of A) the CW-OSL curve shape, S_{CW} and B) the UV/blue ratio, $(UV/B)_P$. The area shaded in red represents S_{CW} while the ratio of the areas shaded in grey and blue represents $(UV/B)_P$. $I_{CW}(t)$, $I_P^{UV+B}(t)$, and $I_P^B(t)$ represent the intensity of the CW-OSL emission, P-OSL combined blue and UV emission, and P-OSL blue emission, respectively.

5.3 Results and Discussion

5.3.1 Proton Irradiations

Figure 5.2 shows the calibration data and curve fits for S_{CW} and $(UV/B)_P$ as functions of both LET_D and LET_ϕ .

Figure 5.2: Calibration curves showing a) CW-OSL curve shape, S_{CW} , and b) UV/blue ratio, $(UV/B)_P$, as functions of LET. Open and filled points represent data points plotted against LET_D and LET_ϕ , respectively. Dashed and solid lines represent curve fits as functions of LET_D and LET_ϕ , respectively.

Clear correlations between LET and each OSL parameter were seen. S_{CW} showed an approximately linear correlation with LET_ϕ , while the plot of $(UV/B)_P$ as a function of LET_ϕ showed some curvature. The LET_D calibration curves showed two distinct regions, each having an approximately linear correlation of differing slope.

For calibration data that was approximately linear, a weighted least squares linear regression was used to fit the data and generate a calibration curve (S_{CW} as a function of LET_ϕ). For other sets of calibration data, however, an obvious curvature or bend was present, which rendered a single linear fit inappropriate. In these cases, either a piecewise linear regression (S_{CW} and $(UV/B)_P$ as functions of LET_D) or a second order polynomial was fit to the data ($(UV/B)_P$ as a function of LET_ϕ). For each piecewise linear fit, the point of intersection of the two lines was chosen by eye. The exact value of this point was somewhat arbitrary, however the resulting calibration curves showed little sensitivity to the chosen point, provided it was within a small range of the evident boundary between the two regions. The results of the curve fits are summarized in Table 5.2.

Table 5.2: Summary of the LET calibration curve equations determined from the data presented in Figure 5.2

OSL parameter	LET	Type of fit	Calibration curve equation
S_{CW}	LET_ϕ	linear	$0.223 \times LET_\phi + 4.157$
S_{CW}	LET_D	piecewise linear	$-0.145 \times LET_D + 4.150$, shape ≤ 4.00 $-0.582 \times LET_D + 4.602$, shape > 4.00
$(UV/B)_P$	LET_ϕ	quadratic	$-0.041 \times LET_\phi^2 + 0.308 \times LET_\phi + 0.697$
$(UV/B)_P$	LET_D	piecewise linear	$0.754 \times LET_D + 0.126$, UV/blue ≤ 0.9 $0.121 \times LET_D + 0.77$, UV/blue > 0.9

Note that the curve fits in Table 5.2 and Figure 5.2 do not represent any underlying theoretical relationship between LET and the *LET parameters*. These fits are entirely empirical.

The discontinuity at $\sim 1 \text{ keV}/\mu\text{m}$ in the LET_D calibration curves can likely be attributed to low energy secondary protons. For the irradiation conditions at this LET_D and lower, the OSLDs were placed at or near the surface of a water phantom, in the plateau regions of beams. At these depths, LET_D is more heavily influenced by the presence of low energy secondary protons (Grassberger *et al* 2011). These low energy protons likely contribute little to the OSL signal due to the decrease in OSL response at high LET (Gaza *et al* 2006a, Sawakuchi *et al* 2008), but contribute substantially to the LET_D . The result is that the LET_D remains nearly constant under these irradiation conditions, but the OSL *LET parameters* vary with primary proton LET. Thus, for irradiations occurring in the plateau region with relatively low LET_D , the calibration curves were different than for higher LET_D conditions. The influence of secondary protons on LET_D is demonstrated in Figure 5.3a. When only primary protons are included in the scoring of LET_D , there is a substantial difference between the surface LET_D in the 140 and 250 MeV beams. However, if all protons are scored (including secondaries), the difference at the surface is negligible. As shown in Figure 5.3b, this effect is not noticed for LET_ϕ scoring, because low energy (high LET) secondaries are not weighted as heavily in LET_ϕ calculation (see Equation 3.3 and 3.4, Chapter 3). This explains why the discontinuity is not present for the LET_ϕ calibration curves in Figure 5.2. Note that this discontinuity effect was not seen in previous studies that calibrated OSLDs for LET measurements, because they used a spectral LET_D scoring method that

neglected the contributions of very low energy protons (Granville *et al* 2014a, Sawakuchi *et al* 2010). In practice, this discontinuity should be of little consequence in clinical applications, since it does not affect the high LET_D regions, where clinical measurements of LET would presumably be of most importance.

Figure 5.3: a) Depth- LET_D and b) Depth- LET_ϕ curves for unmodulated 140-MeV (blue) and 250-MeV (red) beams generated using the TOPAS model of the passive scattering proton therapy nozzle. Average LET values of all protons (solid lines), primary protons only (dashed lines), and secondary protons only (dotted lines) are shown.

With the exception of LET_D values below ~ 1 keV/ μm , there is not a clear benefit to using LET_ϕ versus LET_D to characterize the LET dependence of OSLDs. Both average LET_ϕ and LET_D were used to calibrate the OSLDs in this work, because it is not abundantly clear which parameter will be more useful for clinical applications in proton therapy.

5.3.2 6 MV Photon Irradiations

The dose responses of S_{CW} and $(UV/B)_P$ for OSLDs exposed to a 6 MV photon beam are shown in Figure 5.4. Neither parameter showed strong dependence on absorbed dose within the low dose region up (up to ~ 1 -2 Gy). S_{CW} remained constant (within experimental uncertainties) until 2 Gy, while $(UV/B)_P$ was constant only up to 1 Gy. However, $(UV/B)_P$ was only 2.1% greater at 2 Gy than the average between 0 and 1 Gy. Flint *et al* recently demonstrated that the same result occurs for OSLDs exposed to therapeutic proton beams (Flint *et al* 2015). Additionally, $(UV/B)_P$ has recently been shown to be independent of absorbed dose up to 1 Gy in carbon-ion beams of varying LET (E G Yukihiro, 2015, personal communication). These data suggest that the dose independence of the *LET parameters* below ~ 1 Gy holds true across a broad range of LET values. This is a promising result, because the majority of proton therapy treatment fields deliver absorbed doses below this value. Thus, it is feasible that a single LET calibration curve could be used for all proton LET measurements for absorbed doses up to at least 1 Gy. If a field that delivers a higher absorbed dose is required for a proton therapy treatment, LET measurements could still potentially be performed using OSLDs, by scaling down the monitor units to deliver a smaller dose for pre-treatment verification

QA. Note that similar dose dependencies using different readout protocols and definitions of the OSL curve shape and UV/blue ratio have been reported (Sawakuchi *et al* 2010, Yukihiro and McKeever 2006b).

