The Promise of Protons: LET in Proton Treatment Planning

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Biology, Medicine and Health

Edward A.K. Smith

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School of Medical Sciences
Division of Cancer Sciences
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<td>1D</td>
<td>One Dimensional</td>
</tr>
<tr>
<td>3D</td>
<td>Three Dimensional</td>
</tr>
<tr>
<td>ART-NET</td>
<td>Advanced Radiotherapy Technologies Network</td>
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<td>CCC</td>
<td>Clatterbridge Cancer Centre</td>
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<td>CRUK</td>
<td>Cancer Research United Kingdom</td>
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<td>CT</td>
<td>Computerised Tomography</td>
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<td>CTV</td>
<td>Clinical Target Volume</td>
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<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
</tr>
<tr>
<td>DSB</td>
<td>Double Strand Breaks</td>
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<tr>
<td>DVH</td>
<td>Dose Volume Histogram</td>
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<td>EBT</td>
<td>External Beam Therapy</td>
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<tr>
<td>EPSM</td>
<td>Engineering and Physical Sciences in Medicine Conference</td>
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<tr>
<td>eV</td>
<td>Electron Volt</td>
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<tr>
<td>GATE</td>
<td>GEANT4 Application for Tomographic Emission (software)</td>
</tr>
<tr>
<td>GEANT4</td>
<td>For Geometry and Tracking (software)</td>
</tr>
<tr>
<td>HR</td>
<td>Homologous Recombination</td>
</tr>
<tr>
<td>HU</td>
<td>Hounsfield Unit</td>
</tr>
<tr>
<td>ICRU</td>
<td>International Commission on Radiation Units</td>
</tr>
<tr>
<td>IMPT</td>
<td>Intensity Modulated Proton Therapy</td>
</tr>
<tr>
<td>IMRT</td>
<td>Intensity Modulated Radiation Therapy</td>
</tr>
<tr>
<td>keV</td>
<td>Kilo Electron Volt</td>
</tr>
<tr>
<td>kV</td>
<td>Kilo-Voltage</td>
</tr>
<tr>
<td>LEM</td>
<td>Local Effects Model</td>
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<td>LET</td>
<td>Linear Energy Transfer</td>
</tr>
<tr>
<td>LET_d</td>
<td>Dose Averaged Linear Energy Transfer</td>
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<tr>
<td>LET_t</td>
<td>Track Averaged Linear Energy Transfer</td>
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<tr>
<td>LINAC</td>
<td>Linear Accelerator</td>
</tr>
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<td>LQ</td>
<td>Linear Quadratic</td>
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<tr>
<td>LVH</td>
<td>LET Volume Histogram</td>
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<td>MC</td>
<td>Monte Carlo</td>
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<tr>
<td>MeV</td>
<td>Mega Electron Volt</td>
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<tr>
<td>MKM</td>
<td>Microdosimetric-Kinetic Model</td>
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<td>MFO</td>
<td>Multi-Field Optimisation</td>
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<td>MLC</td>
<td>Multi-Leaf Collimator</td>
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<tr>
<td>MM</td>
<td>Manchester Mechanistic</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>MSS</td>
<td>Max Step Size</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
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<tr>
<td>MV</td>
<td>Mega-Voltage</td>
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<td>NHEJ</td>
<td>Non-Homologous End Joining</td>
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<td>NHS</td>
<td>National Health Service</td>
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<td>NRAG</td>
<td>National Radiotherapy Advisory Group</td>
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<td>OAR</td>
<td>Organ at Risk</td>
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<td>PBT</td>
<td>Proton Beam Therapy</td>
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<td>PET</td>
<td>Positron Emission Tomography</td>
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<td>PIDE</td>
<td>Particle Irradiation Data Ensemble</td>
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<td>PSPBT</td>
<td>Passively Scattered Proton Beam Therapy</td>
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<td>PTV</td>
<td>Planned Target Volume</td>
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<td>RBE</td>
<td>Relative Biological Effectiveness</td>
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<tr>
<td>ROI</td>
<td>Region of Interest</td>
</tr>
<tr>
<td>$S_{\text{tot}}$</td>
<td>Total Stopping Power</td>
</tr>
<tr>
<td>$S_{\text{el}}$</td>
<td>Electronic Stopping Power</td>
</tr>
<tr>
<td>$S_{\text{nuc}}$</td>
<td>Nuclear Stopping Power</td>
</tr>
<tr>
<td>$S_{\text{rad}}$</td>
<td>Radiative Stopping Power</td>
</tr>
<tr>
<td>SFO</td>
<td>Single Field Optimisation</td>
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<tr>
<td>SFUD</td>
<td>Single Field Uniform Dose</td>
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<tr>
<td>SI</td>
<td>International System of Units</td>
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<tr>
<td>SOBP</td>
<td>Spread Out Bragg Peak</td>
</tr>
<tr>
<td>SSB</td>
<td>Single Strand Break</td>
</tr>
<tr>
<td>TPS</td>
<td>Treatment Planning System</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>VMAT</td>
<td>Volumetric Modulated Arc Therapy</td>
</tr>
<tr>
<td>$\mu \text{m}$</td>
<td>Micrometre</td>
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Abstract

Photons have been applied for over a century of radiotherapy treatments and represent the vast bulk of total patients treated. This level of clinical experience of the photon therapeutic effect does not exist for protons due to fewer patient numbers. This provides a strong impetus to unlock the photon data for Proton Beam Therapy (PBT) and necessitates a photon-proton dose conversion. This conversion, known as Relative Biological Effectiveness (RBE), is currently applied as a constant of 1.1 in the clinic. However, there are many in vitro studies which show proton RBE is not constant with dependence on several factors including Linear Energy Transfer (LET), cell type and dose.

LET is one of the most studied parameters demonstrating a link between itself and RBE, with most proton RBE models and in vivo MRI studies incorporate LET in some manner. This focus comes from the relative ease of calculation and a substantial in vitro evidence base. However, there is limited consensus on the type of LET and the methodology to incorporate the parameter into proton treatment planning. This has led to a substantial variability in the literature in proton RBE models approaches, LET definitions and the clinical metrics proposed to bring LET into standard clinic use in PBT.

The overall aim of this thesis is to aid the introduction of LET into standard PBT treatment planning practice. This aim includes studying how different approaches to RBE models may vary in their predicted biologically weighted dose, how the different definitions of LET may affect the outcomes of variable RBE models and other proposed clinical metrics and to increase consensus for a particular type of LET. To satisfy these aims, chapters two, three and four, of this thesis study sections of the route to incorporating LET into PBT. Chapter two compares a recent mechanistic proton RBE model developed by our group to common phenomenological proton RBE models. Chapter three studies common variations in LET definition and their respective effect on proposed clinical metrics for clinical PBT treatment plans. Chapter four investigates different LET averages along with LET spectra in common radiobiology experimental setups and PBT plans.

The major results from the three journal paper chapters provide evidence to aid the use of LET within clinical PBT treatments. Chapter two found comparable results between the mechanistic model and phenomenological model for PBT plans and highlighted the advantage of mechanistic models in predicting multiple endpoints. Chapter three found the choice of LET definition may affect the results of clinical metrics considered in treatment planning, particularly for different particle inclusions. Chapter four found irregular LET distributions in clinical PBT plans which were not present in typical in vitro experimental setups and masked by LET averaging. Overall, these findings will help aid the clinical inclusion of LET affect in PBT planning.
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Preface

This thesis is presented in the alternative journal format dictated by the University of Manchester. Chapter 1 forms an introduction to the subject of the PhD with Chapters 2, 3 and 4 presented as separate investigations. Chapters 2 and 3 are published work with chapter 4 currently in review. Chapter 5 highlights other notable work conducted during the PhD such as co-author publications and conference presentations.

The Author

M.Sc Physics, University College London, 2014
MSc Clinical Science (Medical Physics), Kings College London 2017
ClinSci, Clinical Scientist (Medical Physics) Registration, HCPC, 2017

I began my PhD Studies at the University of Manchester in October 2017 with the PRECISE research group and The Christie NHS Foundation Trust, Manchester, United Kingdom.
1. Introduction

1.1 United Kingdom Clinical Proton Beam Therapy Service

1.1.1 The Beginning

The start of hospital-based proton therapy in the United Kingdom (UK), a world first, began in 1989 with the opening of a 60 MeV proton treatment facility at the Clatterbridge Cancer Centre (CCC). This site was originally designed for fast neutron treatments but was ultimately re-purposed for the treatment of ocular melanomas with protons [1]. While considered a tremendous success with well over 400 patients treated, the low energy of the protons delivered by the cyclotron restricts the treatment range to a shallow treatment depth. The promise of protons extends further to more deep-seated tumours.

In 2007, the National Cancer Action Team, via the National Radiotherapy Advisory Group (NRAG), commissioned a report to investigate the poor levels of advanced radiotherapy in the UK [2]. One key finding highlighted the lack of provision of high energy Proton Beam Therapy (PBT). This was deemed especially detrimental to paediatric and young adult patients along with adult patients with base of skull or spinal cord cancers [3]. The publication gave a strong impetus to begin the Overseas Programme and, shortly afterwards, patients were sent to established PBT centres in the USA and Europe. Initial outcome analysis of these patients has shown favourable results in local control with further studies on normal tissue complications to be conducted in the future [4].

Over time, the number of patients in the Overseas Programme gathered pace and demonstrated a clear need for PBT centres within the UK. A tender process resulted in a national programme of two PBT centres located at The Christie, Manchester, and University College London Hospital (UCLH), London. At a cost of £250 million, these centres represent the state of the art for proton therapy. Each of the three treatment rooms at each site feature a 360-degree gantry with the protons supplied by a single 245 MeV cyclotron.

In December of 2018, the first fraction of high energy protons was delivered at the Proton Beam Therapy Centre at The Christie. This was followed by UCLH in December 2021.

1.1.2 Modern Techniques and Clinical Metrics

The most common form of External Beam Therapy (EBT) for radiotherapy patients uses photons in some manner. Typically, this is delivered via a Linear ACcelerator (LINAC) where high-energy electrons are fired at a high-Z material held in a rotating gantry. These electrons produce an MV energy spectrum of photons via bremsstrahlung radiation as they interact with the target. Further downstream, a combination of highly-attenuating jaws and MultiLeaf Collimators (MLCs) shape the
radiation field to deliver a dose distribution to the target. A more conformal
distribution may be achieved by altering dose rate and jaw / MLC position, known as
Intensity-Modulated RadioTherapy (IMRT). This movement may be in a ‘step-and-shoot’ fashion with a discrete set of beams at different angles or continuous, in the
case of Volumetric Modulated Arc Therapy (VMAT). This therapy successfully
achieves curative treatment for many tens of thousands of patients across the globe
each year [5].

There is typically a greater variability in the delivery of protons compared to
photons. Differences are found in the method of proton acceleration, the use of
passive or active scattering and the presence of gantry-mounted accelerators to
name a few. Further variations will occur as the number of proton centres increases
across the globe and the modality itself develops. The Christie PBT facility is a
single, 245 MeV cyclotron connected to four bunkers via a common beamline.
Currently, three of these bunkers contain gantries capable of rotating 360 degrees
around the patient with gantry-based cone beam imaging. The fourth room holds a
single fixed research beamline. All patients are treated with active scanning using a
‘step and shoot’ approach. As pictured in Fig (1.1), this method paints the target in
the plane perpendicular to the field by using a series of ‘spots’ directed by magnets
in the nozzle. Planes at different depths in the target are treated
by changing the
energy of protons using a degrader in the beam line. When energies lower than 70
MeV are required, ‘ranger shifters’ are manually placed in front of the beam. This
approach is known as Intensity Modulated Proton Therapy (IMPT), analogous to
IMRT.

![Figure 1.1](image_url)

**Figure 1.1:** Typical proton beam delivery in an active scanning system. Steering
magnets, proton beam, target cross section and scanning path shown.

As with other forms of EBT, the PBT patient pathway after diagnosis and
treatment decision begins with imaging scans. A patient undergoes a Computerised
Tomography (CT) scan to produce a 3D image of the patient’s anatomical structure.
The purpose of this image is twofold, to create a 3D image of the tumour and
surrounding healthy tissue and to provide a map of how radiation attenuates through
the patient. Additional scanning using Magnetic Resonance Imaging (MRI) or Positron Emission Tomography (PET) may be used to further delineate tissue, or show an underlying biological process.

The treatments delivered at the Christie PBT facility are designed by staff using the Eclipse™ (v13.7, Varian, Palo Alto, USA), a treatment planning system (TPS). Here, contours of both the Organs At Risk (OARs) and target are created using the acquired image data and clinical knowledge of the disease. A plan is then developed through a feedback loop between the user and TPS via an in-built optimiser and dose calculation algorithm. Dose is calculated by converting the attenuation coefficients in the CT data to proton relative stopping power [6]. The initial optimisation space is set up by the user by selecting beams and stating dosimetric criteria to both OARs and target. The dose distribution is refined in the loop using various clinical metrics and optimisation strategies.

Two major PBT optimisation strategies are Single Field Optimisation (SFO) and Multi-Field Optimisation (MFO). This refers to whether the optimiser will optimise each field with respect to itself (SFO) or to all fields (MFO). This choice is based upon clinical need with SFO plans generally obtaining better plan robustness but MFO plans achieving greater dose conformality.

The optimisation of these plans is driven by the same metrics applied in photon treatment planning. These clinical metrics are used to measure the plan quality and ultimately the effect of treatment, either in terms of tumour control or the prospect of normal tissue complications. Standard metrics include maximum, minimum and mean doses, to both target and OAR volumes as well as Dose Volume Histograms (DVHs). A DVH is a cumulative histogram which shows the percentage of a specific volume (Y-axis) minimally covered by a dose (X-axis). Fig 1.2 shows the DVH for a stereotactic liver patient with heart, liver minus the Planned Target Volume (PTV) and the high dose PTV shown by olive, blue and orange lines, respectively.

It should be noted that while the term ‘PTV’ is used in this thesis, this is due to convention within the wider radiotherapy field as the use of the volume is debated within PBT. A PTV assumes that the dose distribution is not significantly altered by changes in patient anatomy or geometric shifts between beam and patient. Also, as the PTV is generally a homogeneous expansion, that there is no uncertainty bias in one direction from the CTV. This is reasonable to assume for photon therapy but the assumptions may not hold for proton therapy. For instance, range uncertainty, a major treatment uncertainty, is biased along the beam axis.

Instead of a simple margin expansion, robust optimisation incorporates uncertainty directly into the treatment planning optimisation process. For instance, by including the uncertainty of the stopping power into optimisation dose matrices, the potential of overshooting or undershooting may be accounted for. Worst-case
robust optimisation, the type applied at The Christie, finds the worst dose obtained to a voxel (e.g. lowest dose within the CTV) from this uncertainty and seeks to minimise the associated cost function.

**Figure 1.2:** Dose Volume Histogram (DVH) for a photon VMAT treatment plan designed for a stereotactic liver patient. Olive = heart, blue = liver - PTV, orange = high dose PTV.

### 1.1.3 Advantages and Disadvantages of Protons

As present technology stands, the cost of PBT treatments far greater than the cost of photon treatments including VMAT. This cost is found both in the difficulty of engineering, training and day-to-day operations, as well as the financial cost of purchasing a centre. The motivation to pursue PBT is based on the belief that the improved dosimetric characteristics of the proton will lead to improved treatment for certain patients due to an even greater level of conformality in the dose distribution.

The use of proton therapy to treat ocular tumours at the CCC is an illustrative example of this benefit. With practically no dose deposited after the Bragg peak, these radioresistant tumours can be safely treated with lower damage to the critical structures compared to other radiotherapy alternatives. In fact, protons are so suited to this site it is often chosen above surgery as outcomes are comparable with the additional benefit of retaining the eye and potentially vision [7]. Fig (1.3) demonstrates the fundamental advantage protons may have over photons for treating a deep target. While this does not represent a true comparison in the
differences between photon and proton dose distributions, it shows the advantage of protons in a simple case.

For deep-seated cancers, this benefit was especially clear in previous decades when compared to conventional photon therapy. This has reduced with the advent of IMRT, but PBT still demonstrates a significant dosimetric advantage over IMRT in cases where a lower integral dose or sparing of distal OAR is critical. A lower integral dose is essential in paediatric cases as young and growing tissue has a greater radiosensitivity and secondary cancers are more likely over lifetime [8]. In certain cases, these two factors are both required and PBT may be considered crucial. Paediatric ependymomas, where the PTV is often abutting the brainstem, is a strong example of this situation.

However, while the stopping of protons leads to the main benefit of protons, it also leads to the main disadvantage. Common uncertainties in radiotherapy such as bowel gas or patient setup error may affect proton treatments more than those delivered with photons. These concerns led to first daily setup uncertainties study being conducted for PBT [9]. This is further impacted by other issues affecting range uncertainties [10] such as in stoichiometric calibration where CT numbers are converted to proton stopping power [6].
1.2 Radiation Physics

1.2.1 Interactions with Matter

Due to its positive charge, as a proton travels through a material it interacts with the charged components of atoms as well as with the nuclei as a whole. These interactions can be largely broken down into three distinct processes: stopping interactions with the orbital electrons, scattering interactions with atomic nuclei and full nuclear interactions. Besides the initial beam shape, these interactions lead to the main components of a clinical beam; the Bragg peak, lateral scatter and the halo.

The stopping interaction, by far the largest cause of energy loss at the beam level, is effectively continuously due to the large number of electronic collisions as the proton travels through a material. As the proton’s mass is much greater than the mass of an electron, these collisions cause a negligible scatter to the proton’s path, even in their great number. The resulting secondary electrons, stripped from their atom, are released into the medium to deposit dose. The majority of these particles have a short range and thus deposit their dose in ionisations close to the primary proton track. The rate of energy loss to the proton from this interaction increases as the proton energy decreases: the longer the proton spends in the presence of atomic electrons, the greater the transference of energy. This energy dependence contributes the most to forming the Bragg peak, the key advantage of PBT in comparison to photon therapy (shown in Fig (1.3)).
The other electromagnetic interaction, scattering with the nuclei, is less significant at the beam level. However, as nuclei have substantial mass, this interaction can lead to an appreciable lateral scatter to a proton’s path. On average, the deflections of individual events are small but lead to a substantial near-Gaussian angular velocity when summed along a path.

The remaining interaction is a non-elastic collision with the nucleus. These are catastrophic in nature, with the proton causing the nuclei to release fragments of secondary protons, neutrons, or larger nuclei components such as alpha particles. With a much larger scatter angle compared to the nuclear scattering interaction, a ‘halo’ of these secondary particles surrounds a clinical proton beam. The secondary protons, along with the now indistinguishable primary proton, are the biggest component of this halo and have substantially lower energy than the initial energy of the primary proton. Neutrons are also a clinical concern due to the risk of secondary malignancies to the patient [11]. Due to their rare nature and greater complexity, there are significant uncertainties in modelling these inelastic collisions compared to the stopping and scattering interactions. These nuclear interactions also contribute to the Bragg peak with individual wide-angle scattered primary protons also contributing to the halo surrounding a proton beam.

1.2.2 Stopping Power

The effect of interactions on the energy of a proton as it travels through a medium may be considered through the concept of stopping power. This is defined as the force on a charged particle which causes it to lose energy as it travels through a material. It may be written as:

\[
S = \frac{dE}{dt} \quad (1.1)
\]

Where \( E \) is the mean energy lost by a charged particle along the path \( l \). As defined by the International Commission on Radiation Units (ICRU) Report 85 [7], this parameter is often given in the form of mass stopping power where Eq (1.1) is divided by density, \( \rho \). It may be broken down further into three separate components:

\[
S = S_{el} + S_{nuc} + S_{rad} \quad (1.2)
\]

Where \( S_{el} \) is the electronic stopping power and refers to the inelastic collisions with orbital electrons previously mentioned in 1.2.1, \( S_{nuc} \) is the nuclear stopping power and covers the energy loss due to the elastic collisions with the nuclei and \( S_{rad} \) is the bremsstrahlung radiation due to a charged particle ‘braking’ in an electromagnetic
field. The $S_{\text{rad}}$ term is negligible for therapeutic proton energies with $S_{\text{nuc}}$ contributing little except for very low proton energies.

The Bethe Bloch equation was the first theoretical equation for the rate of energy loss in material for a charged particle [8]. Despite only modelling electronic stopping, it approximates overall stopping power well as this interaction contributes the overwhelming majority of stopping power for a proton as it travels through a material. When specified to protons in the therapeutic energy range, travelling in a material of atomic number, $Z$, and relative atomic mass, $A$, we can obtain:

$$\frac{S_{\text{el}}}{\rho} = 0.3072 \cdot Z \cdot \frac{1}{A} \cdot \frac{W_{m}}{I} \cdot (1 - \beta^{2}) \frac{MeV}{g/cm^{2}}$$ (1.3)

Where $\beta$ is the ratio of the proton’s velocity and speed of light, $c$, and $W_{m}$ is the largest possible proton energy loss in a single collision with a free electron at rest (dependent on proton velocity) and $I$ is the mean excitation energy of the material. The parameter, $I$, is difficult to calculate fundamentally at an accuracy high enough for clinical use. It is thus typically obtained via measurement by fitting to range-energy data. Eq (1.3) ignores the $S_{\text{nuc}}$ contribution shown in Eq (1.2), however at proton energies greater than 0.5 MeV this term contributes no more than 0.1% to energy loss.

### 1.2.3 Linear Energy Transfer

ICRU Report 85 [7] defines Linear Energy Transfer (LET) as:

‘The linear energy transfer or restricted linear electronic stopping power, $L_{\Delta}$, of a material, for charged particles of a given type and energy, is the quotient of $dE_{\Delta}$ by $dl$, where $dE_{\Delta}$ is the mean energy lost by the charged particle due to electronic interactions in traversing a distance, $dl$, minus the mean sum of the kinetic energies in excess of $\Delta$ of all the electrons released by the charged particles, thus:’

$$L_{\Delta} = \frac{dE_{\Delta}}{dl}$$ (1.4)

This ICRU definition describes LET as electronic stopping power but removes the energy of higher energy electrons, which may cause ionisations significantly away from the path of the primary proton. This boundary limit, $\Delta$ effectively creates a volume around the particle’s path where the energy deposited is included but the rest is ignored. As will be discussed later in this chapter, this boundary is usually ignored, and unrestricted LET is applied. It should be noted that the ICRU has previously defined LET including the second term in Eq (1.2) [9].
In microdosimetry, this volume may be separated into two regions, the infratrack and the ultratrack, as shown in Fig (1.4). The infratrack area surrounds the primary particle’s path where the charged particle directly causes ionisations. The ultratrack area encapsulates this infratrack region and marks the boundary of the infratrack and the boundary limit. Here, the primary particle indirectly causes ionisations via secondary particles. [10]

**Figure 1.4**: A proton’s path with infratrack and ultratrack regions. \( \Delta \) denotes the boundary applied in the definition of LET in the ICRU Report 85 [7].

### 1.2.4 Absorbed Dose

Absorbed dose is the total contribution of energy depositions for all interactions from radiation. In ICRU Report 85 [7] absorbed dose, \( D \), where \( dE \) is the mean energy imparted by radiation to material of mass \( dm \) may be described as:

\[
D = \frac{dE}{dm} \quad (1.5)
\]

Dose may also be related to mass stopping power if we define fluence, \( \psi \), as the number of protons, \( dN \), travelling perpendicular to the cross-sectional plane (\( dA \)) of a cylinder:

\[
\psi = \frac{dN}{dA} \quad (1.6)
\]

If this cylinder has a thickness, \( dx \), we obtain:

\[
D = dN \frac{dE}{\rho \ dA \ dx} = \frac{dN \ dE}{\rho \ dA \ dx} = \psi \frac{S}{\rho} \quad (1.7)
\]

In any radiation therapy, absorbed dose is the main parameter for estimating the biological effect of radiation. Under SI and standard clinical practice, absorbed dose is expressed in units of Gray (Gy) where 1 Gy corresponds to 1 joule of energy deposited per 1 kilogram. For proton therapy, it is common to express dose in terms of Relative Biological Effectiveness (RBE)-weighted dose in units of Gy\(_{\text{RBE}}\) where the
increased biological effect of protons compared to photons is accounted for by multiplying the physical absorbed dose by 1.1.

1.3 Relative Biological Effectiveness (RBE)

1.3.1 History and Current Clinical Practice

It has been well understood from the early stages of proton therapy that a lower absorbed dose from protons is required to achieve the same biological effect compared to photon absorbed dose. This RBE may be defined as the ratio of the photon dose, \( D_x \), and proton dose, \( D_p \), to acquire the same biological endpoint:

\[
RBE \triangleq \frac{D_x}{D_p} \quad (1.8)
\]

While it is often not considered, it is important to properly define the energy of the reference photon radiation as commonly-used photon energy spectrums are known themselves to vary in biological effectiveness [12,13]. This is the result of differences in the energy spectra of secondary electrons created by the different photon energy spectra.

As proton therapy reached the clinic in the 1970’s, RBE and how it should be applied was a heavily debated topic. Radiotherapy was and still is, planned on the basis that a certain photon absorbed dose has a probability of achieving a certain local tumour control or of causing toxicity in normal tissue. The knowledge base for this relationship has been painstakingly derived from clinical trial and error of photon radiotherapy over the course of a hundred years. Because a similar level of data for proton therapy does not exist to acquire this relationship directly, a method of converting proton dose to photon dose is required.

Eventually a pragmatic solution of applying a constant RBE of 1.1 to all proton therapy treatments was decided upon. This, by and large, is still maintained to the present day. Currently, there is no clear evidence that using this constant RBE has led to suboptimal treatments or is causing avoidable toxicity. However, this decision was made in recognition that the underpinning \textit{in vitro} data has substantial uncertainties and RBE was variable with multiple parameters [14]. This \textit{in vitro} evidence for variable RBE has continued to grow over the last 50 years with data now correlating RBE with dose fractionation [15], total dose [16], specific biological endpoint [14], tissue oxygenation [17], \( \alpha/\beta \) [18], cell cycle phase and LET [19].

1.3.2 \textit{In Vitro} Evidence

1.3.2.1 LET: There is a significant amount of data from cellular experiments demonstrating a relationship between RBE and LET for a range of different particle irradiations [20]. While these experiments have substantial uncertainties, clear
trends can be seen when analysing the body of data [14,21]. With the most commonly used endpoint of clonogenic cell survival, we see an increasing RBE with increasing LET, up to a LET value dependent on particle type. The region past this value is known as ‘overkill’, where RBE begins to fall with increasing LET. This RBE-LET relationship can be explained by the biological mechanism caused by ionising radiation, Double Strand Breaks (DSBs).

Following the widely accepted theory of DSBs, ionising radiation causes cell death by depositing two ionisations close to one another on the cell’s DNA. This cleaves the DNA apart and the cell must correctly repair this damage or face chromosome aberration and death. Increasing LET leads to a greater RBE as the space between ionisations decrease and thus the probability of a DSB occurring and the break complexity increases. As the distance between ionisations continue to reduce past the width of DNA, the region of overkill occurs. These ionisations do not increase the probability of DSBs and thus RBE reduces as we are comparing for the same absorbed dose. This also explains the difference in RBE for particles with the same LET, as seen in Fig 1.5. Typically, lower Z particles have a higher RBE for a given LET: their energy deposited per ionisation event is lower, such that they achieve more ionisations for a given absorbed dose and LET.

There are a large number of cell experiments demonstrating this RBE-LET relationship across a range of cell types and endpoints [16,19,22–30]. For protons, the range of LET values relevant to the clinic do not exceed the initial monotonic increase with RBE. Studies have demonstrated a possible overkill effect, but at very high proton LET values of approximately 30 keV μm⁻¹ [19,24,31]. Protons reach approximately 25 keV μm⁻¹ before their range falls below the width of a human cell and, within voxelated treatment planning, values reach approximately 15 keV μm⁻¹. Other ions maintain higher LET values for substantial ranges and thus this overkill effect has greater clinical relevance.
1.3.2.2 Other RBE Factors: LET is just one parameter among many which contribute to a variable RBE. The total effect of these factors on RBE is complex as they are not wholly independent from each other.

The data for fractionated dose [14,15,32] shows RBE increases with decreasing dose per fraction. Most of this dose data focuses around the traditional 2 Gy per fraction and thus data points below this are limited by the unknown reliability of the Linear Quadratic (LQ) model below 1 Gy [33].

Tissue type is also a significant parameter of study in variable RBE. The LQ model (outlined in section 1.3.5.1 below) is typically applied to define the radiosensitivity of a cell line or organ. The ratio of $\alpha$ and $\beta$, both parameters in this model, are used to define whether an organ is late or early responding to radiation. From available in vitro RBE data, it appears those with a smaller $\alpha/\beta$ ratio (late responding tissue) have an increased RBE effect in the face of decreasing dose per fraction. The origin of this dependence is complex and based upon the function and structure of cells and tissue, with causes including differences in DNA repair pathways and the extent of parallel or serial function in an organ. The value can also be linked to the amount of oxygen present in tissue with tumours being significantly more hypoxic in comparison to healthy tissue [34,35]. Unsurprisingly, the high level of complexity and limited number of cell lines in datasets makes the exact relationship unclear and it is theorised that the relationship between $\alpha/\beta$ ratio and RBE may be non-monotonic and/or non-linear [14].

Finally, as directly stated in Eq (1.5), RBE is also dependent on the chosen biological endpoint. For instance, cell death is often the main focus for in vitro studies.

**Figure 1.5:** Graph showing RBE against LET for various ions such as carbon, helium and hydrogen ions. This data is taken from PIDE [20].
but endpoints such as different forms of chromosome aberrations or misrepair appear to have their own relation to dose or LET [36,37]. The endpoint of interest often depends on what tissue or cells is being studied. Studying the biological effect of radiation on tumour cells makes cell death, senescence or disruption of reproductive capacity the most relevant endpoints. However, there are many clinically relevant endpoints for healthy cells and tissue where the biological mechanism may substantially vary.

1.3.3 In Vivo Evidence

Early work examining a possible in vivo effect from variable RBE focused on a potential increased rate of brainstem necrosis in comparison to equivalent photon EBT. Initial results from a clinical trial demonstrated a rate of necrosis as high as 12.7% compared to 0.6% for photons [38]. Upon changing guidelines on Clinical Target Volume (CTV) expansion and brainstem dose tolerances, this reduced to 0% [38]. The root of this apparent increase was never determined partially due to a low number of proton patients, missing necessary clinical information and a lack of appropriate post irradiation imaging review. However, an increased RBE above the standard 1.1 was considered, particularly due to the trial focusing on ependymoma. As mentioned previously, this site could be sensitive to elevated LET with fields typically stopping in or near the brainstem to ensure full coverage of the CTV.

These concerns about elevated LET causing severe toxicity due to an RBE much greater than the clinical standard of 1.1 appears to have made LET the focus for most in vivo RBE investigations. This is also because as a physical parameter, LET is far easier to calculate in a patient than other parameters shown to vary with RBE. For instance, it would be difficult to individually calculate a patient’s radiosensitivity at a voxel-based level with the current uncertainties in α/β. LET is calculated in this manner with relative ease via Monte Carlo (MC) simulation.

There are now a growing number of studies which attempt to link LET to some clinically significant effect in patients [39–47]. These typically focus on brain patients where low α/β ratios of healthy tissues, the proximity of critical OARs and the extreme nature of potential toxicity makes them important areas of study. By examining pre- and post- irradiation MR imaging of PBT patients, it is hoped image changes can be statistically linked to evaluated LET. These image changes in MR imaging are crucial for identifying types of brain injury caused by radiation [38,39,48,49]. However, despite being considered a clinical response by commonly used toxicity grading criteria [50], MRI image changes do not necessarily lead to a symptomatic effect to the patient.

The voxel-based studies in the literature have had the most success in demonstrating a statistical link between LET and these image changes. From a cohort of paediatric ependymoma patients, Peeler et al [44] found that at low LET
values (<2 keV μm⁻¹) the probability of an image change in a voxel was approximately equal to that seen in photon data (60 – 75 Gy using an endpoint of necrosis of infarction). Higher LET protons (>2 keV μm⁻¹) were found to correlate with image changes at lower doses. Further work demonstrated a similar effect in image changes occurring in breast patients [42] with others confirming image change effects related to elevated regions of LET [41,47].

There have been other attempts to link LET to a biological effect instead of image change analysis, but these have been less successful. The first published study on possible clinical effects of LET was in a cohort of paediatric and young adult Medulloblastoma patients [45]. These patients typically require whole CNS irradiation and are treated with posterior fields to spare healthy organs. Recurrence is a high risk with small dose deviations thought to be one major cause. There was concern LET was a contributing factor by leading to a less-than-thought homogeneous dose distribution. The high α/β of this tumour is also a concern with some proton RBE models predicting an RBE lower than the clinical standard of 1.1. This work did not find a statistical link between LET and areas of recurrence when compared to the mean LET of the entire treatment volume, only with absorbed dose.

1.3.4 RBE Models
1.3.5.1 Linear Quadratic Model: The linear quadratic model has uncertain origins with several works independently deriving similar forms. It is, by far, the most commonly used method for characterising the effect of radiation in both laboratories and the clinic. It is a critical tool in determining the biological effect of competing courses when compensating missed radiotherapy fractions [51].

When applied in in vitro experiments studying the surviving fraction of cells after irradiation, it has the form of:

\[ S = \exp(-\alpha D - \beta D^2) \] (1.9)

Where S is the surviving fraction of the cells, D is the absorbed dose delivered to these cells and α and β are fitting parameters to define the S and D relationship. Eq (1.9) obtains a quadratic function when plotted on a logarithmic scale, with the α term dominating at lower doses and β rising in importance for larger doses. This gives the characteristic linear shoulder and then an increasing curvature as dose increases. The origin and use of fractionation in clinical radiotherapy is the consequence of the shape of this response. Healthy tissue, with typically low α/β values of 2-3 Gy, will be spared damage from a fractionated dose while tumour cells, with higher α/β of often 10 Gy or greater, will have less benefit from fractionation.

The derivation of the LQ model was largely empirical in its early stages with the simple Taylor series describing the polynomial seen in dose response graphs.
However, theories of mechanical action were quickly proposed with target and hit models having significant popularity at one time [33]. These models gave way to various proposed theories on damage and repair of DNA [52–54]. Although it is acknowledged that cell and tissue responses are very complex and cannot alone be described by the LQ model.

1.3.5.2 Phenomenological Models: With building interest in a variable proton RBE, a series of phenomenological models have been constructed using the substantial in vitro data accrued so far [14,20,55]. These types of models are the most common method of estimating proton RBE and rely on the LQ model to compare the difference in biological effect between protons and photons. Largely, they follow a similar form and select cell kill as their endpoint with different assumptions made in the parameters. Models presented in [32,56,57] are widely used examples of this type of model and demonstrate common differences between the wider group. They both incorporate dose per fraction, dose averaged LET (LET_d) and α/β to estimate RBE. These models are obtained from the LQ model by combining Eq (1.7) and Eq (1.8):

\[
S = \exp(-\alpha D - \beta D^2) \rightarrow D = \frac{\alpha_x - \sqrt{\alpha_x^2 - 4\beta_x \ln(S)}}{-2\beta_x} \quad (1.10)
\]

\[
RBE = \frac{D_x}{D_p} = \frac{\alpha_x - \sqrt{\alpha_x^2 - 4\beta_x \ln(S)}}{-2\beta_x} \cdot \frac{-2\beta_p}{\alpha_p - \sqrt{\alpha_p^2 - 4\beta_p \ln(S)}} \quad (1.11)
\]

As we are comparing the same endpoint, we may insert Eq (1.8) in \(\ln(S)\) for protons and rearrange, this obtains:

\[
RBE = \frac{1}{2D_p} \left(\sqrt{\frac{(\frac{\alpha_x}{\beta_x})^2}{4} + 4D_p \frac{\alpha_x \alpha_p}{\beta_x \beta_p} + 4D_p^2 \frac{\beta_p}{\beta_x} - \frac{\alpha_x}{\beta_x}}\right) \quad (1.12)
\]

We now define \(\frac{\alpha_p}{\alpha_x}\) as \(RBE_{\text{max}}\) where RBE is an asymptotic value at \(d = 0\) Gy and \(\sqrt{\frac{\beta_p}{\beta_x}}\) as \(RBE_{\text{min}}\) where RBE is an asymptotic value at \(d = \infty\) Gy.

This obtains:

\[
RBE \left[ D_p \left(\frac{\alpha}{\beta_x}\right), RBE_{\text{max}}, RBE_{\text{min}} \right] = \frac{1}{2D_p} \left(\sqrt{\frac{(\frac{\alpha_x}{\beta_x})^2}{4} + D_p \frac{\alpha_x}{\beta_x} RBE_{\text{max}} + 4D_p^2 \frac{\beta_p}{\beta_x} RBE_{\text{min}} - \frac{\alpha_x}{\beta_x}}\right) \quad (1.13)
\]
The differences between these models lie in their assumptions for RBE\(_{\text{max}}\) and RBE\(_{\text{min}}\), where these models introduce their independence of LET, outlined by Tab (1.1). RBE\(_{\text{max}}\) and RBE\(_{\text{min}}\) in each model take the form of:

\[
a + b \frac{LET}{\alpha_x/\beta_x} \quad (1.14)
\]

Where \(a\) and \(b\) are fitting parameters. The inversely proportional relationship for the tissue parameter in RBE\(_{\text{max}}\) in all three models shows tissues with lower \(\frac{\alpha_x}{\beta_x}\) are affected more by elevated LET than higher \(\frac{\alpha_x}{\beta_x}\) tissues.