Figure 5.4: The dose response of A) the CW-OSL curve shape, S_{CW} and B) the UV/blue ratio, $(UV/B)_P$ for OSLDs exposed to 6 MV photons.

The dose dependence of S_{CW} and $(UV/B)_P$ after exposure to low-LET radiation (Figure 5.4) can be used to qualitatively explain their LET dependence (Figure 5.2). Irradiation with 6 MV photons results in relatively uniform dose deposition within the OSLDs. With proton irradiation, however, dose deposition is non-uniform and clustered around proton tracks. Thus, even if the average absorbed dose to the detector falls within the flat range of the curves shown in Figure 5.4, the regions near proton tracks can have significantly higher doses at which the S_{CW} and $(UV/B)_P$ parameters show strong dependence on dose. Similar arguments have been used to model the dose response of OSL signal intensities to protons and other heavy charged particles (Edmund *et al* 2007a, Sawakuchi and Yukihiro 2012), and could potentially be used to model the LET dependence seen in Figure 5.2.

5.4 Conclusion

The potential of generating a calibration curve for LET measurements in therapeutic proton beams has been demonstrated using two OSL *LET parameters* that are fast (10 s) and easy to evaluate. These calibration curves were generated using a wider range of irradiation conditions and LET values, and a more reliable method of determining LET from MC simulations than past attempts. In addition, the time between OSLD irradiation and readout was carefully controlled in order to drastically reduce any uncertainties caused by the time-dependence of the OSL signals. As a result, these calibration curves have the potential to provide more reliable and accurate measurements of LET than those that have been previously published.

Chapter 6

Calibration of OSLDs for Measurements of Absorbed Dose in Therapeutic Proton Beams

As discussed in section 5.2.6, two categories of OSL parameters are investigated throughout this thesis: *LET parameters* (S_{CW} and $(UV/B)_P$), which are studied for the purpose of measuring LET, and *dose parameters*, which are studied for the purpose of measuring absorbed dose. In Chapter 5, irradiations in proton beams were used to study the LET dependence of the *LET parameters*, and irradiations in 6 MV photon beams were used to study the dose dependence of the *LET parameters*. The end result was a set of calibration curves that could be used to calculate LET from the *LET parameters*.

In this chapter, background information about the use of OSLDs for absorbed dose measurements is presented. Then, the same irradiation conditions presented in Chapter 5 are used to study the LET dependence and the dose dependence (often referred to as ‘dose response’) of the *dose parameters*. The goal of this chapter is to develop a method to measure absorbed dose in proton beams of varying LET using OSLDs. This is done by calibrating the dependence of the *dose parameters* on absorbed dose and LET.

6.1 Introduction

OSLDs were originally developed for the purpose of measuring absorbed dose. To use OSLDs for this purpose, the OSL emission intensity is calibrated against some standard dosimeter (typically an ionization chamber) to produce a dose calibration curve (often called the dose response curve). The OSL emission intensity, which is used for absorbed

dose measurements, represents an absolute amount of OSL signal collected during readout, unlike the *LET parameters* (S_{CW} and $(UV/B)_P$) studied in Chapter 5.

OSLDs have been well studied and characterized for dosimetry of medical treatments involving photon and electron beams (Aznar *et al* 2004, Jursinic 2007, Kerns *et al* 2011, Mrčela *et al* 2011, Omotayo *et al* 2012, Schembri and Heijmen 2007, Viamonte *et al* 2008, Yukihiro *et al* 2010). An advantage of using OSLDs for dosimetry is the inherent flexibility of the optical readout process, which potentially allows for optimization of the readout protocol to suit a user's particular needs. This flexibility, however, also makes it difficult to concisely summarize the dosimetric properties of OSLDs, because these properties depend on readout protocol. Generally, the OSL dose response curve is linear within a low-dose region (0 to ~1 or 2 Gy) before becoming supralinear (Pagonis *et al* 2006, Yukihiro *et al* 2004b). Eventually, at higher doses (~100 Gy), the dose response saturates (Sawakuchi *et al* 2008, Yukihiro and McKeever 2008). Signals containing only the blue emission band show a greater range of linearity and a smaller degree of supralinearity than those containing the UV emission band (Sawakuchi *et al* 2008, Yukihiro and McKeever 2006b).

The linear – supralinear – saturation progression in the OSL dose response curves can be explained qualitatively by $Al_2O_3:C$ energy level models similar to that shown in Figure 4.2 (Chen *et al* 2006, Flint and Sawakuchi 2013, Yukihiro and McKeever 2011). During irradiation, electron-hole pairs are created in the OSLD. The three electron traps (MDTs, STs and DTs) are in competition for these charges. At low doses, there are plenty of vacancies in traps of all three types. However, as dose increases, DTs begin to fill up. The result is reduced competition for MDTs, so they can trap relatively more charge than

at low doses. The MDT is, of course, responsible for trapping charges that ultimately provide the main OSL signal. Thus, the reduced competition results in supralinear response. Eventually, as dose is increased, the MDT vacancies run out, and no more charges are trapped during irradiation. This causes saturation.

The dose response of OSLDs shows little dependence on energy in megavoltage photon and electron beams that are relevant for modern radiotherapy (Agyingi *et al* 2006, Aznar *et al* 2004, Chen *et al* 2009, Mobit *et al* 2006, Yukihiro and McKeever 2008). The same is not true in heavy charged particle beams. In general, OSLD response has been shown to vary with LET over a large range of particle LET values (Sawakuchi *et al* 2008). This has been explained by an effect similar to that described in section 5.3.2, in which the local dose distributions near particle tracks greatly exceeds the average dose to the detector volume (Edmund *et al* 2007a, Sawakuchi and Yukihiro 2012). Within the core of a particle track, the OSL signal can become saturated by large doses, resulting in a reduced response. This effect is not seen in lower LET radiation (i.e. megavoltage photons and electrons) due to the more uniform pattern of energy deposition.