<table>
<thead>
<tr>
<th>RBE Model</th>
<th>RBE(_{\text{max}})</th>
<th>RBE(_{\text{min}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carabe</td>
<td>0.843 + 0.154 (\frac{2.686 \text{LET}}{\alpha_x/\beta_x})</td>
<td>1.090 + 0.006 (\frac{2.686 \text{LET}}{\alpha_x/\beta_x})</td>
</tr>
<tr>
<td>McNamara</td>
<td>0.999 + 0.356 (\frac{\text{LET}}{\alpha_x/\beta_x})</td>
<td>1.101 - (\frac{0.004 \text{LET}}{(\alpha_x/\beta_x)^{-2}})</td>
</tr>
<tr>
<td>Wedenberg</td>
<td>1 + 0.434 (\frac{\text{LET}}{\alpha_x/\beta_x})</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1.1: RBE\(_{\text{max}}\) and RBE\(_{\text{min}}\) for the Carabe, McNamara and Wedenberg Proton RBE Models [32,56,57].

Other phenomenological models in the literature have further differences including the use of track averaged LET instead of dose averaged LET [47] or the use of the full LET spectra [58]. Other models ignore the tissue dependence or may not apply the LQ model at all [59].

1.4 LET in Practice

1.4.1 A Brief History of LET

Ionising radiation leads to a biological effect due to both physical and chemical changes the radiation causes as it traverses through a medium. The magnitude and nature of this effect is mainly controlled by the amount of energy imparted to a unit mass. Measured in Gy in the clinic, this is the main parameter used in radiotherapy to predict therapeutic effect. However, other parameters such as the quality of radiation is also an important component in describing biological effect along with dose rate and fractionation. The term radiation quality describes
the structure of ionisations along the track of the radiation as it deposits the total energy imparted to the unit mass of the material. The difference of this structure drives the variation seen between radiation types at the same absorbed dose.

For a complete description of the effects of radiation, information would be needed on the position and time of ionisations along with the position of any biological sensitive volume, repair proteins etc. This is impractical and, depending on the application, a level of simplification is required. For instance, a radiation specific scaling factor is deployed in radiation protection to account for the varying biological effect across different types of radiation such as alpha, beta and gamma. More complex methods are used in nanodosimetry where position and complexity of DNA breaks are considered [60].

A considerable amount of work in the literature, from the earliest stages of studying the biological effect of radiation, was on deriving various metrics for accounting for this radiation quality factor. Gray [61] proposed Mean Linear Ion Density, $\rho_{MLI}$, to describe the quality of electrons resulting from x-rays, gamma rays and beta radiation. This is defined as:

$$\rho_{MLI} = \frac{\bar{E}_0}{R_{E_0} \bar{W}} \quad (1.15)$$

Where $\bar{E}_0$ is the average kinetic energy of primary electrons, $R_{E_0}$ is the range of electrons of $\bar{E}_0$ and $\bar{W}$ is the average energy expended per ion pair formed in a gas. This was later changed by Cormack and Johns [62] with an improved method of averaging the electron kinetic energies. However, measuring ionisation is difficult in liquids and solids and the use of $\rho_{MLI}$ was limited. This term also ignores the radiation damage induced by excitation and only considers damage caused by ionisation.

Parallel to the work by Gray [61] and Cormack [62], Zirkle [63] introduced the concept of linear energy absorption, later renamed as Linear Energy Transfer (LET) [64]. This is equivalent to the linear density of both ionisation and excitation caused by radiation. It is later improved by Burch [65] to include an energy-weighted component in the mean LET. As research progressed, the definition of LET further developed with the most recent ICRU definition (stated above in ‘1.2.3 Linear Energy Transfer’).

Previously, the ICRU definition (Eq (1.4)) included collisions with the nucleus along with those with orbital electrons. The boundary limit, $\Delta$, aims to remove those secondary electrons which travel far away from the path of the primary particle and do not contribute to the local ionisations.

LET has been one of the most common expressions of radiation quality over time. However, it is not without limitations, realised soon after its inception. These stem directly from the definition of LET as an average of identical particles of the
same energy and velocity travelling along a straight line. If charged particles always travelled in a straight line and continuously deposited their energy with resulting ionisations a negligible distance away from the primary track, LET would be the perfect parameter. These deviations can be mainly separated into four distinct categories: delta rays, rapid particle energy change, LET distributions, and different particles.

1.4.1.1 Delta Rays: One often discussed issue in microdosimetry is the presence of delta rays created by the primary particle. These relatively high energy electrons may cause ionisations a substantial distance from the primary particle track and often do so with a non-negligible curvature in their own track. As LET is regularly applied at the cell or DNA level, counting the energy of this particle in dE overestimates the ionisations delivered to the area of interest. The boundary energy in the ICRU definition of LET serves to remove these electrons from the LET value.

1.4.1.2 Rapid particle energy change: Densely ionising particles may rapidly change in energy along their track. As dE becomes a large proportion of the total energy of the particle, LET is only valid for very short segments of their track as the range of energy is non-negligible. Also, the track of these particles are often highly non-linear.

1.4.1.3 LET Distributions: LET distribution measurements are difficult as these cannot be observed and have to be inferred from other measurements. Energy deposits are measured with a very thin detector window and then related back to LET. However, the actual energy lost by the charge particle is different to the energy absorbed by the detector with approximations required to link the two. Energy deposition occurs via various mechanisms and LET distribution is only one of these.

1.4.1.4 Different particles: The definition of LET is only valid for a specific charged particle. However, radiation is rarely composed of a single particle type and is instead a range of different particle types. For a beam of protons, this includes electrons but also alpha and other heavy particles and therefore a measurement of LET may include these different particles. This is especially an issue when studying the biological effect, as particles of the same LET and dose are known to have a differing biological effect.

1.4.1.5 LET alternatives: In answer to these limitations, a series of papers by Rossi [68–70] defined a series of parameters such as local energy density and individual event size. These were developed for application within microdosimetry in situations where LET is not a suitable parameter. Their additional benefit was the ability to alter the size of interest, which is crucial when investigating possible cellular structures responsible for the biological effect of radiation.

Event size, \( Y \), is defined as:
Where $E_s$ is the energy deposited in a sphere and $d_s$ is the diameter of the sphere. This holds the same units as LET with energy/distance but reduces the issues LET has in dealing with the random nature of energy deposition, delta rays and rapid particle energy change. Also, by defining a sphere, it is a much easier parameter to measure as the detector simply takes this shape. However, for microdosimetry, fluctuations in the number of ionisations for lower doses can be important and these are not covered by either LET or $\Upsilon$. These fluctuations may be better controlled for by defining local energy density as the energy deposited in a sphere divided by the mass of the sphere and not the diameter.

These concepts directly led to the concept of lineal energy and specific energy, analogous to event size and local energy density, respectively. These are often applied in microdosimetry as well as RBE models [71] with measurements made of lineal energy to validate calculated LET distributions [72]. The most recent ICRU definition defines these as:

\['The lineal energy, $y$, is the quotient of $\varepsilon_s$ by $\bar{l}$, where $\varepsilon_s$ is the energy imparted to the matter in a given volume by a single energy-deposition event, and $\bar{l}$ is the mean chord length of that volume, thus:'\]

\[y = \frac{\varepsilon_s}{\bar{l}} \ (1.17)\]

\['The specific energy (imparted), $z$, is the quotient of $1$ by $m$, where $1$ is the energy imparted by ionizing radiation to matter in a volume of mass $m$, thus:'\]

\[z = \frac{\varepsilon}{m} \ (1.18)\]

### 1.4.2 LET in Practical Definition

While it is clear LET is not without issues as a parameter of proton biological effect, the simplicity of the parameter has led to heavy use in radiobiological experiments [14,16,22,28,55,73]. Lineal energy and specific energy parameters are frequently applied in microdosimetry but LET is still the most common track structure parameter quoted in proton radiation cellular studies.

In comparison to other radiation types and applications, the limitations stated above are reduced for LET when studying protons at the patient level. Delta rays produced at clinically relevant proton energies are mostly of a low energy [74] and do not travel a significant distance away from the track. This is especially the case...
when considering the typical millimetre sized voxels applied in treatment planning. Also, the presence of secondary nuclei created in a proton beam is low. At the main area of interest for proton RBE, the elevated LET region distal to the Bragg peak, the presence of both high energy delta rays and heavy secondary particles is low. This is in contrast to heavier particle beams, such as carbon, where the characteristic distal tail past the Bragg peak highlights the presence of this secondary radiation.

While some of the limitations for LET described from a microdosimetry perspective do not apply to the same extent in PBT, other issues emerge. There are a wide number of alterations made to the ICRU statement when practically applied in radiobiology experiments as well in proton treatment planning [75]. This range of differences can be largely split into the following groups: averaging, particle inclusion, scoring and calculation settings.

1.4.2.1 LET Averaging: From the above definition, LET is calculated at a specific point for a particle of defined type and energy. However, in a treatment plan, dose and other parameters are defined in a voxelated geometry which contains a spectrum of particles of different energies due to energy straggling and spanning across a depth. One method of handling this spectrum is to average across these particles and acquire a single LET value for each voxel. There are several LET averaging methods in use within the literature with the most common being dose-averaging (LETd) and track-averaging (LETi). Other LET averages exist, such as volume or nucleus averaging [29,76], but are not typically used in PBT-related applications. Both LETd and LETi are found widely in in vitro and in vivo experiments as well as RBE models for protons [14,15,19,20,23,43,44,47,55,77–79].

Both these LET averages weight the contribution of each particle on a physical parameter. For LETd, the LET for each particle is weighted with respect to its contribution to local dose, this obtains:

\[
\text{LET}_d = \frac{\sum_i dE_i}{\sum_i dE_i} \text{d}l_i \quad (1.19)
\]

For LETi, the LET from each particle is weighted with respect to its step length in each voxel:

\[
\text{LET}_i = \frac{\sum_i dl_i}{\sum_i dE_i} dE_i \quad (1.20)
\]

LETi is also commonly called fluence-averaged LET which stems from earlier definitions in with this type of LET averaging [80]. In both Eq (1.19) and Eq (1.20), N is the total number of particles within the voxel, \( E_i \) is the energy deposited by the \( i \)th particle in the voxel and \( l_i \) is the path length of the \( i \)th particle.
Both parameters behave similarly along a proton beam; slowly increasing in the shallow depth before rapidly increasing at the Bragg peak and beyond (shown in Figure 1.6). By definition, LET\textsubscript{d} is equal to or greater than LET\textsubscript{t} as strongly ionising particles by their nature contribute more to the local dose than a sparsely ionising LET particle. While there is no clear evidence, it is widely accepted that LET\textsubscript{d}, rather than LET\textsubscript{t}, may better correlate to increased proton RBE [81]. It also appears LET\textsubscript{d} may have a greater sensitivity to calculation parameters and thus has a greater uncertainty than LET\textsubscript{t} [72,82,83].

**Figure 1.6:** Graph showing absorbed dose, LET\textsubscript{d} and LET\textsubscript{t} for a SOBP proton beam in water.

While LET is often averaged, it is not clear if this misses important aspects of the proton RBE-LET relationship. By averaging across the spectrum of particles to obtain a single value, both of the main averaging methods, LET\textsubscript{d} and LET\textsubscript{t}, assume a linear relationship with RBE. It is understood for other heavier ions, such as carbon, there is a substantial non-linear LET relationship with RBE, especially when considering the overkill region. For this reason, the RBE models applied in carbon therapy, Microdosimetric-Kinetic Model (MKM) [71,84] and Local Effects Model (LEM) [85], have a non-linear RBE-LET relationship. As explored further in Chapter 4 of this thesis, there is some evidence of a non-linear RBE-LET relationship in proton beams.

**1.4.2.2 Particle Inclusion:** Due to nuclear interactions, a proton beam contains other hadronic particles than solely primary protons as it travels through a patient. There is a small but potentially significant presence of secondary protons...
and heavier nuclei. The biological effect of these heavier nuclei, mostly carbon and alpha particles, is unclear but there is interest in studying their presence in clinical PBT treatments [67]. Currently, clinical TPSs typically include the absorbed dose resulting from secondary protons in their analytical models [86] but the dose contribution of other heavier particles is ignored. While the absorbed dose of these heavier ions is very low, the LET of these particles is much greater than primary or secondary protons and it is a matter of debate within the community whether these should be included [75,87].

There are multiple approaches in the literature for which particles to include in LET calculations. These approaches range from only including primary protons [72,88], to also secondary protons [89] and other heavier particles [21,67,87,90]. A recent study by Hahn [87] further demonstrated the variability in particle inclusions across clinical proton centres. The approaches applied by centres included primary protons only, particles with $Z = 1$, particles with $Z \leq 2$ and all particles. However, it is not clear how these are applied within the LET average.

**1.4.2.3 Scoring** Since the advent of MC simulation in radiotherapy, there has been a considerable debate on whether dose should be scored to water or to medium [91]. From the 1960’s, dose calculation algorithms have assumed the patient is simply composed of water at various densities. Considering that all major dosimetry protocols [92,93] are based on dose to water, it is clear how scoring to water is the clinical standard. However, as MC simulation increased in use in radiotherapy applications in the 1990s, it became clear there are significant differences between dose to medium and dose to water. These differences increase for materials with compositions substantially different to water such as bone. This debate still continues with unresolved questions on convention, accuracy and correlation with biological effect [94,95]. In comparison to photon radiotherapy, protons are more susceptible to the uncertainty between dose to water and dose to medium, with stoichiometric calibration necessary for PBT treatment planning [94,96].

These arguments, both for and against scoring to medium, extend to LET scoring. There is variation in the literature with LET scored to water, to medium and to unit tissue density. In the same manner as mass stopping power (Eq 1.1) LET to unit tissue density is LET scored to medium divided by the unit density of the material [67,97]. It is not certain how significant the LET scoring is to the final results, especially in PBT clinical treatment plans. It has been shown that the difference between LET to water and LET to medium may significantly affect RBE models based upon in vitro data [98].

**1.4.2.4 LET Restriction:** As described above in ‘1.2.3 Linear Energy Transfer’, the ICRU definition of LET applies an upper energy bound on electrons included in the calculated LET value. As LET is used as a descriptor of local track
structure, including high energy secondary electrons which deposit the majority of their energy away from the primary proton track could be misleading.

Generally, unrestricted LET is applied in PBT treatment planning. The energy of secondary electrons produced by clinical proton energies is low, approximately 55 eV in water across depth [99]. The use of voxels in the order of mm and the low energy of secondary electrons in clinical energy range of PBT reduce the relevance of LET restriction in proton treatment planning.

1.4.2.5 Calculation settings MC simulations are considered the gold standard for dose calculation in PBT and other forms of radiotherapy. These simulations require various initial parameters to be defined to obtain an accurate simulation. The parameters range from the physics list, where models of interactions are described, to step limits and production cuts, where the type of particles and their increment in the simulation are established. These parameters are sensitive to the application and work within PBT calculating for absorbed dose still continues to find optimal parameters for clinical plans [100].

Careful consideration of these parameters is also required when calculating LET. However, the calculation of LET is far less established than absorbed dose and optimum parameters are less clear. Further to the initial parameters, there are also various methods of calculating LET such as the pre- kinetic energy ratio or by the step-by-step ratio. There have been several studies [72,82,83] which have examined the effect of these methods and parameters on LET\textsubscript{u} and LET\textsubscript{i}. However, these studies are not exhaustive as there are many parameters and a near endless number of combinations of parameters.

1.4.2.6 Potential LET Alternatives: As discussed in ‘1.4.1.5 LET Alternatives’, a series of alternatives were proposed for LET shortly after being first defined in early microdosimetry. Several of these proposed parameters have also been applied in the same practical applications as LET.

Lineal Energy, $\gamma$, has been applied in particle treatment planning including proton therapy [101–103]. As with LET, the parameter is often further averaged in the form of dose-averaged lineal energy, $\gamma_D$, or frequency-averaged lineal energy, $\gamma_F$. This are analogues of dose-averaged LET and track averaged LET defined in Eq(1.19) and Eq(1.20), respectively. One proposed benefit of lineal energy is the ability to be physically measured and thus verified within a treatment plan [101].

Track ends have also been proposed as an alternative to LET in clinical applications [104]. This parameter is defined the number of primary proton tracks ending in a volume such as a voxel in a TPS plan. As the main increase of RBE occurs at the end of a proton track, it is hoped track ends will correlate well without the issues surrounding the LET stated above.
1.4.3 LET in Clinical Application

1.4.3.1 Clinical Metrics for LET: With a considerable in vitro evidence base, an increasing amount of in vivo data, and the relative ease of calculation, LET is consequently the most common parameter incorporated into treatment planning studies to optimise for a variable RBE. To do so, clinical metrics and methodologies for LET are used to judge the plan quality and to guide optimisation alongside absorbed dose. The metrics for dose are well established but the clinical metrics for LET remain up for debate. One proposed solution is to apply LET and dose in a proton RBE model to obtain an RBE-weighted dose. However, these suffer from large uncertainties within in vitro data [105] and lack a method for in vivo validation. Other proposed methods and techniques applied in the literature to incorporate LET into treatment planning mirror those already applied in the clinic for dose. These methods include:

Qualitative checks [106]: Visually inspecting the resulting LET distribution of a plan to ensure components of elevated LET do not fall within critical structures such as the brainstem.

Single Value LET/Dose criteria [45,104,107]: Maximum or mean values of LET may be calculated within isodose regions of clinically relevant dose. A limit may be placed on a level of maximum or mean LET in certain iso-dose regions. For instance, no voxels receiving LET values above 6 keV μm⁻¹ in the isodose region of 80% of the prescribed dose.

LET Volume Histograms [42,106,107]: Analogous to the common DVHs as previously described. These graphs demonstrated a cumulative histogram of LET values for a particular volume, however spatial information is lost.

RBE Models [77,108,109]: LET is applied in an RBE-weighted dose model with dose to obtain a predicted RBE-weighted dose. As discussed in section ‘1.3.4 RBE models’, these models vary in form, with many applying a form of the LQ model and including the tissue specific parameter, $\alpha/\beta$.

1.4.3.2 Indirect LET Optimisation: Before inverse optimisation reached radiotherapy, a planner would guide the dose optimisation process by iterative dose calculation and applying knowledge of both how tissue responds to dose and how dose deposited by radiation is affected by field size, tissue inhomogeneity and so forth. The first attempts to optimise LET also followed this process of indirect optimisation where LET is optimised without the use of an optimisation algorithm. To do so, the planner needs knowledge of where elevated LET regions can occur and which situations where LET may have particular importance.

As shown in Figure 1.5, it is understood that LET increases at the distal edge of the beam. With in vitro evidence, it is believed this increase leads to an effective range uncertainty when changing from a constant RBE value to a variable RBE-weighted dose. One study demonstrated a potential 2 – 3 mm range extension in a
clinical proton beam due to this effect [10,32]. However, this is not the only consideration as LET increases at the lateral edge of a beam due to the greater presence of low energy protons. Also, in active scanning planning, MFO plans may produce more unexpected LET distributions due to complex weighting of spots.