A number of studies have investigated the dosimetric properties of OSLDs exposed to proton beams (Bartz *et al* 2011, Edmund *et al* 2007b, Kerns *et al* 2012, Reft 2009, Şadel *et al* 2013). However, these studies have been performed under limited irradiation conditions, LET ranges, and readout protocols. Although OSL signals containing just the blue emission band have shown only small LET dependence at the centre of proton SOBPs (Kerns *et al* 2012, Reft 2009), a more significant LET dependence has been demonstrated under higher proton LET conditions (Bartz *et al* 2011, Gaza *et al* 2006a). Signals containing the UV emission have even greater

dependence on LET (Chapters 4 and 5, Sawakuchi *et al* 2008). The LET dependence of OSL dose response curves is problematic for dosimetry of proton beams, because it implies that different dose calibration curves would be required for beams of differing LET. A general method to correct for the LET-dependent response of OSLDs has not yet been demonstrated, but would be useful for dosimetry in therapeutic proton beams.

The dose response of OSLDs exposed to beams of varying quality is often quantified using a parameter called the *relative luminescence efficiency* or *relative absorbed dose sensitivity*. These two terms represent the same quantity: the ratio of the signal per dose acquired in a beam of interest to the signal per dose acquired in a reference beam. The signal per dose should be evaluated in the linear region of dose response (i.e. below ~1 Gy for OSLDs) when calculating this parameter. Throughout this thesis, the term *relative luminescence efficiency* (usually denoted as η) will be used, as this term is more commonly found in OSL dosimetry literature. Mathematically, η can be calculated by the following equation:

$$\eta = \frac{\left(I_o/D_o\right)_Q}{\left(I_o/D_o\right)_{ref}}, \quad (6.1)$$

where $(I_o/D_o)_Q$ represents the OSL intensity per unit absorbed dose in a beam of quality Q and $(I_o/D_o)_{ref}$ is the OSL intensity per unit absorbed dose in a reference beam. The subscript ‘o’ represents evaluation in the linear region of dose response, such that the value is independent of dose.

The value of η can vary due to two separate energy (or LET) dependencies: the absorbed dose energy dependence, and the intrinsic energy dependence (Rogers 2009).

The absorbed dose energy dependence is defined as the ratio of the absorbed dose to water in the absence of the detector, to the absorbed dose in the detector volume. This dependence arises from the fact that OSLDs irradiated with equal absorbed doses to water, but in beams of varying quality, can have differing doses deposited within them. This, in turn, can lead to changes in the OSL signal. The absorbed dose energy dependence can be approximated using stopping power ratios and mass energy absorption coefficients. The second type of energy dependence, the intrinsic energy dependence, is defined as the ratio of the dose to the detector volume to the detector signal. In many cases, it is constant with changes in beam quality, however this is not always true. The intrinsic energy dependence is not simple to compute analytically.

In this chapter, characterization of the dose-dependence and LET-dependence of a variety of OSL signal intensities (CW-OSL and P-OSL signals containing blue, UV or a combination of both emission bands) is performed. Intensities from different OSL readout protocols are directly compared for OSLDs irradiated under the same conditions, in order to help assess the limitations of each. A new method is introduced to correct for the LET-dependent dose response, which allows for measurements of absorbed dose in proton beams using OSLDs calibrated in a reference photon beam.

6.2 Methods

OSLD preparation, irradiations and readouts, as well as the MC simulations were performed as described in section 5.2. The only exception is that this chapter also presents data from CW-OSL readouts performed using the Kopp 5113 filters, as

described in section 4.2.4. In this section, the definitions of the *dose parameters* are presented, and the analyses performed on them are outlined.

6.2.1 OSL Signal Parameterization

This chapter focuses on characterization of the *dose parameters*, which represent OSL emission intensity, I , for various readout protocols. Parameter notation and the OSL signals that they represent are listed below. When referring to these *dose parameters* as a whole, I is used in equations to indicate a generic OSL intensity or *dose parameter*.

- C_B CW-OSL emission intensity from readouts performed using Kopp 5113 Filters (contains blue emission only);
- C_{UV+B} CW-OSL emission intensity from readouts performed using Hoya U-340 filters (contains UV and blue emission);
- P_{UV+B} P-OSL emission intensity of the combined blue and UV bands (counter A, contains blue and UV emission);
- P_B P-OSL emission intensity of the blue band only (counter B, contains blue emission only);
- P_{UV} P-OSL emission intensity of the UV band only (counter A – counter B, contains UV emission only).

Each of these *dose parameters* were defined as the sum of the PMT counts acquired during a 10-s readout.

6.2.2 6 MV Photon Irradiations – Dose Response

OSLDs exposed to varying doses (0.1 – 500 Gy) in 6 MV photon beams were used to calibrate each of the *dose parameters* listed in section 6.2.1 as a function of absorbed dose (i.e. generate dose response curves). The 6 MV beam was used as the reference beam for calculations of the relative luminescence efficiency, η . The slope within the linear region of 6 MV dose response was used to obtain $(I_o/D_o)_{6MV}$, which is necessary for calculation of η (as described in the following section). Note that the inverse of $(I_o/D_o)_{6MV}$ can be used as an absorbed dose calibration coefficient, to calculate absorbed dose in a 6 MV beam from an OSL *dose parameter*.

As mentioned in Chapter 5, the high doses are not necessarily relevant for proton therapy applications. However, the OSL response at high doses was studied because it may allow better understanding of OSL response to high LET radiation.

6.2.3 Proton Irradiations – LET Dependence

The LET dependence of the *dose parameters* discussed in section 6.2.1 was investigated by calculating η for OS LDs exposed to therapeutic proton beams of varying LET (Table 5.1). These OS LDs received an absorbed dose to water of 0.2 Gy, which is within the linear region of dose response. The OSL intensity per unit absorbed dose after proton exposure, $(I_o/D_o)_{p+}$, was used along with $(I_o/D_o)_{6MV}$ to calculate η :

$$\eta = \frac{(I_o/D_o)_{p+}}{(I_o/D_o)_{6MV}}. \quad (6.2)$$

For comparison, the approximate theoretical values of η (based on absorbed dose energy dependence) were also calculated for the LET range investigated. This was done

by dividing the stopping power ratio for $\text{Al}_2\text{O}_3:\text{C}$ and water at each proton LET by the ratio of mass energy absorption coefficients in a 6 MV beam (Berger *et al* 1998, Hubbell and Seltzer 2004). Note that these theoretical values do not account for any intrinsic energy dependence.

6.3 Results and Discussion

6.3.1 6 MV Irradiations – Dose Response

The 6 MV dose response curves for all *dose parameters* are shown in Figure 6.1. The OSL intensities from all readout protocols remained approximately linear until an absorbed dose to water of $\sim 1\text{-}2\text{ Gy}$. *Dose parameters* containing only the blue emission band (C_B and P_B) showed a smaller degree of supralinearity than those containing UV emission (C_{UV+B} , P_{UV+B} , and P_{UV}). P_{UV} showed the most supralinearity, as expected.