Some studies have highlighted certain plan parameters which can be altered to indirectly optimise LET. For instance, careful consideration of beam angles has been shown to significantly reduce regions of high LET in healthy tissue with wide angle beams often achieving the most favourable LET distribution [106,110]. This occurs as the high LET part of one field is at least partially cancelled out by the low LET part of the opposing field. However, in case of spot sizes there is disagreement in the literature whether these significantly affect LET distributions [106,111]. Others have designed planning strategies which act to feather the distal edge and help keep the elevated LET regions within the PTV and out of healthy tissue [110,112]. However, these strategies require relatively complex segmentation of the target reducing their practicality in a clinical environment.

1.4.3.3 Direct LET Optimisation: Direct optimisation of LET is a process where LET is inputted into an optimiser algorithm. Approaches to incorporating LET into PBT with an optimisation algorithm have been varied and range from using multicriteria optimisation, two-part optimisation to full optimisation [97,111,113]. The central issue with all approaches is that without a validated proton RBE model, it is difficult to appropriately cost a degradation in either LET or absorbed dose over the other. Ideally a similar dose distribution to a dose-only optimised distribution would be achieved but with an improved LET distribution. Fortunately, due to the substantial degeneracy present in proton treatment planning, this appears achievable. In the two-part optimisation, this outcome was forced with the first round of optimisation locking in a clinical acceptable dose distribution before optimising the LET distribution within this [111]. Work on full optimisation found similar results [113].

Further work has applied LET optimisation in proton arc treatment planning [114]. This work highlighted a key advantage of proton arc therapy, namely the ability to position an elevated LET region into the centre of a target while delivering a clinically acceptable dose distribution to the PTV and surrounding healthy tissue.

1.5 Summary and Aims

The increased numbers of cancer patients receiving proton therapy is a trend not just restricted to the United Kingdom. With the advent of IMPT, the potential dosimetric advantages of protons are clear and there has been a growth of proton centre construction across the globe. These centres ubiquitously apply an RBE value of 1.1 to clinical PBT plans as a simple method to unlock the wealth of clinical knowledge from a century of photon radiotherapy treatments. However, substantial in vitro evidence suggests a proton RBE which varies considerably with dependence
on a multitude of parameters such as LET, \( \alpha/\beta \) and dose per fraction among others. While there is currently no evidence of a detrimental clinical effect through applying a constant RBE rather than variable value, there is a sustained and growing interest in accounting for variable RBE within the clinic.

LET has emerged as one of the main parameters of study in RBE. This is in part due to the relative ease of its calculation and the large amount of \textit{in vitro} data demonstrating an RBE-LET relationship. In recent years, \textit{in vivo} data from image-based studies using patient data has emerged. However, there are roadblocks in the path to routine application of LET and wider RBE models in the clinic. There is little consensus on the ‘type’ of LET with differences in the literature for fundamental parts of its definition. There is also significant variation in how LET is applied from standard clinical metrics such as LVH to full proton RBE models.

The overall aim of this thesis is to aid the introduction of LET into standard PBT treatment planning practice. This aim includes studying how different approaches to RBE models may vary in their predicted biologically weighted dose, how the different definitions of LET may affect outcome of variable RBE models and other proposed clinical metrics and to build a consensus for a particular type of LET.

Chapter 2 compares a mechanistic RBE model developed by the PRECISE group against other common phenomenological RBE models for a common PBT patient type. Chapter 3 investigates the differences between common LET definitions and the effect of this on proposed clinical metrics such as LVHs, maximum/mean values as well as the effect of being applied in a simple fitted LET-weighted RBE model. Chapter 4 studies the LET spectra found in typical experimental radiobiological experiments used to obtain RBE data applied in proton RBE models to the LET spectra found in clinical PBT plans. Chapter 5 highlights major contributions to other co-authored papers and conference proceedings on work related to the aim of this thesis.
2. In Silico Models of DNA Damage and Repair in Proton Treatment Planning: A Proof of Concept

The work in this chapter was published by the Nature Scientific Reports journal in December 2019 as the first manuscript to be published from the thesis. Our group had previously published a series of papers detailing our Manchester Mechanistic (MM) model of biological effect. The aim of this work was to show the ‘proof of concept’ of applying our mechanistic model on a clinical plan as well as comparing it against common phenomenological proton RBE models.

The MM model was used to produce several RBE correlations using absorbed dose and LET for endpoints of misrepaired DSBs, residual DSBs and combined yields of DSBs. These were compared to the McNamara model and LET-weighted model. Generally, the three models predicted similar RBE-weighted dose with some differences in magnitude and relative distribution. As the combined yield of misrepaired and residual DSBs is not fully equated to cell death these differences were expected. However, it demonstrates the promise of the mechanistic method in comparison to phenomenological RBE models.

The results highlighted one major benefit of the MM model; the potential for multiple endpoints. As a known factor in RBE, it is usually not incorporated by phenomenological models which almost exclusively predict in vitro cell death. Further endpoints may be fitted to different parts of the MM model to establish another predicted endpoint. This is a key aim as the MM model moves further from the DSBs to immunological responses and so forth.

This work highlighted the number of LET definitions in use as MM model used LET\textsubscript{t} rather than the LET\textsubscript{d} seen in the two phenomenological models in this work. It was also observed some authors in the literature were applying different forms of LET\textsubscript{d} in those phenomenological models. This ultimately led to the two papers in this manuscript for studying the effect of this variation in definition and whether an averaged LET is sufficient.

Author Contributions

With NH, JWW and SI, I developed the Manchester Mechanistic model to give RBE values for the misrepair, residual and combined misrepair and residual. I examined the model assumptions in accordance to applying at the patient level. I selected the patient and created the simulation pipeline required to calculate RBE maps on Christie plans using AUTOMC along with developing the data visualisation tools. I wrote the manuscript with review from all co-authors.
In Silico Models of DNA Damage and Repair in Proton Treatment Planning: A Proof of Concept

Edward A. K. Smith 1,2, N. T. Henthorn 1,3, J. W. Warmenhoven 1,3, S. P. Ingram 1,2, A. H. Aitkenhead 1,2, J. C. Richardson 2, P. Sitch 2, A. L. Chadwick 1,3, T. S. A. Underwood 1,3, M. J. Merchant 1,3, N. G. Burnet 1,3, N. F. Kirkby 1,3, K. J. Kirkby 1,3 & R. I. Mackay 1,2

1 Division of Cancer Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, United Kingdom

2 Christie Medical Physics and Engineering, The Christie NHS Foundation Trust, Manchester, United Kingdom

3 The Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom

There is strong in vitro cell survival evidence that the relative biological effectiveness (RBE) of protons is variable, with dependence on factors such as linear energy transfer (LET) and dose. This is coupled with the growing in vivo evidence, from post-treatment image change analysis, of a variable RBE. Despite this, a constant RBE of 1.1 is still applied as a standard in proton therapy. However, there is a building clinical interest in incorporating a variable RBE. Recently, correlations summarising Monte Carlo-based mechanistic models of DNA damage and repair with absorbed dose and LET have been published as the Manchester mechanistic (MM) model. These correlations offer an alternative path to variable RBE compared to the more standard phenomenological models. In this proof of concept work, these correlations have been extended to acquire RBE-weighted dose distributions and calculated, along with other RBE models, on a treatment plan. The phenomenological and mechanistic models for RBE have been shown to produce comparable results with some differences in magnitude and relative distribution. The mechanistic model found a large RBE for misrepair, which phenomenological models are unable to do. The potential of the MM model to predict multiple endpoints presents a clear advantage over phenomenological models.
2.1 Introduction

The primary advantage of proton beam therapy (PBT) over photon therapy is found in the apparent superior dose distribution delivered to the patient where the same target dose is delivered with a dose reduction to the surrounding healthy tissue [115]. Currently, total patient numbers treated by PBT are relatively small compared to the total for photon treatments and, consequently, the wealth of clinical knowledge of the biological effect of radiation is for photon absorbed dose. The translation of this knowledge to protons would be simple if the absorbed dose of photons and protons had equal biological effect. However, there is a known difference in the biological effect of the two radiation qualities [14], and thus this translation is not trivial. To translate photon dose into proton dose, the concept of Relative Biological Effect (RBE) is commonly used:

\[
RBE = \frac{D_\text{photon}}{D_\text{proton}}
\]

(2.1)

where \(D_\text{proton}\) is the proton dose required to obtain the same endpoint, \(x\), as the reference photon dose, \(D_\text{photon}\). There is no formally defined reference radiation quality, although experiments typically use a photon energy spectrum of a nominal 250 kV or Cobalt-60 source.

\textit{In vitro} experiments reported in the literature demonstrate a dependence of RBE on many factors such as dose, linear energy transfer (LET), oxygenation, tissue type and biological endpoint [14]. However, the variability in the ensemble of \textit{in vitro} data is too great to obtain a robust value of RBE across all of these factors. Instead, a constant RBE of 1.1 is applied to the absorbed dose in proton therapy treatment plans [116]. At present, there is no evidence demonstrating an adverse symptomatic effect. The use of this constant value of RBE means for the same dose, protons are assumed to be 10\% more effective than photons across all parameters.

In recent years, further \textit{in vitro} data has been published making the variation in RBE harder to ignore [73]. Nonetheless, the issues with the translation between \textit{in vitro} and \textit{in vivo} must be thought of when considering this data. Clinically, there is little evidence to suggest that the application of a constant RBE of 1.1 has a detrimental effect on patient outcome. However, studies outlining image changes in healthy tissue [44,78] are beginning to challenge this argument along with evidence that the use of a constant RBE could produce sub-optimal treatment plans causing degradation in clinical effect [117]. There is a growing awareness within the community that variable RBE should be considered in the treatment planning process. However, the optimal method of doing so is not clear and stringent evidence that safety of treatments will not be compromised is required.
Given these uncertainties, the incorporation of LET has been proposed as an intermediate step [118] to the full implementation of variable RBE into clinical plans. LET is a commonly used parameter to describe a particle’s track structure and is defined as the amount of energy deposited per unit length along a charged particle’s path [119]. There is strong in vitro evidence linking LET to biological effect and, as a physical parameter, LET can be calculated to a high degree of accuracy compared to biological parameters [14]. Furthermore, the clinical evidence [44,78] of variable RBE suggests a link between the increased biological effect (i.e. image change) at the end of proton range with regions of elevated LET.

Approaches to incorporate LET into clinical plans have been varied. Some authors have explored the use of combinations of dose and LET, such as L*D [120] or D(1 + κL) [111,120] where L is dose-averaged LET (LET_d), D is absorbed dose and κ is a fitting parameter. However, uptake in the clinic has been slow due to a lack of consensus and concerns of the uncertainties in the appropriate way to combine LET and dose and how to determine appropriate fitting parameters. There is also a paucity of evidence demonstrating symptomatic toxicity through the lack of use of such models in treatment planning. Also, L*D has been shown to have a poor fit with data [120].

Others have modelled RBE using phenomenological methods [56–58,121], despite the restrictive uncertainty in the experimental data [14]. Generally, these models use parameters of dose, LET and the tissue-specific parameter, α/β. Again, their uptake in the clinic has been limited due to uncertainty in the fitting data and thus how reliable the models are in predicting clinical effect. The experimental data used to fit these models is sometimes from non-human cell lines, and the phenomenological nature of the models makes it difficult to apply them to other endpoints or situations.

An alternative to these approaches is mechanistic modelling. There are several models of this type in the literature with varying complexity in how radiation damage and repair of DNA double-strand breaks (DSBs) are modelled [71,122,123]. Recently, a suite of mechanistic models to examine the DNA damage resulting from different radiation qualities has been developed [60,124]. These models have been used to investigate some of the factors surrounding RBE by simulating the effect of different radiation qualities on combined DNA and cell geometries in the Monte Carlo (MC) toolkit Geant4-DNA [125,126]. The structure and pattern of energy deposition on the DNA from these simulations is recorded and passed to the DNA Mechanistic Repair Simulator (DaMaRiS). Here, predictions are made on the efficacy and fidelity of repair at various time points up to 24 hours after radiation.

Previously published work using this model [60,124] has demonstrated an increase in complex damage and DSBs in proximity to one another, with increasing LET. These breaks in close proximity were then predicted by the model to lead to an
increased probability of incorrect DNA repair [124]. A series of simple correlations were established with inputs of absorbed dose and LET and outputs of endpoints of predicted yields of residual and misrepaired DSBs. These correlations allow for the accurate reproduction of the detailed model results. In this paper, the model compromising of both the damage and repair processes will be referred to as the Manchester Mechanistic (MM) model.

The work in this paper applies these previous findings into clinical treatment planning as a ‘proof of concept’ to demonstrate the potential of such an approach. GATE [127], a framework for the MC toolkit Geant4 [128], has been used to calculate the absorbed dose and LET in each voxel of a proton therapy plan. Using the previously published correlations, we present maps showing predicted yields of residual and misrepaired DSBs in cells at each voxel. In principle, these maps may provide the clinician with additional valuable information on expected biological outcomes, allowing for identification of regions of heightened biological effect for differing endpoints.

2.2 Method

2.2.1 Workflow for the variable RBE calculation in a treatment plan.

This study is a retrospective analysis of a patient treatment plan. The patient gave informed consent for their data to be used for this purpose, and all data was handled according to GDPR regulations. The research was approved by the Radiotherapy Related Research committee at The Christie.

The patient presented in the case study is a 24-year-old female ependymoma patient treated with passively scattered proton beam therapy (PSPBT). An ependymoma case was selected as these patients are considered particularly at risk of severe toxicity, such as brainstem necrosis, if RBE values are above 1.1 [38]. For the purpose of this study, a spot-scanning treatment plan was created at The Christie according to the protocol for this tumour site. A three-field beam arrangement (two lateral and one superior) Single Field Uniform Dose (SFUD) treatment plan with 1.8 Gy per fraction was created using a Varian ProBeam beam model in Eclipse™ (v13.7, Varian, Palo Alto, USA) treatment planning system (TPS). The target and organs at risk (OARs) volumes were given clinician approval. The plan was assessed separately for robustness under a range uncertainty of 3.5% and under 3 mm shifts of the patient in the x, y, and z coordinates.

AUTOMC (v20180613) is an in-house MC dose calculator built in Octave (v4.2.2). The basic process of the software is to translate the DICOM RT files of an Eclipse-made proton therapy plan into .mac text files. The software then drives the GATE (v8.1) [127] / Geant4 (v10.3.3) [128] environment and a computational cluster system to obtain a MC dose calculation before performing gamma analysis between the MC and TPS dose. The combination of the GATE and GEANT4 versions is
known as GATE-RTion v1.0 which is constructed and dedicated for clinical use in
light ion beam therapy. Its main role is to form part of the dosimetric verification of
proton therapy plans at The Christie. For this work, AUTOMC was used to calculate
absorbed dose and LET distributions for the patient plan.

GATE [127] is a framework designed to aid medical physics simulations in
the MC toolkit Geant4 [128]. For this work, absorbed dose to water, \( \text{LET}_t \) to water
and \( \text{LET}_d \) to water was calculated in 2 mm voxels using the QGSP_BIC physics list.
Cuts of 0.1 mm were used for gamma, electron and positron radiation while cuts of
1 mm were applied for protons. The QGSP_BIC physics list has been previously
shown to match other well-established physics lists used for proton therapy
applications [129]. A beam model representative of a Varian ProBeam delivery
system was used. The in-built LET scorer calculated \( \text{LET}_t \) and \( \text{LET}_d \) using the
Geant4 method ‘GetElectronicStoppingPowerDEDX’. This method is insensitive to
different initial MC parameters, which is particularly important for \( \text{LET}_d \) [82,83]. The
number of histories was scaled to achieve an approximate uncertainty of 1% Gy\( \text{RBE} = 1.1 \)
within the high dose region.

The MC-simulated absorbed dose and LET were then used as inputs to
different biological models calculated within the MATLAB\textsuperscript{TM} (R2017A Mathworks
Inc., USA) environment. The models were also evaluated and visualised within this
environment.

2.2.2 \( \text{LET}_d \) and \( \text{LET}_t \)

The following definitions of averaged LET were used in the variable RBE
models in this paper:

2.2.2.1 \( \text{LET}_d \): The LET from each particle is weighted with respect to its
contribution to local dose in each voxel, obtaining Eq. 2.2:

\[
\text{LET}_d = \frac{\sum_{i} \Delta E_i \Delta l_i}{\sum_{i} \Delta E_i \Delta l_i} \quad (2.2)
\]

where \( N \) is the total number of particles within the voxel, \( \Delta E_i \) is the energy
deposited by the \( i \)th particle in the voxel (keV) and \( \Delta l_i \) is the path length of the \( i \)th
particle (\( \mu \)m).

2.2.2.2 \( \text{LET}_t \): The LET from each particle is weighted with respect to its step
length in each voxel, obtaining Eq. 2.3:

\[
\text{LET}_t = \frac{\sum_{i} \Delta l_i \Delta E_i}{\sum_{i} \Delta l_i \Delta E_i} \quad (2.3)
\]
where $N$ is the total number of particles within the voxel, $\Delta E_i$ is the energy deposited by the $i$th particle in the voxel (keV) and $\Delta l_i$ is the path length of the $i$th particle ($\mu$m). Track-averaged LET is also known as the fluence-averaged LET.

### 2.2.2.3 Biological models

The following models were used to calculate RBE-weighted dose using the MC-calculated absorbed dose and LET:

**LET$_d$ - weighted Dose Model:** Several authors have applied this weighted dose model [120,130]. Its form is derived from the linear quadratic (LQ) model by assuming the concept of biologically effective dose will result in Eq. 2.4:

$$ \text{Dose}_w = D \cdot (1 + \kappa \cdot \text{LET}_d) \quad (2.4) $$

where $\text{Dose}_w$ is the LET$_d$-weighted dose, $D$ is the proton absorbed dose, LET$_d$ is the dose-averaged LET and $\kappa$ is a fitting parameter. A $\kappa$ value of 0.055 $\mu$m keV$^{-1}$ (shown in Table 2.1) was obtained by minimising the biological uncertainties of *in vitro* experimental data [120].

**McNamara Model** [57]. This phenomenological model of RBE for PBT is based on the linear quadratic (LQ) model. The model was derived via a nonlinear regression fit to *in vitro* experimental data. The RBE-weighted dose is obtained via Eq. 2.5:

$$ \text{Dose}_\text{Mc} = D \left( \frac{1}{2D} \left( \frac{\alpha}{\beta} \right)_x^2 + 4D \left( \frac{\alpha}{\beta} \right)_x \left( Z_1 \frac{Z_2}{Z_3} \text{LET}_d \right) + 4D^2 \left( Z_3 - Z_4 \sqrt{\left( \frac{\alpha}{\beta} \right)_x^2 - \left( \frac{\alpha}{\beta} \right)_x} \right) \right) $$

(2.5)

where $D$ is the proton absorbed dose (Gy), $(\alpha/\beta)_x$ is the tissue-specific parameter of tissue $x$ (Gy), LET$_d$ is the dose-averaged LET (keV $\mu$m$^{-1}$) and $Z_1$–$Z_4$ are the parameters derived by fitting to cell survival data [57] (shown in Table 2.1).