Figure 6.1: Dose response curves in a 6 MV photon beam, for each of the *dose parameters*.

To better visualize deviations from linearity, the supralinearity index is plotted as a function of absorbed dose for each *dose parameter* in Figure 6.2. The supralinearity index is the quotient of the OSL intensity per unit absorbed dose at dose D to the intensity per unit absorbed dose in the linear region. It was calculated according to the following equation:

$$\text{supralinearity index} = \frac{(I/D)_{6\text{MV}}}{(I_o/D_o)_{6\text{MV}}}. \quad (6.3)$$

A supralinearity index of 1 indicates linear response, while an index greater than 1 indicates supralinear response. With the scale shown in Figure 6.2, it appears that response is linear until 2 Gy for all readouts. However, at 2 Gy the values are all more than 1 uncertainty bar greater than unity, indicating a small (<2.5%) deviation from linearity. Because absorbed doses in typical radiotherapy fields are below 1-2 Gy, the supralinearity at higher doses is of little concern for many radiotherapy applications. Furthermore, for OSLDs irradiated in therapeutic proton beams, it has recently been shown that OSLDs show a greater range of linearity, and a smaller degree of supralinearity than for 6 MV photons (Flint *et al* 2015).

Note that the dose response data has been corrected for PMT dead time (Williamson *et al* 1988). This is typically a minor effect, but it can reduce the PMT counts by as much as 6% at the highest dose studied (500 Gy), depending on the readout protocol. However, it is negligible at low doses.

Figure 6.2: Supralinearity index versus absorbed dose to water in a 6 MV photon beam, for each of the *dose parameters*.

Based on the 6 MV dose-response curves alone, the five *dose parameters* presented in this chapter are equally appropriate for measurements of absorbed dose in typical radiotherapy applications. However, for higher dose applications, it is advantageous to choose a signal that collects only the blue emission due to the improved linearity.

6.3.2 Proton Irradiations – LET Dependence

The relative luminescence efficiency, η , versus LET_ϕ for all *dose parameters* is shown in Figure 6.3. These data were acquired from OSLDs irradiated with an absorbed dose to water of 0.2 Gy under the proton irradiation conditions listed in Table 5.1. The CW-OSL parameters, C_B and C_{UV+B} , showed relatively small dependence on LET compared to the spread in data and uncertainties. However, for C_B , η showed a small but consistent

decrease, from approximately 0.93 to 0.82, with increasing LET. For C_{UV+B} , η initially increased from approximately 0.87 to 0.92, reaching a maximum near 1.5 keV/ μm before decreasing to ~ 0.89 .

Figure 6.3: Relative luminescence efficiency, η , versus LET_ϕ for a) CW-OSL (C_B and C_{UV+B}) and b) P-OSL (P_{UV+B} , P_B , and P_{UV}) signal intensities for OSLDs irradiated with an absorbed dose of 0.2 Gy in therapeutic proton beams of varying LET. The solid black lines represent theoretical values of η based on absorbed dose energy dependence, calculated using ratios of stopping power and mass energy absorption coefficients.

For P-OSL readouts, P_B showed the least variation with LET, remaining nearly constant at ~ 0.87 until $1.5 \text{ keV}/\mu\text{m}$, before dropping to ~ 0.81 . For P_{UV+B} and P_{UV} , η increased with increasing LET by about 15% and 35%, respectively, over the LET range investigated.

The data in Figure 6.3b demonstrate that within the LET range investigated, the intensity of the blue OSL emission decreases, while the intensity of the UV emission increases. Thus, the behavior of signals containing both depends on the relative intensities of the two emission bands. This explains why the relationship between η and LET is different for C_{UV+B} and P_{UV+B} (both of which contain UV and blue emission). As stimulation time increases during OSL readouts, the relative contribution of the UV emission band to the total signal decreases. During P-OSL readouts, the stimulation sources are only active 40% of the time, while they are active 100% of the time during CW-OSL readouts. Thus, the relative contribution of UV to P_{UV+B} is larger than that to C_{UV+B} .

The response of both C_B and P_B to LET variations behaves similarly to the predicted response, based on the theoretical absorbed dose energy dependence. This suggests that the intrinsic energy dependence is much smaller for the blue emission band than the UV.

For measurements of absorbed dose in therapeutic proton beams, OSL signals with small LET dependence are the most desirable. For specific readout protocols, previous studies have concluded that the LET-dependence of OSLDs exposed to proton beams is small enough to neglect LET-dependent correction factors (Edmund *et al*

2007b, Kerns *et al* 2012). However, these conclusions were made for limited irradiation conditions, and are not true in general, as seen from the data in Figure 6.3. Additionally, the readout techniques presented in those studies offer no potential for simultaneous LET and dose measurements, because they do not collect the UV emission band.

6.3.3 LET-Dependent Correction Factors for Absorbed Dose Measurements

Because the dose-response of OSLDs varies with LET in therapeutic proton beams, a single absorbed dose calibration coefficient (i.e. $(I_o/D_o)_{6MV}$) cannot be used for all beams without an appropriate correction factor. The inverse of the relative luminescence efficiency, η , can be used as such a multiplicative correction factor. Thus, to measure absorbed dose in a proton beam of known LET, the following general procedure could be performed: 1) measure the OSL *dose parameter*, 2) divide the *dose parameter* by $(I_o/D_o)_{6MV}$ to obtain an uncorrected value of absorbed dose, and 3) multiply by the appropriate LET-dependent correction factor, η^{-1} . The general equation would be as follows:

$$D_{p^+} = \frac{I_{p^+}}{(I_o/D_o)_{6MV}} \times \eta^{-1} \quad (6.4)$$

where D_{p^+} represents the absorbed dose to water in a proton beam, and I_{p^+} represents a *dose parameter* evaluated after exposure to a proton beam. The problem with this approach is obvious; the LET under a given irradiation condition is not generally known in advance, so an appropriate value of η^{-1} can not be determined. However, as shown in Chapter 5, it is possible to determine a parameter of the OSL signal that correlates with LET (S_{CW} and $(UV/B)_p$). Thus, by calibrating the correction factor, η^{-1} , as a function of

S_{CW} or $(UV/B)_P$, it could be possible to correct for the LET dependence without prior knowledge of the LET. A similar technique has been demonstrated using OSLDs for applications in space dosimetry (Gaza *et al* 2006b).