**Manchester mechanistic model.** The MM model [60,124] explicitly considers the radiation damage to DNA and one of the primary repair pathways of DSBs, namely Non-Homologous End Joining (NHEJ). In both the damage and repair parts of this model, the various mechanistic components of the process have been fitted to biological data found in the literature. This process has been simulated in the Monte Carlo (MC) toolkit Geant4-DNA [125,126].

The model starts with irradiating a spherical cell with a range of doses and LET (if a charged particle) of specified radiation type. The resulting energy depositions made by the radiation, directly and indirectly, are then re-simulated onto DNA strands and the probability distribution of break type is created with
dependence on both dose and LET. The resulting pattern and geometry of DSBs is then passed to the repair portion of the model, named DaMaRiS.

DaMaRiS simulates the two broken ends of DSBs as they undergo sub-diffusion in the cell nucleus. During sub-diffusion, the attachment sequence of repair proteins necessary for DSB repair, via NHEJ, is given a chance to occur. After 24 hours, this process either results in a misrepaired, residual or fully repaired DSB. Residual refers to DNA damage which has not been repaired after the 24-hour period and misrepair refers to DSBs which has been incorrectly repaired. All cells are assumed to be in the G1 phase where NHEJ is dominant [131].

The MM model is simulated at a cellular level and therefore is not suited for geometries at the scales relevant to clinic application. Instead, simple correlations have been fitted to the results from the MM model so residual and misrepaired DSB yields can calculated on a patient geometry. These correlations take inputs of absorbed dose and LET, and have been shown to be in good agreement to the full MM model in previously published work [124]. It should be noted the a-h parameters in these models do not have a physical meaning.

These correlations have been applied with Eq. 2.1 to obtain RBE-weighted dose for endpoints of residual yield (Dose_r), misrepair yield (Dose_m) and combined yield (Dose_ram). This is shown below in Eqs. 2.6, 2.7 and 2.8 where the yields for protons and photons for the specified endpoint are the numerator and denominator, respectively.

\[
Dose_r = D \cdot \frac{(d \cdot \text{LET}_t + e) \cdot c}{\gamma_r} = D \cdot \text{RBE}_r \quad (2.6)
\]

\[
Dose_m = \frac{D(d \cdot \text{LET}_t + e) \cdot (a \cdot (f \cdot \text{LET}_t^2 + g \cdot \text{LET}_t + h) + b) \cdot (1 - c)}{\gamma_m}
= D \cdot \text{RBE}_m \quad (2.7)
\]

\[
Dose_{ram} = \frac{D(d \cdot \text{LET}_t + e) \cdot c + (d \cdot \text{LET}_t + e) \cdot (a \cdot (f \cdot \text{LET}_t^2 + g \cdot \text{LET}_t + h) + b) \cdot (1 - c)}{\gamma_r + \gamma_m}
= D \cdot \text{RBE}_m \quad (2.8)
\]

where D is absorbed dose (Gy), LET_t is track-averaged LET (keV μm⁻¹) and a, b, c, d, e, f, g, and h are parameters derived to fit the DaMaRiS model to experimental data for endpoints of residual and misrepaired DSB yields. Parameters \(\gamma_r\) and \(\gamma_m\) are the average yields of residual and misrepair DSBs respectively, per Gy of Cobalt-60 photon irradiation. Values for a, b, c, d, e, f, g, h, \(\gamma_r\) and \(\gamma_m\) are shown in Table 2.1.

Equation 2.8 combines the end points of both residual and misrepaired DSB yields. By doing so, an assumption is made that these yields equally contribute to
biological effect. It may also be assumed that all residuals and misrepaired DSBs present after 24 hours will result in cell kill.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value ± %</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Z_1$</td>
<td>0.99064 ± 1.4</td>
<td>-</td>
</tr>
<tr>
<td>$Z_2$</td>
<td>0.35605 ± 4.2</td>
<td>$\text{Gy \ \mu m \ keV}^{-1}$</td>
</tr>
<tr>
<td>$Z_3$</td>
<td>1.1012 ± 0.5</td>
<td>-</td>
</tr>
<tr>
<td>$Z_4$</td>
<td>0.00367 ± 23.6</td>
<td>$\text{Gy}^{-1/2}$</td>
</tr>
<tr>
<td>$\kappa$</td>
<td>0.055 ± -</td>
<td>$\mu m \ \text{keV}^{-1}$</td>
</tr>
<tr>
<td>$a$</td>
<td>0.1966 ± 0.4</td>
<td>-</td>
</tr>
<tr>
<td>$b$</td>
<td>0.008 ± 3.4</td>
<td>-</td>
</tr>
<tr>
<td>$c$</td>
<td>0.0736 ± 0.2</td>
<td>-</td>
</tr>
<tr>
<td>$d$</td>
<td>1.149 ± 1.0</td>
<td>$\mu m \ \text{keV}^{-1} \ \text{Gy}^{-1}$</td>
</tr>
<tr>
<td>$e$</td>
<td>24.1 ± 0.6</td>
<td>$\text{Gy}^{-1}$</td>
</tr>
<tr>
<td>$f$</td>
<td>4.879E-4 ± 0.8</td>
<td>$\mu m^2 \ \text{keV}^{-2}$</td>
</tr>
<tr>
<td>$g$</td>
<td>2.84E-3 ± 4.7</td>
<td>$\mu m \ \text{keV}^{-1}$</td>
</tr>
<tr>
<td>$h$</td>
<td>5.13E-2 ± 1.6</td>
<td>-</td>
</tr>
<tr>
<td>$\gamma_r$</td>
<td>1.726 ± 2.0</td>
<td>$\text{Gy}^{-1}$</td>
</tr>
<tr>
<td>$\gamma_m$</td>
<td>0.0427 ± 16.7</td>
<td>$\text{Gy}^{-1}$</td>
</tr>
</tbody>
</table>

Table 2.1: Shows the parameter values and standard error, as a percentage, (if available) for Eqs. 2.4, 2.5, 2.6, 2.7 and 2.8. $Z_1$, $Z_2$, $Z_3$ and $Z_4$ are taken from the McNamara [57], $\kappa$ is taken from McMahon [120] and $a$, $b$, $c$, $d$, $e$, $f$, $g$ and $h$ are taken from Henthorn [124].
2.3 Results

Figure 2.1: Calculation maps for the three field SFUD ependymoma case. (A) Absorbed dose (Gy). (B) Track-averaged LET (keV/μm). (C) Ratio of predicted average residual DSBs per cell against predicted average misrepaired DSBs per cell using previously published correlations [124]. (D–F) Relative Biological Effectiveness (RBE) maps of yields of residual DSBs, misrepaired DSBs and combined misrepair and residual DSBs. (D) Map of RBEr (Eq. 2.6). (E) Map of RBEm (Eq. 2.7). (F) Map of RBEr&m (Eq. 2.8). Critical organs contours (white) and the CTV contours (black) are shown.

Figure 2.1 presents a range of distributions calculated for the SFUD plan of the ependymoma case with a central sagittal CT slice shown. Figure 2.1A shows the absorbed dose to water and Fig 2.1B shows the LET to water. LET is elevated in the posterior wall of the nasopharynx and, to a lesser extent, the anterior brainstem.
This elevation is expected in these regions as they coincide with the overlap of the distal or lateral edges of the three fields. It is known these parts of the fields have higher LET values [107].

Figure 2.1C shows the ratio of predicted residual DSBs yield and misrepaired DSBs yield calculated by the MM model. This demonstrates the yield of residual DSBs is always greater than the yield of misrepair DSBs. However, this ratio decreases at the distal edge of the beams corresponding to a relative increase in misrepair. This decrease is expected as misrepair has a greater dependence on LET and therefore more closely follows the range increase of LET in comparison to the residual yield.

Figure 2.1D–F shows the spatial distributions of RBE for residual DSBs (RBE_r), misrepaired DSBs (RBE_m) and combined misrepair and residual DSBs (RBE_r&m) for the three field SFUD plan of the ependymoma case. These maps follow Eq. 2.1 and compare the specified endpoint (residual, misrepair and residual + misrepair) between protons and photons for a given dose using Eqs. 2.6, 2.7 and 2.8. The relative distributions of the different RBE end- points are broadly similar with the main differences being the magnitude of RBE values and a slightly greater distal expansion for the misrepair RBE.

RBE_r ranges from 1.1–1.3 across the planned target volume (PTV) and critical structures. Small regions out- side of these structures fall slightly below 1.1 to a minimum of 1.03. RBE_m is considerably larger with values ranging between 10 and 16 in the ROIs. These very high RBE values are due to the relatively low yield of misrepaired DSBs in photon radiation. This suggests that this is a mode of damage which occurs more frequently under proton irradiation than in photons. The endpoint of RBE_r&m is the sum of both misrepair and residual yields. As the yield of misrepair is low in comparison to the yield of residual, RBE_r&m is considerably closer to RBE_r than RBE_m in magnitude.

It should be noted that, as with other RBE models, all endpoints from the MM model are predicting a distal range extension (1–3 mm) of biological effect beyond the absorbed dose distribution. The magnitude of the shift is ordered (smallest - largest): RBE_r, RBE_r&m and RBE_m.

Figures 2.2A–C show the dose volume histograms (DVHs) for the RBE-weighted dose of various RBE models for the PTV, brainstem and spinal cord. These are: constant RBE of 1.1 (RBEConstant), RBE_{D(1+\kappa L)}, RBE_{McNamara}, RBE_r and RBE_{r&m}. RBE_m is not shown on the DVHs as the values are much higher than the other models. The effect of RBE_m can be seen in RBE_{r&m}. An \(\alpha/\beta\) of 2 Gy has been assumed for the brainstem and spinal cord in the McNamara model.

In Figure 2.2D–F, the RBE models broadly follow the same shape although there is a substantial difference in magnitude. For the endpoints predicted by the MM model, the patterns are broadly similar across the three ROIs. RBE_r follows
RBE_{\text{Constant}} closely in the PTV, brainstem and spinal cord while RBE_{\text{r&m}} is consistently larger than the RBE_{\text{Constant}}, leading to predicted higher dose per fraction and total dose.

RBE_{\text{r&m}} is in close agreement with the McNamara model for the PTV where both follow RBE_{\text{Constant}}. However, for the different $\alpha/\beta$ tissue, in this case assuming 2 Gy for brainstem and spinal cord, the difference is substantial with the McNamara larger at all dose-volume points. A change of $\alpha/\beta$ will lead to differences between the MM and McNamara models as only McNamara takes this parameter as an input; the MM model is developed for a generic cell. RBE_{\text{r&m}} is either smaller than or equal to the RBE_{D(1+\kappa L)} for all ROIs.

RBE_{\text{r&m}} is consistently larger than RBE_{\text{D(1+\kappa L)}} in all ROIs. However, its relationship with RBE_{\text{Mc}} has greater complexity. For the PTV, it is much larger than all other models including RBE_{\text{Mc}}, which in this case gives the lowest biological dose. However, this changes for the brainstem and spinal cord where $\alpha/\beta = 2$ Gy. For these ROIs, RBE_{\text{Mc}} is higher at lower doses before becoming lower than RBE_{\text{r&m}} at the higher doses. This is especially significant for serial organs such as the brainstem and the spinal cord, as the primary clinical concern is the maximum dose. RBE_{\text{r&m}} is consistently greater than the D(1 + $\kappa$L) with the difference between them increasing at higher doses.

Figure 2.2A–C displays the line plots and their position within the patient anatomy. These plots show similar relationships to the DVHs with additional spatial information. The MM model estimates a greater RBE-weighted dose across the clinical target volume (CTV), central nervous system (CNS) and partially the body. The McNamara model predicts a higher dose in the low dose region surrounding the target. This is due to the combination of both high LET, as the region overlaps with the lateral edges and distal falloff of the beams, and the low $\alpha/\beta$ of the body.

It should be noted that the McNamara and LET-weighted dose models use LET_{d} as the averaging method for LET while the MM model uses LET_{t}. It is often stated in the literature that LET_{d} has greater biological relevance than LET_{t} although rigorous investigation has not been carried out [132]. Unlike the majority of RBE models, our residual and misrepair correlations use LET_{t} as they derive from DNA level simulations. At this length scale, the non-homogeneous nature of the dose distribution makes LET_{d} very noisy and therefore unsuitable [133].
**Figure 2.2:** (A–C) Dose-volume histograms (DVHs) for the planned target volume (PTV) and organs at risk (OARs) for the SFUD ependymoma patient showing RBE-weighted dose using a constant RBE (dashed black), $D(1 + \kappa L)$ (dot-dash red), the McNamara model (solid yellow), an endpoint of residual DSB yield (solid green) and an endpoint of combined misrepaired and residual DSB yield (solid blue). $\kappa = 0.055 \, \mu m \, keV^{-1}$, $\alpha/\beta = 2 \, Gy$ for spinal cord and brainstem and $\alpha/\beta = 10 \, Gy$ for PTV. (A) PTV DVH. (B) Brainstem DVH. (C) Spinal Cord DVH. (D–F) Line plots of RBE-weighted dose against voxel number with spatial position in patient anatomy. The same legend is followed for line plots as for DVHs. (D) Line plot A. (E) Line plot B. (F) Line plot positions of (A, B) are shown on the patient with CNS (white) and CTV (black contours and RBE-weighted dose $Dose_{r&m}$).
2.4 Discussion

In this work, we calculate predicted yields of residual and misrepaired DSBs using the correlations established in previous work by our group [124]. These correlations have been extended to RBE with endpoints of residual and misrepair DSBs. The RBE-weighted dose for these endpoints was subsequently calculated on a representative PBT clinical plan anatomy for the first time and compared to the McNamara model and LET-weighted dose model.

In its present form, the use of the MM model instead of the other models in this paper may have a clinical effect on treatment planning. In the vast majority of voxels, the predicted RBE-weighted dose (for Dose_{r&m}) is greater than both the McNamara and LET-weighted dose model. In the presented case and cases with similar geometry (critical structure distal to target), this may result in a treatment planner expending more effort in reducing the dose to the brainstem and the PTV-brainstem overlap area in the optimisation process to remain within standard dose protocols. Also, methods used to reduce LET in critical structures, such as avoiding distal fall off into such structures via the alteration of beam angles and beam number [134], may be applied more strongly. As this constrains the optimisation problem further, it may lead to a degraded absorbed dose distribution.

As previously stated, the MM model finds very high RBE values for misrepair, an endpoint of DNA damage. This means the MM model is predicting that misrepaired DSBs are occurring at a much greater frequency in proton therapy than photon treatments. This difference highlights an issue with phenomenological models, since applying an RBE value resulting from fitting to in vitro cell survival data would not be able to distinguish between the different modes of damage which, in some combination, result in cell death or other clinically relevant endpoints such as tissue toxicity.

Furthermore, it is known that RBE varies with endpoint [14]. Thus, any potential method to obtain a variable RBE model must be able to predict multiple endpoints for a full account of variable RBE. Existing phenomenological models are intrinsically unable to do so and can only predict a single RBE value. In contrast, mechanistic models, such as the MM model [124], can provide any number of outputs, by predicting different types of damage and incorporating multiple number of different repair pathways.

While these results show the potential of mechanistic models, there are several steps to be completed before the ultimate aim of clinical application can be realised. It is not currently understood in the literature how and in what proportion residual and misrepaired DSBs lead to the endpoints of cell death or overall tissue toxicity. By comparing Dose_{r&m} to Dose_{M} and Dose_{w}, it is implied combined residual and misrepair yield is equivalent to in vitro cell kill. However, it is reasonable to assume the two damage modes have different probabilities of resulting in this
endpoint as well as others. Consideration of the resultant chromosome aberrations from both damage modes is required to close the gap and estimate cell death.

The inclusion of chromosome aberrations may also be important in discerning whether the prediction of misrepair can be correlated with carcinogenesis. Several different types of chromosome aberrations, such as dicentric chromosomes, make up the misrepaired DSB yield and have differing survivable probabilities. The risk of carcinogenesis is an important concern in proton therapy, especially when the case mix includes a high proportion of paediatric patients. Therefore, this is a key motivation for the development and clinical implementation of mechanistic models.

In the literature, the RBE models can be broadly separated into two groups, those which keep to the physical parameters of absorbed dose and LET (e.g. LET-weighted dose) and those which add more consideration of biology through \(\alpha/\beta\) ratios (e.g. McNamara model). The MM model sits between these two with its consideration of initial DSBs and the consequence of DNA repair for a generalised cell. While there is good evidence for RBE dependence on \(\alpha/\beta\), the significant uncertainties in the \(\alpha/\beta\) values themselves restrict their use in the clinic. Instead, it would be better to describe the parameters of the different pathways leading to cell death. Only mechanistic models can achieve this and this is one of the future aims of the DaMaRiS model.

In addition, the DaMaRiS repair model is currently restricted to modelling NHEJ, which is considered the dominant DNA repair pathway in human cells [135]. However, another DSB repair pathway, homologous recombination (HR), has a significant impact on repair within human cells in some phases of the cell cycle and is required for a complete understanding of DSB repair. The introduction of HR into the model will lead to, and allow incorporation of, the cell cycle and tissue-specific parameters into the model. This work is currently underway.

Both the incorporation of HR and linking residual and misrepaired DSBs to endpoints with greater clinical relevance are longer-term goals. In the short term, validation of some underlying assumptions in the model is required to improve confidence in its accuracy. Currently, the simulation consists of an irradiated spherical water volume with the resulting energy depositions are then transferred onto the DNA structure with consideration of DNA’s greater density (1.406 g cm\(^{-3}\)). This assumes the difference between proton ionisation cross sections of water and the molecules constituting DNA (guanine, adenine, thymine and cytosine) do not significantly differ. While this is a common assumption made in Geant4 DNA simulations of DNA damage and treatment planning in general, there is evidence demonstrating substantial differences [136]. As the damage proportion of the model has been fit to experimental data the effect of this assumption should be reduced, but further examination is required.
There are several other assumptions which may also require investigation. Firstly, only the DNA damage caused by protons and the secondary electrons created by the primary protons in the nucleus is modelled. The lack of neutrons in the model may affect the ability to predict secondary cancers [115], a principal aim. Secondly, the predicted misrepair yield has been shown to match other models in the literature but has not yet been directly compared to experimental data.

Furthermore, an assumption which affects most RBE models is the ability of a single averaged LET value to inform on the biological effect at each voxel. At each voxel in one or more beam paths, there is a distribution of particles with differing energy and thus a spectrum of LET values. A single value for LET is obtained by using an averaging method, commonly LET₀ or LETₜ. Then, two voxels of the same single value of LET and absorbed dose, according to all RBE models discussed in this paper, have the same clinical effect, despite the potential for vast differences in the LET spectra. It is feasible that these differences in spectra can have a differing radiobiological effect of clinical significance.

These issues are challenges to the model, but as these are resolved, the model will provide further insight and draw attention to areas which require further study. We suggest that one of the key advantages of mechanistic models is their ability to make predictions outside of a posteriori knowledge for further study.

Clinically, several further steps need to be explored if these models are to be applied in treatment planning. Firstly, further validation work is crucial before any clinical application. Initially, this will include cellular experiments into the mechanical processes of DNA damage, DNA repair and chromosome aberrations, where experimental data in the literature is currently lacking. The next step would be providing the clinician with maps of residual, misrepair or other endpoints for patients as well as investigation of indirect optimisation strategies such as beam angle selection and target segmentation techniques [110]. After this, direct optimisation, where DNA damage parameters are used alongside absorbed dose in the TPS optimiser, could follow. While full optimisation is some distance away due to the considerable validation work required, the concept of ‘no-’ or ‘low-cost’ optimisation, proposed by others [111], can be achieved in the short term. This optimisation is one which does not cause clinically significant degradation in the absorbed dose distribution and is achievable via multi-field optimisation (MFO) in IMPT. It would also be beneficial to conduct statistical analysis on a range of Christie patients to study any trends in prediction of biological effect.
3. A Monte Carlo Study of Different LET Definitions and Calculation Parameters for Proton Beam Therapy

This work was published by the Biomedical Physics & Engineering Express journal in December 2021 and is the second accepted paper from the thesis. A major roadblock in implementing LET into the clinic is the considerable variation in definition throughout the literature. Currently, there is no consensus on what type of LET to calculate nor a clear understanding of the effect these differences cause in clinical metrics. The aim of this paper was to investigate whether varying LET definition has a significant effect when compared with potential clinical methodologies on clinical PBT treatment plans.

The variations in LET definition can be broadly separated in four categories; averaging, scoring, particle inclusion and MC calculation parameters. In this article, common deviations in each category were calculated for a simple SOBP and four clinical PBT plans covering a range of typical anatomical sites treated at The Christie. The resulting distributions were compared using clinical methodologies common to the clinic, including qualitative comparison, LET Volume Histograms (LVHs) as well as maximum and mean values. In the case of the MC parameters, hit type and the Max Step Size (MSS) were investigated as it was discovered that GATE was using non-typical settings compared to other MC codes. A definition of dose-averaged LET scored in water for primary and secondary protons using a random hit type with an automated MSS were used as the base standard to limit the number of calculated parameters. A method of comparing the definitions in a fitted RBE model was also devised to investigate whether the differences in RBE-weighted dose may occur from selection of a LET type.

It was demonstrated that varying the LET definition in all categories resulted in substantially different absolute values of LET. In many of the cases, this difference in absolute values may not change the interpretation of results from a clinical metric. For instance, dose- and track- averaged LET acquired differing values but showed the same elevated regions qualitatively and matched trends in LVHs and maximum and mean values. However, in some cases there were substantial differences in absolute values and in the general trend. In the case of particle inclusion, LET for all particles showed up to a 100% difference in critical organs at risk such as the brainstem and a flat distribution compared to the other scorings. Grid artefacts were also observed in the case of the post hit type applied by GATE. The LET-weighted dose fitting showed how many of the differences in LET values were greatly reduced when combined with dose and fitted to an RBE. The exception is when scoring LET
for all particles compared to the other scorings where differences in LET weighted dose was observed.

It is hoped this work may aid the route to consensus on a particular definition of LET to help eventual implementation in standard clinical PBT treatment planning.

Author Contributions

I selected the LET parameters to include and the clinical metrics for comparison. I made edits to both the AUTOMC and GATE source core. I simulated, analysed and studied the data. I wrote the manuscript with review from all co-authors.

A Monte Carlo Study of Different LET Definitions and Calculation Parameters for Proton Beam Therapy

Edward A K Smith\textsuperscript{1,2}, Carla Winterhalter\textsuperscript{1,3}, Tracy S A Underwood\textsuperscript{1,3}, Adam H Aitkenhead\textsuperscript{1,2}, Jenny C Richardson\textsuperscript{1,2}, Michael J Merchant\textsuperscript{1,3}, Norman F Kirkby\textsuperscript{1,3}, Karen J Kirby\textsuperscript{1,3} and Ranald I Mackay\textsuperscript{1,2}

\textsuperscript{1} Division of Cancer Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, United Kingdom

\textsuperscript{2} Christie Medical Physics and Engineering, The Christie NHS Foundation Trust, Manchester, United Kingdom

\textsuperscript{3} The Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom

The strong in vitro evidence that proton Relative Biological Effectiveness (RBE) varies with Linear Energy Transfer (LET) has led to an interest in applying LET within treatment planning. However, there is a lack of consensus on LET definition, Monte Carlo (MC) parameters or clinical methodology. This work aims to investigate how common variations of LET definition may affect potential clinical applications. MC simulations (GATE/GEANT4) were used to calculate absorbed dose and different types of LET for a simple Spread Out Bragg Peak (SOBP) and for four clinical PBT plans covering a range of tumour sites. Variations in the following LET calculation methods were considered: (i) averaging (dose-averaged LET (LET\textsubscript{d}) & track-averaged LET); (ii) scoring (LET\textsubscript{d} to water, to medium and to mass density); (iii) particle inclusion (LET\textsubscript{d} to all protons, to primary protons and to particles); (iv) MC settings (hit type
and Maximum Step Size (MSS)). LET distributions were compared using: qualitative comparison, LET Volume Histograms (LVHs), single value criteria (maximum and mean values) and optimised LET-weighted dose models. Substantial differences were found between LET values in averaging, scoring and particle type. These differences depended on the methodology, but for one patient a difference of \(~100\%\) was observed between the maximum LET\(_d\) for all particles and maximum LET\(_d\) for all protons within the brainstem in the high isodose region (4 keV \(\mu m^{-1}\) and 8 keV \(\mu m^{-1}\) respectively). An RBE model using LET\(_d\) including heavier ions was found to predict substantially different LET-weighted dose compared to those using other LET definitions. In conclusion, the selection of LET definition may affect the results of clinical metrics considered in treatment planning and the results of an RBE model. The authors’ advocate for the scoring of dose- averaged LET to water for primary and secondary protons using a random hit type and automated MSS.

3.1 Introduction

The concept of Relative Biological Effectiveness (RBE) is applied in Proton Beam Therapy (PBT) to convert proton doses to equivalent photon doses. This conversion is required as different radiation modalities have different biological effects at matched doses and the vast majority of clinical dose-response relationships have been established for photon radiotherapy. For decades, it has been standard clinical practice within PBT to apply a constant RBE value of 1.1 to proton absorbed dose to bring biological equivalence to photons. This constant value was selected to limit complexity in response to incomplete data and to limit potential underdosing to the tumour [137].

Parameters such as dose per fraction, Linear Energy Transfer (LET), total dose, tissue \(\alpha/\beta\), and biological endpoint have been shown to affect RBE [21,73]. LET has become a particular focus as the \textit{in vitro} evidence is especially strong [21] and, in principle, physical parameters can be calculated with high accuracy. Consequently, LET features in the majority of radiobiological models aiming to predict the variable RBE effect [138]. However, these models suffer from the large uncertainties in \textit{in vitro} data [105] and there is currently no method to validate these models \textit{in vivo}. Despite these uncertainties, there is a growing opinion in the clinical PBT community that LET should be considered during the treatment planning process. How this should be performed remains up for debate, but proposed solutions and methods used to study LET in the literature include simple qualitative checks [106], LET Volume Histograms (LVHs) [42,106,107], single value LET/dose criteria [45,104,107] and the full use of an RBE model [77,108,109].

As well as variation in how LET distributions are analysed as part of the treatment planning process, there is also substantial methodological variation in the
calculation of LET values. Previous work has investigated the impact of varying MC parameters such as secondary production threshold and voxel size [82,83]. However, the existing literature does not cover all common differences between MC LET calculation methods, such as variations in the exact scoring methodology or the types of particles included. Here we comprehensively explore this topic and consider the impact of LET definition on clinical plan analyses.

Recently Kalholm et al [75] elegantly demonstrated that a wide range of different LET definitions is in use within the proton community. A significant proportion of this variation results from the practical issues associated with applying the concept of LET to radiobiological experiments or radiotherapy treatment plans. In ICRU report 85a [119], LET is well-defined: it is calculated at a point, for a specific material, for charged particles of a given type and energy. However, in a treatment plan, parameters are defined in a voxelated geometry and thus a single LET value must be derived from a group of particles of varying quality. The most common methods to acquire a single value are dose-averaging (LET_d) and track-averaging (LET_t). Both \( \text{LET}_d \) and \( \text{LET}_t \) are used in PBT RBE models [57,77] and in the search for in vivo evidence of RBE [42–44,47].

There are also variable approaches to handling the multiple particle types which may exist within a voxel. Within the literature, some groups have scored LET for primary protons only [72,88], whereas others have also included secondary protons in their LET scoring [89]. Additionally, there is a wider discussion in the PBT community on whether LET scoring should consider non-proton secondary particles created by nuclear interactions [21,67,90]. These secondary particles contribute a small amount of dose compared to primary protons but their contributions to LET distributions can be substantial [67].

Further discrepancies between groups arise over LET calculation medium. This variation is part of a long-standing debate within PBT [94] and, in fact, the wider radiotherapy community, on whether the clinical standard of dose to water should be replaced with dose to medium [91,95]. The debate includes questions relating to: accuracy, convention and biological effect. Currently, there is no clinical consensus on whether LET to water or LET to medium should be considered. In line with mass stopping power, calculations of: LET to medium, divided by mass density, (‘LET in unit density tissue’) are also performed by some groups [67,97]. It has been shown that the difference between LET to water and LET to medium may significantly affect RBE data [98]. Despite differences in units for these scoring types (e.g. keV/\( \mu \text{m} \) versus \( \text{[keV/} \mu \text{m]}/[\text{g/cm}^3] \)), these are often used interchangeably.

Finally, Monte Carlo simulations of LET require certain input parameters to be set, such as a physics list and production cuts on secondary particles [100]. The defaults and typical choices for these parameters vary across MC codes and versions. One parameter which varies between LET scorers is ‘hit type’. ‘Hit type’
refers to where information is stored along each particle’s step in the simulation. For example, a hit type of ‘random’, a common default, means that energy is deposited at a random position along the particle’s step. This contrasts to hit types of ‘pre’, ‘mid’ and ‘post’ where the energy is deposited at the start, middle and end of the particle’s step, respectively. The Maximum Step Size (MSS) may also be explicitly defined in a simulation instead of using the MC code’s automated selection. Little discussion exists in the literature on the effects of these different scoring options upon LET [72].

If the use of LET in clinical proton therapy is to become widespread it is important to understand options available in LET calculations and the impact that various methodological choices can make. This work aims to investigate how the major variations in LET methodology may affect potential clinical application. The forms of LET considered in this work are as follows:

- LET_d and LET_t
- LET_d scored to primary protons, all protons and particles
- LET_d scored to water, to medium, and to medium with a mass-density normalisation then applied
- LET_d scored with a post hit type setting and a random step hit type setting, with and without a set MSS.

3.2 Method

3.2.1 Monte Carlo Simulations

We consider two scenarios: (i) Simulation of a Spread-Out Bragg Peak (SOBP) field delivered to a homogeneous phantom, and (ii) simulation of a series of clinical plans calculated for patient CT scans.

For the SOBP, absorbed dose and different flavours of LET were obtained via MC simulations using GATE [127,139,140] (vEAKS01) / GEANT4 [128,141] (v10.3.3). GATE (vEAKS01) is an in-house version of GATE (v8.1, same version as used in GATE-RTion[142]) modified to allow the step hit type to be changed for the LET actor. In GATE (v8.1), this step hit type is hardcoded to a ‘post’ hit type. The SOBP was comprised of 10 spots with minimum and maximum proton energies of 127.5 MeV and 150 MeV, respectively. The spots have dimensions of 3 mm (sigX and sigY of a gaussian lateral profile). The medium was a homogeneous material (water, bone or brain tissue). Absorbed dose and various LET options were scored in 2 mm slabs sliced perpendicular to the beam. 10^7 histories were run for each SOBP.

For the patient cases, absorbed dose and the different types of LET were obtained using AUTOMC [143] (vES01), a piece of software that performs independent MC dose calculations for plan quality assurance. The software operates by generating the files required for GATE MC simulations from the plan DICOM data.
and driving the GATE (vEAKS01) / GEANT4 (v10.3.3) environment. For simulations within the patient anatomy, LET and dose were scored in a 2 mm grid with the number of histories selected to achieve an approximate uncertainty of 1.2% GY$_{RBE=1.1}$ within the high dose region [144]. A clinical beam model for the Varian ProBeam delivery system was used for simulation on patient anatomy.

All simulations settings were chosen to closely match clinical AUTOMC settings as these had undergone substantial validation [143]. For electrons, a production cut of 5 mm was selected inside the MC world while a cut of 0.1 mm was applied inside the CT image or tank. ‘QGSP_BIC’ was the selected physics list for both the 1D SOBP and patient simulations. The human material compositions in the tank and patient simulations were taken from ICRP 110 [145]. Ionisation values for elements were selected as described in [143]. The AAPM TG 268 report for reporting MC radiation transport studies was followed in this paper. [146]. The output from AUTOMC and GATE was processed using Python (v3.6) and the following python packages: NumPy [147] (v1.18.1), SciPy (v1.4.1), Suspect (edited v0.3.9), Nibabel (v3.0.0) and PyDicom (v1.3.0).

### 3.2.2 Scoring Parameters

#### 3.2.2.1 Absorbed Dose.

Absorbed dose to medium was calculated using the in-built scorer within GATE while absorbed dose to water was calculated using the method of [94] for converting dose to medium to dose to water in PBT.

#### 3.2.2.2 LET.

The LET scorer within GATE was used to obtain different LET distributions. This scorer uses the GEANT4 method ‘GetElectronicStoppingPowerDEDX’ where a lookup is performed using the particle’s energy to find electronic stopping power [82,83]. In this work, our default definition of LET is dose-averaged LET (LET$_d$) scored to water for primary and secondary protons with a random step hit type and automated MSS. If a change is not explicitly stated, the default setting is applied.

The different LET definitions we consider (shown in Table 3.1) stem from the definition of LET in ICRU report 85a [119]. Here, unrestricted LET is defined as, dE, the mean energy lost by the charged particles due to electronic interactions in traversing a distance, dl:

\[
\text{LET} = \frac{dE}{dl} (3.1)
\]
<table>
<thead>
<tr>
<th>LET Type</th>
<th>Calculation Technique</th>
</tr>
</thead>
</table>
| **Dose-Averaged LET, LET<sub>d</sub>** | Using Eq.(3.1), the LET from each particle is weighted with respect to its contribution to local dose in each voxel, obtaining Eq.(3.2):  
\[
LET_d = \frac{\sum_i^N dE_i}{\sum_i dE_i} \quad (3.2)
\]
Where \( N \) is the total number of particles within the voxel and \( i \) is the \( i \)th particle. |
| **Track-averaged LET, LET<sub>t</sub>** | Using Eq.(3.1), the LET from each particle is weighted with respect to its step length in each voxel, obtaining Eq. 3.2:  
\[
LET_t = \frac{\sum_i^N dl_i}{\sum_i dl_i} \quad (3.3)
\]
LET<sub>t</sub> is also known as fluence-averaged LET. |
| **LET<sub>d</sub> for Primary Protons and Secondary Protons, LET<sub>d,pro</sub>** | Only protons are included within Eq(3.2). This was implemented in GATE using a particle filter for protons. |
| **LET<sub>d</sub> for Primary Protons, LET<sub>d,prim</sub>** | Only primary protons are included within using Eq(3.2). This was implemented in GATE using a particle filter for protons with a track ID of 1. |
| **LET<sub>d</sub> for Particles, LET<sub>d,part</sub>** | All hadronic particles with a \( Z \) between 1 and 8 are included within the Eq(3.2). This was implemented in GATE by applying a series of particle filters from \( Z = 1 \) to \( Z = 8 \). It should be noted that as GATE (v8.1) is unable to score LET<sub>d,part</sub> to water but only to medium. LET<sub>d,pro</sub> and LET<sub>d,prim</sub> were also scored to medium for comparison. |
| **LET<sub>d</sub> to Water, LET<sub>d,wat</sub>** | The proton energy at the pre-step point is used in a lookup table to acquire the stopping power in water, regardless of the material composition in the voxel. |
| **LET<sub>d</sub> to Medium, LET<sub>d,med</sub>** | The proton energy at the pre-step point is used in a lookup table to acquire the electronic stopping power of the material composition in the voxel. |
| **LET<sub>d</sub> to Mass Density, LET<sub>d,mass</sub>** | LET<sub>d,mass</sub> is divided by the physical density in the voxel. The physical density is derived during the stoichiometric CT calibration when the scanner parametrisation is applied to the ICRP110 references tissues. This gives LET<sub>d,mass</sub> units of keV \( \mu m^{-1} g^{-1} cm^3 \) instead of keV \( \mu m^{-1} \) as for the other forms of LET. |
| LET$d$ with Random Hit Type, LET$d,ran$ | LET$d$ is scored using the ‘random’ hit type and using the automated MSS within GATE/GEANT4. |
| LET$d$ with Post Hit Type, LET$d,post$ | LET$d$ is scored using the ‘post’ hit type and using the automated MSS within GATE/GEANT4. |
| LET$d$ with Random Hit Type and MSS, LET$d,ran,mss$ | LET$d$ scored with a ‘random’ hit type and a selected MSS of 0.5 cm |
| LET$d$ with Post Hit Type and MSS, LET$d,post,mss$ | LET$d$ scored with a ‘post’ hit type and a selected MSS of 0.5 cm |

Table 3.1: Different LET definitions in categories of averaging, particle inclusion, scoring and hit type/max step size are shown.

3.2.3 Patient Data and Consent.

Four patients are presented in this work, with a single case for ependymoma, nasopharynx, Ewing’s sarcoma and a phase 2 treatment of a whole CNS case. This phase was chosen as the brainstem was at risk of elevated LET values.

The PBT plans presented in this work are from patients previously treated with the Proton Therapy Centre. All plans were generated according to clinical protocols and underwent appropriate patient-specific QA.

3.2.4 Clinical Comparison Methods

3.2.4.1 Qualitative Comparison. Clinical plans were qualitatively examined within the >2% dose region (relative to maximum dose). Colour bar windowing was set individually for each map as this is likely how the distributions would be reviewed clinically.

3.2.4.2 LET Volume Histograms (LVHs). LET Volume Histograms (LVHs) were generated for the different forms of LET for the Planned Target Volume (PTV) and a selected Organ At Risk (OAR) for each clinical case. Only LET values within the >2% dose contour (relative to the maximum dose) were defined in the LVH. For this reason, LVHs, where OARs are partially covered with the >2% dose contour, do not show 100% of the volume covered by any LET value.