For pre-treatment QA of RBE- or LET-optimized proton therapy treatment plans, it would be ideal to have an OSL technique capable of simultaneously measuring both absorbed dose and LET. This necessitates that both an *LET parameter* and *dose parameter* be obtained from the same readout. All readout protocols investigated in this work have *dose parameters* associated with them, but only CW-OSL using U-340 filters and P-OSL readouts can be used to obtain *LET parameters*. Thus, both of these readout protocols can potentially be used for simultaneous measurements of LET and absorbed dose. For CW-OSL, S_{CW} can be used to measure LET with the calibration curve in Figure 5.2a. To measure absorbed dose from the same readout, C_{UV+B} can be used with Equation 6.4. For P-OSL readouts, $(UV/B)_P$ can be used to determine LET with the calibration curve in Figure 5.2b, and one of the P-OSL *dose parameters* (P_{UV+B} , P_B , or P_{UV}) could be used to measure absorbed dose with Equation 6.4. From the data presented in Figure 6.3b, it is evident that P_B is the best choice for this purpose, due to its small LET dependence. Of course, using Equation 6.4 requires knowledge of η^{-1} . To determine η^{-1} , the curves shown in Figure 6.4 can be used. These describe η^{-1} corrections for C_{UV+B} as a function of S_{CW} , and corrections for P_B as a function of $(UV/B)_P$. Polynomial fits were performed for each of the curves, using the lowest order required to achieve a reasonable fit. Note that these fits do not represent any theoretical model to describe the LET-dependence of η^{-1} ,

but are entirely empirical and meant only to facilitate the calculation of an appropriate correction factor based on the data obtained.

Figure 6.4: LET-dependent correction factor, η^{-1} , for a) CW-OSL intensity (C_{UV+B}) calibrated as a function of CW-OSL curve shape (S_{CW}) and b) P-OSL blue emission intensity (P_B) as a function of the UV/blue ratio $(UV/B)_P$. The solid black lines show polynomial curve fits.

The use of a constant correction factor rather than an LET-dependent one may be a reasonable estimate. This is particularly true for C_{UV+B} , which has a relatively small spread in η^{-1} of $\sim 4\%$ in the curve fit and $\sim 8\%$ in the raw data. However, these calibration curves can likely improve accuracy further by accounting for the small LET dependence. Additionally, similar correction techniques may be useful for dosimetry in applications with larger LET variations, including carbon-ion therapy.

6.3.4 Supralinearity and LET Dependence

The differing dose response for UV and blue emission can qualitatively explain the LET dependence of $(UV/B)_P$. The UV emission band shows more supralinearity than the blue emission band with increasing dose. As discussed in section 5.3.2, the local doses deposited near a proton track in the OSL material can be much larger than the average dose over the entire volume. The dose within and surrounding a proton track increases with LET, and can be in the supralinear or saturation region of the dose response. In these regions, the UV and blue emission bands respond differently to changes in absorbed dose. Thus, the ratio $(UV/B)_P$ varies with LET.

6.4 Conclusion

The combined results of Chapters 5 and 6 offer two potential methods to simultaneously measure LET and absorbed dose in therapeutic proton beams. One method uses the *LET parameter* S_{CW} and the *dose parameter* C_{UV+B} obtained from CW-OSL readouts with Hoya U-340 filters. The second uses the *LET parameter* $(UV/B)_P$ and the *dose parameter* P_B obtained from P-OSL readouts. The *LET parameters* are used to determine both LET

and an LET-dependent correction factor, η^{-1} . The absorbed dose is determined using the *dose parameters* and η^{-1} .

In the next chapter, the potential of these techniques is demonstrated by using them to measure LET and absorbed dose under proton irradiation conditions with varying LET, and in real patient-specific proton therapy treatment fields.

Chapter 7

Simultaneous Measurements of Absorbed Dose and LET Using Optically Stimulated Luminescence Detectors

The work from Chapters 2-6 culminated in the development of a CW-OSL technique and a P-OSL technique to simultaneously measure LET and absorbed dose. In this chapter, the potential of both techniques is demonstrated by using them to perform measurements of LET and absorbed dose under new conditions in therapeutic proton beams. These measurements are performed in both simple square fields and complex patient-specific treatment fields.

7.1 Methods

7.1.1 OSLD Irradiations

Square Proton Fields

OSLDs were irradiated with an absorbed dose to water of 0.2 Gy at varying depths along the central axis of a 180-MeV beam with an 8-cm SOBP. At these depths, the LET values spanned nearly the entire range used to create the LET calibration curves (Figure 5.2).

The water equivalent depths and associated LET_{ϕ} and LET_D (determined using MC simulations) are summarized in Table 7.1. The preparation procedure for the OSLDs was the same as was used in Chapters 4-6. Note that beams of this energy and SOBP width were not included in the generation of the calibration curve.

Table 7.1: Summary of OSLD irradiations in the 180-MeV proton beam with an 8-cm SOBP. The range was 16.1 cm at the central axis. Water equivalent depth, LET_ϕ , and LET_D (LETs determined using MC) at the OSLD position are listed.

Water equivalent depth (cm)	LET_ϕ in H ₂ O (keV/ μ m)	LET_D in H ₂ O (keV/ μ m)
0.0	0.61	1.01
7.0	0.83	1.20
9.0	0.98	1.55
11.0	1.14	1.86
13.0	1.41	2.25
15.0	2.10	3.22

Patient-Specific Proton Therapy Treatment Fields

To test the LET and absorbed dose measurement techniques under more realistic clinical scenarios, OSLDs were also irradiated in real patient-specific treatment fields. These fields included patient-specific apertures and range compensators, as discussed in Chapter 2. Irradiations were performed at the centre of each SOBP, along the central axis. Patient-specific fields have more complex, non-uniform distributions of absorbed dose and LET than simple square fields. Due to this spatial variance, OSLDs were packaged in single units and irradiated one at a time in the patient-specific fields.

Four different fields were studied, each from a proton therapy treatment plan for a different patient and treatment site. The treatment plan's prescribed dose was delivered for each field. For doses that greatly differed from the calibration dose (0.2 Gy), irradiations were also performed in the same field with the monitor units scaled down to deliver 0.2 Gy. The LET_D and absorbed dose distribution (calculated from MC simulations) for each patient field are shown in Figure 7.1 through Figure 7.4. In all of figures, LET_D values are shown only for regions where the absorbed dose is greater than

10% of the maximum. Additionally, LET_D values greater than 5 keV/ μ m are all shown in the same colour, to improve contrast in lower LET regions.

Figure 7.1: Patient Beam A. Dose distributions (left) and LET_D distributions (right) for three orthogonal cross-sections intersecting at the centre of the SOBP.

Figure 7.2: Patient Beam B. Dose distributions (left) and LET_D distributions (right) for three orthogonal cross-sections intersecting at the centre of the SOBP.

Figure 7.3: Patient Beam C. Dose distributions (left) and LET_D distributions (right) for three orthogonal cross-sections intersecting at the centre of the SOBP.

Figure 7.4: Patient Beam D. Dose distributions (left) and LET_D distributions (right) for three orthogonal cross sections intersecting at the centre of the SOBP.

The treatment site, nominal beam energy, SOBP width, range, absorbed dose, LET_ϕ and LET_D for each treatment field are summarized in Table 7.2. Note that patient

beams A1 and A2 were identical, with the exception of the dose delivered. The same is true for B1 and B2.

Table 7.2: Summary of OSLD irradiations in patient-specific treatment fields. The treatment site, nominal energy, SOBP width, range at central axis, water-equivalent depth, absorbed dose to water, LET_ϕ , and LET_D at the OSLD position are included.

Beam #	Site	Energy (MeV)	SOBP (cm)	Range (cm)	Depth (cm)	Dose (Gy)	LET_ϕ (keV/ μ m)	LET_D (keV/ μ m)
A1	brain	180	9.0	14.3	9.8	0.20	1.23	2.01
A2	brain	180	9.0	14.3	9.8	0.73	1.23	2.01
B1	esophagus	200	13.0	17.9	11.4	0.20	1.32	2.16
B2	esophagus	200	13.0	17.9	11.4	0.58	1.32	2.16
C	lung	160	6.0	12.9	6	0.17	1.56	2.48
D	liver	180	6.0	13.8	6	0.16	1.56	2.47

7.1.2 OSL Readouts

Both CW-OSL readouts (using Hoya U-340 filters) and P-OSL readouts were performed. From CW-OSL readouts, C_{UV+B} and S_{CW} (as defined in section 5.2.6) were calculated for each OSLD. From P-OSL readouts, P_B and $(UV/B)_P$ were calculated. A total of four OSLDs were evaluated for each irradiation condition, and readout protocol. The results presented were acquired using the average of four irradiations and readouts.

7.1.3 LET Measurements

Measurements of LET were performed using both S_{CW} and $(UV/B)_P$ along with their respective LET calibration curves (Figure 5.2). Both LET_ϕ and LET_D were measured and compared against those determined using MC simulations. The scoring volumes used to determine LET in MC simulations of the patient-specific fields were smaller than those used in the square field, due to the increased spatial variance of LET. In simulations of

patient-specific fields, the LET scoring volumes were cylinders of 7-mm diameter and 0.3-mm thickness, which approximately matched the size of a single OSLD. The scoring volumes in the square fields were the same as used in Chapters 4-6 (rectangular volumes with a $4 \times 4 \text{ cm}^2$ surface area, and 0.3 mm thickness).

7.1.4 Absorbed Dose Measurements

Measurements of absorbed dose were performed using the two *dose parameters*, C_{UV+B} and P_B , according to Equation 6.4. LET dependent correction factors, η^{-1} , were determined using S_{CW} and $(UV/B)_P$ and the curves in Figure 6.4. Absorbed dose measurements performed using the OSLDs were compared against measurements performed using a calibrated ionization chamber (PTW TN23343).

7.2 Results and Discussion

7.2.1 LET Measurements

Figure 7.5 summarizes the results of the LET measurements performed using OSLDs in the 180-MeV proton beam with an 8-cm SOBP. For measurements of both LET_ϕ and LET_D , the *LET parameter* $(UV/B)_P$ provided the best agreement with the reference MC LET values. For LET_D , all values measured using $(UV/B)_P$ agreed within the experimental uncertainties. The maximum discrepancy was $(3.7 \pm 5.2)\%$. Only one measurement of LET_ϕ using $(UV/B)_P$ disagreed with MC, resulting in a difference of $(5.4 \pm 2.5)\%$ at a depth of 11 cm in water. Using S_{CW} , LET_ϕ measurements were within a maximum $(11.4 \pm 10.5)\%$ and LET_D measurements were within $(7.1 \pm 4.6)\%$ of the MC values.

Figure 7.5: Summary of a) LET_{ϕ} and b) LET_D measurements performed using OSLDs at varying depth in a 180-MeV proton beam with an 8-cm SOBP. Results obtained using the CW-OSL curve shape (S_{CW}) and UV/blue ratio $[(UV/B)_P]$ are shown along with the reference values obtained using MC simulations. The PDD is included to guide the eye.

LET measurements performed in the patient-specific fields are summarized in Figure 7.6. Again, $(UV/B)_P$ provided measured LET values that better agreed with the MC predicted values. Using $(UV/B)_P$, LET_{ϕ} was measured within $(6.1 \pm 4.3)\%$ and LET_D

measurements were within $(7.9 \pm 3.2)\%$. Using S_{CW} , LET_ϕ was measured within $(8.6 \pm 6.5)\%$ and LET_D measurements were within $(12.1 \pm 5.7)\%$.

Figure 7.6: Summary of a) LET_ϕ and b) LET_D measurements performed using OSLDs in patient-specific proton therapy treatment beams. The ratio of LET as measured using each LET parameter (S_{CW} and $(UV/B)_P$) to the MC reference value is shown for each patient beam. Dashed black lines indicate agreement within 10%, and the solid black lines represent perfect agreement.

7.2.2 Absorbed Dose Measurements

Figure 7.7 shows a comparison between absorbed dose to water measurements performed using OSLDs and ionization chambers at various depths in the square proton beam.

Absorbed dose to water was measured using: 1) C_{UV+B} with a correction factor obtained from S_{CW} , and 2) P_B with a correction factor obtained from $(UV/B)_P$. Using both measurement procedures, the absorbed dose values obtained using the OSLDs agreed with ionization chamber measurements within the experimental uncertainties ($< 2\%$).

Figure 7.7: Ratio of the absorbed dose to water measured using OSL detectors (D_{OSL}) to the absorbed dose obtained from ionization chamber measurements (D_{IC}) at various depths in a 180-MeV proton beam with an 8-cm SOBP. D_{OSL} measurements were performed using the CW-OSL technique (red squares), and P-OSL technique (blue triangles). An absorbed dose to water of 0.2 Gy was delivered at all depths.

A similar comparison between absorbed dose values measured using OSLDs and an ionization chamber is shown in Figure 7.8 for the patient-specific fields investigated.