3.2.4.3 Single Value Criteria. Maximum and mean values of LET within a range of isodose regions were compared between the different forms of LET. Isodose regions from >2% to >80% of the maximum absorbed dose in the plan were calculated in 2% increments.
3.2.4.4 LET-Weighted Dose. Several authors [77,105,111,120] have applied a simple, linear LET-weighted dose model to calculate RBE-weighted dose:

\[ Dose_w = D(1 + \kappa \times LET) \] (4)

where \( Dose_w \) is the LET-weighted dose, \( D \) is the proton absorbed dose, \( LET \) is the LET input and \( \kappa \) is a fitting parameter.

Here, we use this model to compare the different LET definitions by deriving a specific \( \kappa \) for each definition. Each \( \kappa \) value was derived by assuming an RBE of 1.1 for the initial part of the SOBP in brain. The slabs within the SOBP region were selected so that they are within 1% dose and 1 keV \( \mu m^{-1} \) of each other. Thus, in fitting \( \kappa \) for each LET definition, we assigned an RBE of 1.1 to a region with relatively homogenous absorbed dose and LET values. Concerns over elevated RBE in clinical PBT are primarily related to end of range effects, it is usually assumed that an RBE of 1.1 is reasonable for the initial portion of a SOBP [105]. A similar method was applied in [111]. The python package ‘SciPy.minimize’ (v1.4.1) was used to find the optimum \( \kappa \) value for each LET definition in averaging, scoring and particle groups to obtain the same dose as RBE =1.1 in the initial portion of the SOBP using Eq 3.3.

3.3 Results
3.2.1 1D SOBP

Figure 3.1 shows absorbed dose and the various forms of LET scored in 2 mm slabs for a SOBP, in a tank geometry. Fig 1B shows LET\(_d\) and LET\(_t\) versus depth in water. The two averaging methods give similar results in the entrance region, but differences appear in the SOBP region, reaching a maximum at the end of range. These higher values for LET\(_d\) are driven by high LET particles delivering more dose than low LET particles. Figure 3.1C and 3.1D show LET\(_d,\text{wat}\), LET\(_d,\text{med}\) and LET\(_d,\text{mass}\) in brain and bone, respectively. For brain, the differences between the three scoring options are minimal since water and brain tissue are similar in characteristics of physical density and Z composition. However, differences between these scoring options become particularly relevant when bone is considered due to dissimilar physical density and Z composition. While LET\(_d,\text{wat}\) and LET\(_d,\text{mass}\) deliver similar values in bone except at the end of range, LET\(_d,\text{med}\) is higher at all depths.

Figure 3.1E shows LET\(_d,\text{prim}\), LET\(_d,\text{pro}\) and LET\(_d,\text{part}\) scored versus depth in water. Both LET\(_d,\text{prim}\) and LET\(_d,\text{pro}\) are similar, with LET\(_d,\text{pro}\) values very slightly higher in the entrance region. LET\(_d,\text{part}\) meanwhile is substantially higher within the entrance region as this is where the majority of nuclear fragments are created. LET\(_d,\text{part}\) also reaches higher values at the end of range, due to its background of heavier nuclei fragments (few primary protons remain).
Figure 3.1F shows LET$_{d,\text{ran}}$, LET$_{d, \text{post}}$, LET$_{d, \text{mss}}$ and LET$_{d, \text{post mss}}$ scored at depth in water. LET$_{d, \text{ran}}$, LET$_{d, \text{post}}$ and LET$_{d, \text{mss}}$ obtain virtually identical results. However, the values for LET$_{d, \text{post mss}}$ are very different from the other hit types. Large fluctuations are seen in the result with the amplitude of this artefact at a maximum in the entrance before decreasing towards the end of the SOBP. Changing the value of MSS changes the amplitude and frequency of the artefact with smaller values leading to a smaller artefact.

Figure 3.1: An example proton 1D SOBP in a tank geometry with a maximum energy of 150 MeV. Panels show absorbed dose in water (A), dose-averaged LET (LET$_d$) and track-averaged LET in water (B), LET$_d$ scored for water, medium and mass density scored in brain tissue (C), LET$_d$ scored for water, medium and mass density scored in bone tissue (D), LET$_d$ for primary protons only, primary and secondary protons only and particles in water (E) and LET$_d$ scored for random and post hit type with and without a max step size of 0.5 cm in water (F).
Figure 3.2: Contours (A), absorbed dose (B), dose-averaged LET (LET_d) (C), track-averaged LET (LET_t) (D), LET Volume Histograms (LVH) PTV (E), LVH brainstem (F) and single value (maximum and mean) (G) for the brainstem for patient 1.

(A) Contours show PTV in dark red with the brainstem shown in a white contour. (B), (C), (D) Maps are windowed to 2% of the maximum dose. (E), (F), (G) LET_d and LET_t are shown by blue and red lines, respectively. (G) Dashed lines show max values for varying isodose regions, solid lines show mean values for varying isodose regions.

3.3.2 Effect of Different LET Averaging

Figure 3.2 shows maps of contours, absorbed dose, LET_d and LET_t as well as associated LVHs and single values graphs calculated for Patient 1 (ependymoma). Similar results in the clinical metrics were seen for the 3 other patient sites (Results are shown in supplementary materials).

3.3.2.1 Qualitative Comparison. In the LET maps shown in Figure 3.2C-D, the LET_d and LET_t distributions appear broadly similar. The regions of elevated LET values appear in the same anatomical positions with no visible differences occurring at tissue junctions. The elevated regions may appear brighter in the LET_d maps than the LET_t, since LET_d obtains greater maximum values with similar minimum values. This relationship is demonstrated in Fig 1B.

3.3.2.2 LVHs. The LVHs in Figure 3.2E-F show that in either the PTV or selected critical OAR (brainstem), LET_d values are greater than LET_t values, with an
approximate difference of 1 keV μm⁻¹ to 100% of the volume. This difference increases as smaller fractions of the volume are considered, rising to a maximum difference of approximately 2-3 keV μm⁻¹ in peak LET. For patient 1, these differences reached a maximum in the highest LET values within the brainstem, where ~3 keV μm⁻¹ and ~6 keV μm⁻¹ were calculated for LET₁ and LETₐ respectively.

### 3.3.2.3 Single Values (Maximum & Mean)

The maximum and mean values for LETₐ and LET₁ in Figure 3.2G are substantially different with the largest difference found between these LET definitions than the other definition groups. Generally, the difference was constant across the isodose regions with a difference of 2 - 3 keV μm⁻¹ for maximum values and 1 - 1.5 keV μm⁻¹ for mean values.

**Figure 3.3:** Contours (A), absorbed dose (B), dose-averaged LET scored to water (LETₐ,wat) (C), dose-averaged LET scored to mass density (LETₐ,mass) (D), dose-averaged LET scored to medium (LETₐ,med) (E), LET Volume Histograms (LVH) PTV (F), LVH temporal lobe (left) (G) and single value (maximum and mean) for the temporal lobe (left) (H) for patient 2.

(A) Contours show PTV in dark red with the brainstem shown in a white contour. (B), (C), (D), (E) Maps are windowed to 2% of the maximum dose. (F), (G), (H) LETₐ,wat, LETₐ,mass and LETₐ,med are shown by blue, purple and green lines, respectively.

(H) Dashed lines show max values for varying isodose regions, solid lines show mean values for varying isodose regions
3.3.3 Effect of Different LET Scoring

Figure 3.3 shows maps of contours, absorbed dose, LET$_{d,\text{wat}}$, LET$_{d,\text{mass}}$ and LET$_{d,\text{med}}$ as well as associated LVHs and single value graphs calculated for Patient 2 (naso-cavity). Similar results in the clinical metrics were seen for the other patient sites unless specified (additional patient results are shown in supplementary materials). It should be noted that LET$_{d,\text{mass}}$, LET$_{d,\text{med}}$ and LET$_{d,\text{wat}}$ are quantities with different units. However, these definitions are often used interchangeably in radiobiological data [98].

3.3.3.1 Qualitative Comparison. There are clear differences between the distributions of the three scoring options (Figure 3.3C-E). LET$_{d,\text{wat}}$ and LET$_{d,\text{mass}}$ have substantially larger values in air cavities compared to LET$_{d,\text{med}}$. This is reversed in bone, where LET$_{d,\text{med}}$ reaches greater values.

3.3.3.2 LVHs. Figure 3.3F-G shows the differences discussed in the qualitative comparison clearly in both the LVHs for PTV and OAR (Temporal Lobe (left)). In both LVHs, LET$_{d,\text{med}}$ shows significant differences to the other two scorings. These differences emerge when voxel materials differ substantially from water. For the PTV LVH, the percentage of volume covered by a minimum of 2 keV $\mu$m$^{-1}$ is substantially reduced when scored to medium. This is caused by a non-negligible volume of the low density (air-filled) naso-cavity being included within the PTV. The left temporal lobe LVH demonstrates the opposite situation: greater values are evident when LET to medium is scored. This is caused by the inferior part of the lobe including simulation voxels which contain both brain and bone tissue (due to the simulation grid having a lower resolution than the CT grid). This mixture of brain and bone tissues increases the density and thus leads to greater LET$_{d}$ values when scored to medium. These differences were smaller in the other 3 patients.

3.3.3.3 Single Values (Maximum & Mean). Across all isodose regions, LET$_{d,\text{wat}}$ and LET$_{d,\text{mass}}$ values are broadly similar, whereas LET$_{d,\text{med}}$ values are somewhat higher (Figure 3.3H). This is due to the presence of bone within certain regions of interest (consistent with Figure 3.1D).
Figure 3.4: Contours (A), absorbed dose (B), dose-averaged LET for all protons (\(\text{LET}_{d,\text{pro}}\)) (C), dose-averaged LET for primary protons (\(\text{LET}_{d,\text{prim}}\)) (D), dose-averaged LET scored for particles (\(\text{LET}_{d,\text{part}}\)) (E), LET Volume Histograms (LVH) PTV (F), LVH brainstem (G) and single value (maximum and mean) for the temporal lobe (left) (H) for patient 3.

(A) Contours show PTV in dark red with the brainstem shown in a white contour. 
(B), (C), (D), (E) Maps are windowed to 2% of the maximum dose. 
(F), (G), (H) \(\text{LET}_{d,\text{pro}}\), \(\text{LET}_{d,\text{prim}}\) and \(\text{LET}_{d,\text{part}}\) are shown by green, turquoise and pink lines, respectively. 
(H) Dashed lines show max values for varying isodose regions, solid lines show mean values for varying isodose regions

### 3.3.4 Effect of Different Particle Inclusion on LET\(_d\)

Figure 3.4 shows maps of contours, absorbed dose, \(\text{LET}_{d,\text{pro}}\), \(\text{LET}_{d,\text{prim}}\) and \(\text{LET}_{d,\text{part}}\) as well as associated LVHs and single values graphs calculated for Patient 3 (phase 2 treatment of whole CNS). Similar results in the clinical metrics were seen for the 3 other patient sites unless specified (additional patient results are shown in supplementary materials).

#### 3.3.4.1 Qualitative Comparison.

In Figure 3.4C-E, there are clear differences between the distributions of the three particle options. While \(\text{LET}_{d,\text{pro}}\) and \(\text{LET}_{d,\text{prim}}\) are similar, \(\text{LET}_{d,\text{part}}\) is greater throughout the anatomy and its distribution is more difficult to interpret. In the \(\text{LET}_{d,\text{part}}\) colour wash, the viewer’s eye is drawn to high maximum LET values stemming from single particles, in regions of low dose.
(this colour wash is sensitive to dose thresholding, here a threshold of 2% of the maximum dose is considered). This is expected as low energy nuclear fragments created by proton beams can have much greater LET values than protons. If windowed further, the distribution still appears flatter than the other particles scorings, with the elevated regions less clear.

3.3.4.2 LVHs. The LVHS for the PTV and the brainstem are shown in Figure 4F-G. For the proton scorings, $\text{LET}_{d,\text{pro}}$ is either equal to or slightly greater than $\text{LET}_{d,\text{prim}}$. This is expected as the inclusion of lower energy secondary protons increases $\text{LET}_d$. $\text{LET}_{d,\text{part}}$ is substantially greater for all voxels within the PTVs and OARs.

3.3.4.3 Single Values (Maximum & Mean). For particle type, $\text{LET}_{d,\text{pro}}$ and $\text{LET}_{d,\text{prim}}$ obtain very similar results for both maximum and mean values across the isodose regions. However, $\text{LET}_{d,\text{part}}$ shows large differences in comparison to $\text{LET}_{d,\text{pro}}$ and $\text{LET}_{d,\text{prim}}$. For mean values, this difference is approximately 2 - 3 keV $\mu$m$^{-1}$ across all isodose regions. For maximum values, this difference reaches 5 keV $\mu$m$^{-1}$ in the lower isodose regions before reducing to approximately 2 keV $\mu$m$^{-1}$ in the high isodose regions.

3.3.5 Effect of Hit Type and Maximum Step Size Setting on LETd

Figure 3.5 shows maps of contours, absorbed dose, $\text{LET}_{d,\text{ran}}$ and $\text{LET}_{d,\text{post}}$ as well as associated LVHs and single values graphs for $\text{LET}_{d,\text{ran}}$, $\text{LET}_{d,\text{post}}$, $\text{LET}_{d,\text{ran,mss}}$ and $\text{LET}_{d,\text{post,mss}}$ for Patient 4 (pelvic sarcoma). Similar results in the clinical metrics were seen for the 3 other patient sites unless specified (results are shown in supplementary materials).

3.3.5.1 Qualitative Comparison. The $\text{LET}_{d,\text{ran}}$ and $\text{LET}_{d,\text{post}}$ maps in Figure 3.5C-D are largely similar with the same areas highlighted in the distributions. However, $\text{LET}_{d,\text{post}}$ shows a grid artefact running throughout the whole distribution (the white arrow highlights the especially visible area). The grid artefact was found to reduce in magnitude and grid spacing if the MSS was decreased but at a cost of increased simulation time. This artefact is not visible in the three other patients analysed for this study, but it has been observed by the authors in other cases.

The maps for $\text{LET}_{d,\text{ran,mss}}$ and $\text{LET}_{d,\text{post,mss}}$ (not shown) matched their respective hit type with automated MSS.

3.3.5.2 LVHs. All LET types for hit types and MSS Settings in Figure 3.5E-F exhibit similar values in the LVHs for all PTVs and selected OARs.

3.3.5.3 Single Values (Maximum & Mean). In Figure 3.5G, mean values for all hit type and MSS combinations appear identical. However, the effect of the hit type can be seen on the maximum values with $\text{LET}_{d,\text{post,mss}}$ and $\text{LET}_{d,\text{post,mss}}$ slightly raised in isodose regions.
**Figure 3.5:** Contours (A), absorbed dose (B), dose-averaged LET with a random hit type setting \( \text{LET}_{d, \text{ran}} \) (C), dose-averaged LET with a post hit type setting \( \text{LET}_{d, \text{post}} \) (D), LET Volume Histograms (LVH) PTV (E), LVH brainstem (F) and single value (maximum and mean) (G) for the brainstem for patient 4.

(A) Contours show PTV in dark red with the brainstem shown in a white contour.
(B), (C), (D) Maps are windowed to 2\% of the maximum dose.
(D) White arrow shows especially large grid artefact.
(E), (F), (G) \( \text{LET}_{d, \text{ran}}, \text{LET}_{d, \text{post}}, \text{LET}_{d, \text{ran, mss}} \) and \( \text{LET}_{d, \text{post, mss}} \) are shown by blue, light pink, orange and green lines, respectively.
(G) Dashed lines show max values for varying isodose regions, solid lines show mean values for varying isodose regions.

### 3.3.6 LET-Weighted Dose and \( \kappa \) Optimisation

Figure 3.6A shows the SOBP region selected to fit \( \kappa \) in Eq(3.4) for the different LET definitions (method explained in section 3.2.4.4). Figures 3.6B-D shows results from fitting \( \kappa \) in Eq(3.4) for each LET definition and Figure 3.6E-G show DVHs for the brainstem of patient 1 calculated using Eq(3.4) for each LET definition and accompanying \( \kappa \) value (Table 3.2).

The \( \kappa \) values generated in the fitting process are shown in Table 3.2. All \( \kappa \) values had associated \( R^2 >0.99 \) in matching to Dose\( \text{RBE}=1.1 \) in the region defined in Figure 3.6A when applied Eq(3.4) with their corresponding LET definition. Our default setting \( \text{LET}_d \) and \( \text{LET}_{d, \text{prim}} \) obtained the same fitted \( \kappa \) value of 0.040 keV \( \mu \text{m}^{-1} \) which is similar to the values of 0.039 keV \( \mu \text{m}^{-1} \text{g}^{-1} \text{cm}^3 \) and 0.037 keV \( \mu \text{m}^{-1} \) obtained
by LET\textsubscript{d,\textit{mass}} and LET\textsubscript{d,\textit{med}}. Relative to our default, a \(\kappa\) value 55% lower was obtained for LET\textsubscript{d,\textit{part}} and a \(\kappa\) value 72.5% higher was obtained for LET\textsubscript{t}.

When paired LET definitions and \(\kappa\) values were applied, all LET definitions, except LET\textsubscript{d,\textit{part}}, resulted in similar RBE-weighted dose in both the SOBP (Figure 6B-D) and in the brainstem of Patient 1 (ependymoma case). Eq(3.4) using LET\textsubscript{d,\textit{part}} and its associated \(\kappa\) from Table 3.2 leads to practically no increase in dose at the end of the SOBP and in the brainstem of Patient 1 compared to dose\textsubscript{RBE=1.1}. This is due to the greater homogeneity in the LET\textsubscript{d,\textit{part}} compared to the other LET definitions.

Similar results to those in Figure 3.6E-G were seen in the selected OARs for the other 3 patients. This work was repeated with the SOBP in bone and the same pattern of relative results was observed for different LET definitions. Different \(\kappa\) values were obtained but LET definitions again matched each other besides LET\textsubscript{d,\textit{part}}.

<table>
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<tr>
<th>LET Definition</th>
<th>Optimised (\kappa) value</th>
<th>(\kappa) value relative to the default setting</th>
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<tr>
<td>(LET_d) (default setting)</td>
<td>0.040 (\mu) m keV(^{-1})</td>
<td>1.000</td>
</tr>
<tr>
<td>(LET_t)</td>
<td>0.069 (\mu) m keV(^{-1})</td>
<td>1.725</td>
</tr>
<tr>
<td>(LET_d,\text{prim})</td>
<td>0.040 (\mu) m keV(^{-1})</td>
<td>1.000</td>
</tr>
<tr>
<td>(LET_d,\text{part})</td>
<td>0.018 (\mu) m keV(^{-1})</td>
<td>0.450</td>
</tr>
<tr>
<td>(LET_d,\text{mass})</td>
<td>0.039 (\mu) m keV(^{-1}) g(^{-1}) cm(^{-3})</td>
<td>0.975</td>
</tr>
<tr>
<td>(LET_d,\text{med})</td>
<td>0.037 (\mu) m keV(^{-1})</td>
<td>0.925</td>
</tr>
</tbody>
</table>

*Table 3.2:* Optimised \(\kappa\) for Eq(3.4) for various LET definitions are shown. \(\kappa\) values were optimised for their respective LET so Eq(3.4) matched Dose\textsubscript{RBE=1.1} in the initial proportion of an SOBP in brain tissue. The chosen proportion of SOBP was selected as to not deviate more than 1\% in dose and less than 1 keV \(\mu\) m\(^{-1}\) in LET.
Figure 3.6: (A) Spread Out Bragg Peak (SOBP) absorbed dose and LET$_d$ with the defined region for LET-weighted dose optimisation. (B), (C) and (D) show optimised LET-weighted dose for different LET definitions on a SOBP in brain tissue. (E), (F) and (G) show DVHs for optimised LET-weighted dose for different LET definitions of the brainstem for patient 1.