The agreement was generally worse in the patient-specific fields, but was still within (2.5

$\pm 1.9\%$) using the P-OSL technique and $(3.0 \pm 1.3)\%$ using the CW-OSL technique.

Despite the good agreement, measurements of absorbed dose using OSLDs in the patient-specific beams were systematically lower than the ionization chamber measurements by approximately 2%. It is suspected that this discrepancy is due to a systematic error in the dosimetry on the day of the patient-specific field irradiations but the exact source of error is not known at this time.

Figure 7.8: Ratio of absorbed dose measured using OSL detectors (D_{OSL}) to the absorbed dose obtained from ionization chamber measurements (D_{IC}) in patient-specific proton therapy treatment beams. D_{OSL} measurements were performed using the CW-OSL technique (red squares), and P-OSL technique (blue triangles). Absorbed dose to water was between 0.16 cGy and 0.74 cGy, depending on the beam.

Based on both the LET and dose results, there is not an obvious advantage to using either CW-OSL or P-OSL readouts. Although P-OSL readouts provided better results, the margin was not large. An inherent advantage of using the P-OSL readout protocol is that the blue emission band can be collected separately from the UV. For

dosimetry purposes, this is advantageous due to the smaller dependence on time and LET, and the greater range of linearity in the dose response (demonstrated in previous chapters). However, the correction method presented in this work reduces the concern about LET dependence, the time dependence could potentially be corrected for (see Appendix A), and both the UV and blue emission bands have a linear response within the dose range typically relevant to proton therapy. Thus, both readout modes show strong potential for simultaneous measurements of absorbed dose and LET in therapeutic proton beams.

7.3 Conclusion

The potential of the CW-OSL and P-OSL techniques developed in this thesis has been demonstrated. From 10-s OSLD readouts, it was possible to measure absorbed dose within 2.5%, LET_{ϕ} within 6.1% and LET_D within 7.9% in the fields investigated using the P-OSL technique. The techniques developed in this work may prove to be useful QA tools. In particular, as proton therapy moves toward implementing biological effects in plan optimization, these techniques could be useful for pre-treatment QA. This has the potential to enhance patient safety, and improve patient outcome should RBE- or LET optimization be found to improve proton therapy efficacy. In the following chapter, future considerations that could further improve these techniques are discussed.

Chapter 8

Conclusion

8.1 Summary

The goal behind this work was to develop an optically stimulated luminescence technique that has potential for clinical measurements of LET and absorbed dose in therapeutic proton beams. A large portion of the thesis (Chapters 2-5) was dedicated to developing the required infrastructure and techniques to create an LET calibration curve. A fundamental challenge was the lack of a readily available and accepted gold standard against which calibration could be performed. This challenge led to a series of MC studies to determine LET under calibration conditions. To this end, a detailed MC model of the proton therapy nozzle that was used for OSLD calibration was implemented and validated against ionization chamber measurements (Chapter 2). Additionally, several different techniques for scoring LET in MC simulations of therapeutic proton beams were investigated, and a reliable, consistent method was determined (Chapter 3).

Two characteristics of the OSL signal from $\text{Al}_2\text{O}_3:\text{C}$, were identified as having potential for LET measurements, and appropriate readout protocols to elucidate them were established (Chapter 4). These two OSL characteristics (CW-OSL curve shape and P-OSL UV/blue ratio) were parameterized to create LET calibration curves (S_{CW} and $(UV/B)_P$), and their dose response was found to be suitable for clinical LET measurements (Chapter 5).

After developing an LET calibration curve, useful parameters for absorbed dose measurements were studied, and a technique to measure absorbed dose in therapeutic proton beams of varying LET was introduced (Chapter 6).

Lastly, OSLDs were irradiated under new proton irradiation conditions, including real patient-specific treatment fields, and evaluated to demonstrate their potential for performing simultaneous measurements of absorbed dose and LET in therapeutic proton beams (Chapter 7).

8.2 Impact

The techniques developed in this study may have a positive impact on proton therapy delivery and treatment, because they could lead to a method of verifying LET and absorbed dose simultaneously. As part of a pre-treatment QA program, such a technique would help to ensure the accurate delivery of LET- or RBE-optimized proton therapy treatment plans. In addition, the MC LET scoring techniques studied in Chapter 3 could lead to improved uniformity and consistency in the MC values of LET reported in the literature, by highlighting a technique that is insensitive to small variations in MC simulation parameters.

The studies presented in this thesis represent the most thorough characterization of the OSL response to proton irradiation performed to date. By exposing OSLDs to a broad variety of proton irradiation conditions, and evaluating them using different readout protocols, the benefits and limitations of the different OSL components of $\text{Al}_2\text{O}_3:\text{C}$ were assessed. Based on this work, it was concluded that OSLDs show strong potential for simultaneous measurements of absorbed dose and LET in therapeutic proton

beams, specifically. However, the results and methodology presented in this work could also lead to developments in other OSL dosimetry techniques. For example, in carbon-ion therapy, where LET variations are even greater than in proton therapy (Romano *et al* 2014), similar techniques to those presented in this thesis may prove useful for QA. Additionally, similar OSL techniques could prove to be useful in space dosimetry, where radiation fields of mixed or unknown qualities (and biological effectiveness) are often present (Yukihara *et al* 2006). Lastly, the results presented in this thesis could improve the overall understanding of the OSL process in $\text{Al}_2\text{O}_3:\text{C}$, and lead to improved analytical models to predict and understand the response under new conditions.

8.3 Limitations, Potential Improvements and Future Directions

Time Dependence of OSLDs

It has been mentioned several times throughout this thesis that the time between irradiation and readout of OSLDs was controlled for, in order to reduce the effects of time-varying OSL signals. It has been demonstrated in the literature that the UV emission band increases in intensity with time following irradiation (Yukihara and McKeever 2006b). Both of the *LET parameters* studied in this thesis and one of the *dose parameters* contain contribution from the UV emission band. Thus, they are expected to depend on time. This represents a potential disadvantage of the OSL techniques presented in this study. However, a long-term time-dependence study that was supervised and partially performed by the author (Appendix A) suggests that these time dependencies can be characterized, and corrected for.

End of Range Exposures

Problems can arise when irradiating OSLDs at or very near the end of the proton range (Edmund *et al* 2007b, Granville *et al* 2014a). In this region, protons are very low in energy, and thus have very high LET and are close to stopping. Several problems can arise as a result of this. Firstly, the implicit assumption that LET is constant over the depth of the OSLDs can break down. Thus, different depths within the OSLD sensitive volume can be exposed to very different average LET values. Secondly, partial volume irradiation can occur due to protons stopping within the detector volume. These problems are exacerbated by the high density of $\text{Al}_2\text{O}_3\text{:C}$ relative to water (3.97 g/cm^3), which causes protons to slow more rapidly in the detector volume than they otherwise would in water.

Regions at the end of the proton range represent some of the highest LETs found in typical proton therapy beams. Thus, it would be ideal to improve upon this limitation. Potentially, improvement could result from using thinner OSLDs. For example, new OSLD films made with a thin $50 \mu\text{m}$ layer of $\text{Al}_2\text{O}_3\text{:C}$ have been studied for 2D dosimetry purposes (Ahmed *et al* 2014). OSLDs made from the same material could potentially result in improved reliability near the end of the range in proton exposures. These films could also potentially be used to perform 2D measurements of LET distributions.

Statistical Uncertainties

In many cases, the statistical uncertainties of the OSL parameters relative to their sensitivities to variations in LET was fairly large. This could potentially be improved

using several different approaches, including pre-screening detectors and improving reader stability.

It has been demonstrated that the detector-to-detector variation of OSLDs can be reduced by performing individual calibration, or pre-selecting detectors (Jursinic 2010, Yukihiro *et al* 2008, 2014). This consists of irradiating OSLDs under a reference condition, and evaluating the OSL parameter of interest to determine its response. Afterward, the acceptable OSLDs can be optically bleached and reused. These methods were not used in this thesis, due to the high number of OSLDs necessary to complete the work presented (>1300). Pre-screening and eliminating a large portion of OSLDs would have required that multiple different batches of OSLDs be used in this work. We found that variations in the *LET parameters* were much greater between batches than between detectors from the same batch during preliminary studies. For most applications, however, such a large number of OSLDs would not be necessary, and pre-screening may be a viable option.

Additionally, we performed all measurements using an in-house built OSL reader, due to its flexibility in manipulating readout protocols. It is possible that better system stability and reproducibility would be achieved using a commercial-grade OSL readout system.

LET Values

Because a gold standard device for measuring LET was not available, LET values were determined using MC simulations. However, in Chapter 3, it was demonstrated that different techniques of scoring LET result in substantially differing values. It is not clear which technique best represents the actual LET.

Another limitation is associated with the LET concept, rather than with the specific techniques developed in this work. In realistic proton therapy treatments, there is an entire spectrum of LET values present, and a simple average (either LET_{ϕ} or LET_D) may not be appropriate to quantify it. The response of detectors depends on the entire spectrum (and, presumably, so does the biological effect). Thus, a parameter that better accounts for the entire LET spectrum (e.g. considers symmetry and width) may prove to better correlate with detector response and biological effect. It is not yet known what LET parameter will prove most useful for treatment plan optimization. This, however, is outside the scope of this thesis.

Clinical Acceptance

This work demonstrated the potential of using OSLDs for measurements of absorbed dose and LET in therapeutic proton beams. In their current state, however, the techniques developed do not represent procedures that are ready for clinical implementation. In addition to implementing the potential improvements listed in the previous section, the techniques should be tested under a large variety of real LET-optimized (i.e. with IMPT) patient-specific treatment plans to better test their limits, and assess situations in which they may be unreliable. Only after more thorough acceptance testing would such a technique be ready for clinical implementation.

Appendix A

Dependence of OSL Signals on Time Following Irradiation

The data presented in this Appendix summarize a long-term (1000 hour) study of OSL time-dependence. The values of the two *LET parameters* and five *dose parameters* studied in this thesis were evaluated as a function of time between irradiation and readout. The time-dependence of the UV emission band is a potential limitation of the OSL techniques presented in this thesis. Thus, characterizing the time dependence allows for a better assessment of the techniques' potential. Ideally, the OSL parameters would not vary with time. However, if the time dependence does not vary with LET, and is easily characterized, then it could be accounted for with a simple correction factor.

In this study, OSLDs were irradiated with an absorbed dose to water of 1 Gy in a 6 MV photon beam or a 3.8 keV/ μm proton beam. These two beams were chosen because they cover nearly the entire range of beam qualities presented in this thesis. Thus, if the time dependence varies with proton LET, it should be made evident by differences between the OSLDs irradiated with photons and the high LET protons.

OSLDs were evaluated at times ranging from 1 minute to 1000 hours following irradiation. Particular emphasis was placed on characterizing the short-term time dependence (< 24 hours), as this would likely be the most useful in clinical applications.

LET Parameters

The *LET parameters*, normalized to their values 20 minutes after irradiation, are shown in Figure A.1. S_{CW} decreased as a function of time, likely due to the increase in the fast-decaying UV component of the OSL signal. S_{CW} decayed at a similar rate for OSLDs

irradiated in the photon and proton beams until ~10 hours post-irradiation. At ~48 hours post-irradiation, the agreement was no longer within experimental uncertainties, however it was within 2.5% until ~1000 hours post-irradiation.

$(UV/B)_P$ increased with time following irradiation. The rate of increase after proton irradiation was mostly consistent with that following photon irradiation. This suggests that the rate is independent of LET in this range, and that the time dependence of $(UV/B)_P$ could be easily corrected for. The approximately logarithmic increase of $(UV/B)_P$ is consistent with that reported in the literature for a different readout protocol, and a beta dose of 20 Gy (Yukihara and McKeever 2006b).

The *dose parameters*, normalized to their values 20 minutes post-irradiation, are shown in Figure A.2. As expected, the rate of increase is greater for parameters that contain contribution from the UV emission. The rates of signal change were generally consistent between OSLDs irradiated with photons and protons. The similarity suggests that a generic time correction procedure could be used for the entire range of proton LETs investigated in this thesis without introducing a large uncertainty. This is especially true if OSLDs are read within a reasonably small window of time (e.g. between 20 minutes and 24 hours). Note that the time independence for signals containing only blue emission (C_B and P_B) contradicts other reports in the literature. Previously, this emission band has been shown to decay rapidly for ~8 minutes following irradiation, before stabilizing (Jursinic 2007, Omotayo *et al* 2012).

Figure A.1: (a) S_{CW} and (b) $(UV/B)_P$ as a function of time following irradiation with a 6 MV photon beam and a 3.8 keV/ μm proton beam. Values are normalized to 20 minutes post-irradiation.

Figure A.2: (a) CW-OSL dose parameters (C_B and C_{UV+B}) and (b) P-OSL dose parameters (P_{UV+B} , P_B and P_{UV}) as a function of time following irradiation with a 6 MV photon beam (open points) and a 3.8 keV/ μ m proton beam (solid points). Values are normalized to 20 minutes post-irradiation.

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