(A) – (G) show dose$_{RBE=1.1}$ via a black dashed line

(A) shows regions of SOBP used to optimise $\kappa$ for different LET definitions via two horizontal lines in slate grey.

(B), (E) show LET$_d$ and LET$_t$ with blue and red lines, respectively.

(C), (F) show LET$_{d,\text{wat}}$, LET$_{d,\text{mass}}$ and LET$_{d,\text{med}}$ with blue, purple and green lines, respectively.
(D), (G) show LET$_{d,\text{pro}}$, LET$_{d,\text{prim}}$ and LET$_{d,\text{part}}$ with green, turquoise and pink lines, respectively.

3.4 Discussion

Variable RBE remains a concern within the PBT community and consequently, there is considerable interest in how LET should be incorporated into treatment planning. Currently, there is no consensus on how LET should be defined, calculated, or used to inform clinical decisions. There is much variation in the literature regarding LET formulation [75,87][75] and the use of LET in treatment planning studies. It is important we understand how LET definitions differ in potential clinical application. Consensus will be important as we strive to collaborate and interpret results from different institutions.

In this work, LET was simulated for clinical PBT plans using a range of common methodologies and the impact of changing the LET definition was assessed using potential clinical metrics. This carries the work by others such as [148,149] further by studying the differences of LET in the common metrics used to judge treatment planning quality. Our results highlight the need for careful understanding/selection of LET definition and chosen clinical metric. Substantial differences were found between LET values simulated using different methods for averaging or scoring and filters for particle type with variation across chosen metric. For instance, LET$_{d}$ and LET$_{t}$ differed substantially in LVH (Figure 3.2) but produced similar results for optimised LET-weighted dose (Figure 3.6). The results presented in this paper also highlight the contribution of non-proton particles to the LET distribution occurring in clinical PBT treatments. In many cases, it is typical for only protons to be included in LET values quoted in experimental radiobiological studies, ignoring the LET contributions from heavier nuclei such as alpha particles. However, some studies do quote LET values encompassing all particles and while these heavier particles contribute a small amount to the absorbed dose, they have much greater LET values and so can make substantial contributions to LET distributions [75]. The results in this paper demonstrate that there are substantial differences between LET calculated for different particles in potential clinical metrics, which are not removed after applying within an optimised RBE model.

If LET is to be combined with dose in clinical practice, having a reliable process for physical verification of both absorbed dose and LET would be desirable. However, this is complicated by the fact that LET is not a measurable parameter by definition, and instead requires the measurement of some other microdosimetric parameter (such as lineal energy [103]) as a surrogate. In the current paper we focus only on the implications of the issues relating to the calculation, rather than measurement, of LET.
It is difficult to state a recommended LET definition as this should depend on use and rely on significant clinical data on biological effect. While this data is growing [41–44,150], more is required. However, careful consideration of each component of the definition may lead to a preference in the community.

In the averaging component, LET_\text{d} is largely chosen instead of LET_\text{t} for both radiobiological and patient applications. This is usually justified by evidence suggesting LET_\text{d} fits radiobiological data better than LET_\text{t} [81]. This has theoretical support when considering a high LET particle will deliver more dose locally than a low LET particle and thus contribute more to the biological effect [120]. As has been demonstrated elsewhere (Kempe et al., 2006), the former is consistently higher than the latter.

For particle type, it follows that secondary protons should be included along with primary protons in the LET value to remain consistent with dose calculation in PBT. Clinical PBT TPSs include secondary protons when calculating dose to avoid dose underestimation by up to 15% [86]. The question of including other ions in the LET value is less clear. As shown in Figure 3.1E, heavier particles also make a significant contribution to the LET_\text{d} distribution but particles resulting from target fragmentation have a very low dose contribution [67,81]. It is also difficult to justify including particles of different types in a single LET value as different particles at the same LET are known to have a different biological effect [19]. Further to this, Figure 3.3E demonstrates how the comparatively homogenous distribution in LET_\text{d,part} masks the elevated regions of LET seen in proton LET which leads to practically no increase in RBE-weighted dose increase when using the LET-weighted dose model (shown in Figure 3.6). However, further work in measuring the biological effect of heavier ions in a proton beam is required before a definite statement can be made.

For LET scoring, the choice should be consistent with which material dose is scored to. Combining dose and LET with a different scoring method would cause inconsistency in units. Currently, most centres use dose to water as this is the standard dose calculated in PBT TPSs.

For hit type and MSS, a hit type of random and automated MSS should be applied. Using a post hit type is incorrect when using a condensed history algorithm as this would suggest zero energy loss along a step. The selection of a post hit type causes the unphysical grid artefact in Figure 3.4D and the spikes in LET in Figure 3.1F when combined with an MSS.

On this basis, the authors advocate the calculation of dose-averaged LET scored to water for primary and secondary proton (broadly consistent with most proton RBE models such as that proposed by [57] with a random hit type and automated MSS.
3.5 Conclusion

This study has shown how the selection of LET definition may affect the results of different clinical metrics considered in treatment planning as well as the output of RBE models. We believe that this work can contribute to the discussion regarding consensus and standardisation of LET for clinical PBT. A common framework for reporting LET will be desirable as we attempt to link variable RBE to outcome in clinical trials. For this purpose, we advocate the scoring of dose-averaged LET to water for primary and secondary protons using a random hit type and automated maximum step size.

3.6 Supplementary Materials

3.6.1 Patient Geometry: Contour, Absorbed Dose and LET$_d$

![Figure 3.7: Contour geometry, absorbed dose per fraction (Gy (RBE =1.1)) and dose-averaged LET (LET$_d$) are shown for four patient cases of varying tumour sites: ependymoma (patient 1), nasopharynx (patient 2), Ewing's sarcoma (patient 3) and phase 2 treatment of a whole CNS case (patient 4). For contour geometry, the PTV is shown in dark red while OARs are shown in white outline (Patient 1 = brainstem, patient 2 = temporal lobes, optical nerves and brainstem, patient 3 = bladder, uterus, ovaries and rectum, patient 4 = brainstem).]
3.6.2 Effect of Different LET Averaging

![Figure 3.8: Dose-averaged LET (LETd) and track-averaged LET (LETt) maps and associated LET Volume Histograms (LVHs) are shown for the PTV and selected OAR of four patient cases. OARs are shown by white contours (Patient 1 = brainstem, patient 2 = temporal lobes, optical nerves and brainstem, patient 3 = bladder, uterus, ovaries and rectum, patient 4 = brainstem). For LVHs, LETd and LETt are shown by blue and red lines, respectively.](image)
3.6.3 Effect of Different LET Scoring

**Figure 3.9:** Dose-averaged LET (LET$_{d}$) maps scored to water (LET$_{d,\text{wat}}$), mass density (LET$_{d,\text{mass}}$), and medium (LET$_{d,\text{med}}$) and associated LET Volume Histograms (LVHs) are shown for the PTV and relevant OARs of four patient cases. OARs are shown by white contours (Patient 1 = brainstem, patient 2 = temporal lobes, optical nerves and brainstem, patient 3 = bladder, uterus, ovaries and rectum, patient 4 = brainstem). For LVHs, LET$_{d,\text{wat}}$, LET$_{d,\text{mass}}$ and LET$_{d,\text{med}}$ are shown by blue, purple and green lines, respectively.
3.6.4 Effect of Different Particle Inclusion on LET$_d$

**Figure 3.10:** Dose-averaged LET (LET$_d$) maps scored to water (LET$_{d,\text{wat}}$), mass density (LET$_{d,\text{mass}}$), and medium (LET$_{d,\text{med}}$) and associated LET Volume Histograms (LVHs) are shown for the PTV and relevant OARs of four patient cases. OARs are shown by white contours (Patient 1 = brainstem, patient 2 = temporal lobes, optical nerves and brainstem, patient 3 = bladder, uterus, ovaries and rectum, patient 4 = brainstem). For LVHs, LET$_{d,\text{wat}}$, LET$_{d,\text{mass}}$ and LET$_{d,\text{med}}$ are shown by blue, purple and green lines, respectively.
3.6.5 Effect of Hit Type and Maximum Step Size Setting on LET$_d$

![Figure 3.10: Dose-averaged LET (LET$_d$) maps using a random hit type with automated Maximum Step Size (MSS) (LET$_d$, ran), a random hit type with MSS of 0.5 cm (LET$_d$, ran mss), a post hit type with automated MSS (LET$_d$, post) and post hit type & MSS (LET$_d$, post mss) and associated LET Volume Histograms (LVHs) are shown for the PTV and selected OAR of four patient cases. OARs are shown by white contours (Patient 1 = brainstem, patient 2 = temporal lobes, optical nerves and brainstem, patient 3 = bladder, uterus, ovaries and rectum, patient 4 = brainstem). For LVHs, LET$_d$, ran, LET$_d$, post, LET$_d$, ran mss and LET$_d$, post mss are shown by blue, pink, orange and light green lines, respectively.](image)
4. Relevance of Linear Energy Transfer Spectra in Models of Biological Effect for Clinical Proton Beam Therapy

This work was submitted as the third manuscript from this thesis, to the British Journal of Radiology in February 2022. It is currently awaiting resubmission as of September 2022. The manuscript version in the thesis is the first submission draft to the journal with no changes made besides re-formatting.

The previous chapter (‘3. A Monte Carlo Study of Different LET Definitions and Calculation Parameters for Proton Beam Therapy’) detailed common variations in averaged LET definition and a study investigating the potential effect these differences in clinical applications. However, while the LET parameter is applied as an averaged value in the vast majority of proton RBE models, there is some evidence which suggests LET spectra (or a similar parameter) may better predict biological effect. This is clear in the case of heavy ion therapy, where the two main models applied in clinical treatments, the MKM and LEM models, apply a LET spectrum or equivalent.

The work in this chapter aims to investigate the differences in LET spectra present in typical radiobiological experiments and the clinical proton therapy plans. MC simulations were used to obtain averaged LET values and LET spectra for both cases. The results demonstrated substantially different distributions exist in those in vitro experiments used to create proton RBE models compared to clinical PBT plans. The latter shows irregular LET distributions due to the greater complexity of the geometry e.g. beam angle and tissue homogeneity.

Author Contributions

I developed the method to obtain LET spectra from AUTOMC/GATE and simulated and analysed the resulting data. I wrote the manuscript and produced the figures. All co-authors reviewed and approved the manuscript.
Relevance of Linear Energy Transfer Spectra in Models of Biological Effect for Clinical Proton Beam Therapy

Edward A. K. Smith MSc 1,2, Tracy S. A. Underwood PhD 1,3, Adam H. Aitkenhead PhD 1,2, Carla Winterhalter PhD 1,2, Jenny C. Richardson PhD 1,2, Michael J. Merchant PhD 1,3, Norman F. Kirkby PhD 1,3, Karen J. Kirby PhD 1,3, Ranald I. Mackay PhD 1,2

1 Division of Cancer Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, United Kingdom
2 Christie Medical Physics and Engineering, The Christie NHS Foundation Trust, Manchester, United Kingdom
3 The Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom

Objectives: Variable Relative Biological Effectiveness (RBE) in Proton Beam Therapy (PBT) has received significant research, but is still not applied in routine clinical practice. Various issues need to be considered including a full understanding of RBE parameters such as Linear Energy Transfer (LET). We investigate averaged LET (dose-averaged LET (LET_d) and track-averaged LET (LET_t)) and LET spectra present in both typical radiobiological experiments and patient plans.

Methods: MC simulations (GATE/GEANT4) were used to calculate LET_d, LET_t and LET spectra for a range of geometries relevant to radiobiological experiments and a clinical nasopharynx PBT plan.

Results: When comparing across all geometries, voxels with similar LET_d or LET_t values were observed to have substantially different underlying spectra. This was particularly clear when comparing the LET spectra between the patient case, the pristine Bragg peak and the simple SOBP scenarios. Clear bi-modal distributions and greater LET spreads (within clinically relevant dose levels) were seen in the patient case, despite averaged LET values being similar for both the patient and simple cases.

Conclusions: These results demonstrate that irregular LET distributions found in patient treatment plans can be masked by simple LET averaging. Usually, only simple geometries and averaged values of LET are considered in radiobiological irradiations. The authors suggest that the biological impact (or otherwise) of proton LET spectra should be further considered in radiobiological experiments.
Advances in Knowledge: Patient plans produce LET distributions of greater complexity and shape to those in radiobiological experiments.

4.1 Introduction

Variable Relative Biological Effectiveness (RBE) has been a focus of research for decades and it remains a key issue for many in the Proton Therapy Beam (PBT) community [151-153]. However, it has not yet reached standard clinical practice and the vast majority of PBT centres continue to apply a constant RBE of 1.1. This constant value was selected at the early stages of PBT in the face of limited and uncertain radiobiological data. Nonetheless, it was understood through in vitro data that RBE was in fact variable with a dependence on parameters such as absorbed dose, Linear Energy Transfer (LET) and the tissue-specific $\alpha/\beta$ ratio. At present, this in vitro data for variable RBE has grown [22,55,73] and the evidence base for effect within patients continues to build [42,43,47]. This growth of evidence has strengthened the drive to incorporate some variability of RBE into proton treatment planning.

Within the parameters linked to a variable proton RBE, LET is a particularly well-studied parameter. This stems from the strong link between LET and RBE, and the relative ease of calculation of a physical parameter. Consequently, nearly all models for predicting variable proton RBE use LET as an input. This is typically in the form of dose-averaged LET (LET$_d$) with an assumption of a linear RBE-LET relationship [138]. The other common variation is track-averaged LET, where a single LET value is acquired from a set of particles by weighting each particle’s LET contribution by their track length. These averaging methods are applied to acquire a single value of LET in the presence of a large spectrum of particles with differing characteristics in a voxelated geometry. They implicitly assume the relationship between LET and RBE is linear for their respective averaging method.

However, there are questions as to whether averaged LET values are sufficient predictors of proton biological effect. A sufficiently non-linear relationship between LET and RBE could mean two proton irradiations, with similar averaged LET values but different underlying LET spectra, could have significantly different biological effects. This is accepted in heavier ion therapy, such as carbon, where non-linear models such as MKM [84] or LEM [85] are used to create treatment plans.

There is in vitro evidence of a non-linear relationship in protons, albeit to a smaller extent than in heavy ion therapy. Belli et al shows an overkill effect occurring at high LET values (>31 keV $\mu$m$^{-1}$) but also the possibility of a non-linear RBE-LET occurring at lower LET values for several in vitro endpoints of V79 cells [19,24,31]. Further work using high throughput techniques and human cell lines [154], demonstrates a non-linear response for RBE-LET approximately occurring at 10-13 keV $\mu$m$^{-1}$ for LET$_d$. A smaller non-linear relationship was also demonstrated in [155]
after optimising MC parameters for the in vitro data in [154]. These results are supported by other work using pristine and SOBP proton beams to irradiate human cell lines [22,25]. A small difference in RBE-LET relationships could be seen between the two modalities although experimental uncertainties, common in radiobiology, make conclusions difficult to draw.

Furthermore, there is evidence that proton RBE models with a non-linear RBE-LET relationship may outperform those using LET$_d$ in predicting proton RBE. One RBE model demonstrated a considerable non-linear increase in RBE for LET values greater than 10 keV $\mu$m$^{-1}$ [58]. While there was no decisive result, this work provided evidence that a combination of weighting for uncertainties and a non-linear RBE-LET relationship can improve the fit to in vitro data. Other models have also demonstrated non-linear relationships occurring at LET values greater than 16 keV $\mu$m$^{-1}$ [156] and for endpoints of DNA misrepair [77]. Another study compared LET$_d$ and LET spectra using LEM to calculate the biological effect for pristine and mixed radiation fields for protons for multiple endpoints [81]. It was concluded that LET$_d$ is reliable only for narrow LET distributions with reliability decreasing as field arrangements become more complex. However, [103] applied MKM, a non-linear RBE model, and a generic linear RBE model using LET$_d$ and found no preference for the ability to predict biological effect after fitting to in vitro data covering a range of human cell lines.

Current evidence for the effect of LET spectra is largely based upon in vitro data demonstrating differences between pristine and SOBP irradiation. This effect may be greater for patient treatments as multiple fields in complex arrangements and non-homogeneous anatomy could lead to wider distributions with greater complexity. This work aims to study the LET spectra occurring in typical pristine Bragg peak and SOBP fields used for in vitro radiobiological experiments and, in geometries with greater complexity, such as multiple SOBP fields and patient treatment plans. The four studied cases are:

- Pristine Bragg Peak
- Simple SOBP
- Complex SOBP
- Patient Case

4.2 Method

4.2.1 Monte Carlo Simulations

We consider four scenarios in this work: (i) pristine Bragg peak, (ii) simple Spread-Out Bragg Peak (SOBP), (iii) complex SOBP and (iv) clinical PBT treatment plan created for a nasopharynx patient.

For the simple geometries of (i), (ii) and (iii), absorbed dose, LET$_d$, LET$_t$ and LET spectra were obtained via MC simulations using GATE [127,142] (vEAKS01, an
inhouse version of GATE 8.1) / GEANT4 [128,141] (v10.3.3). The pristine Bragg was comprised of a single 150 MeV spot while the SOBPs were constructed from spots with minimum and maximum proton energies of 127.5 MeV and 150 MeV, respectively. All spots have dimensions of 3 mm (sigX and sigY of a gaussian lateral profile). The fields were simulated in homogenous water with absorbed dose and LET scored in 1 mm³ voxels. For each simulation, $10^7$ histories were run and the absorbed dose was normalised to a maximum of 2 Gy$_{RBE}$.

For (iii), the complex SOBP was constructed using an arrangement of four equally-weighted SOBPs identical to the SOBP in (ii). Here, one SOBP is perpendicularly overlapped by the 155 mm depth of the three other SOBPs at three depths (60, 125 and 145 mm) (shown in Fig 1A). This aims to mimic the complex field arrangements potentially present in clinical plans and present a possible ‘worst case’.

In (iv), absorbed dose, LET$_d$, LET$_t$ and LET spectra were obtained using AUTOMC [143], an in-house piece of software that performs independent MC dose calculations for plan quality assurance. The software operates by generating the files required for GATE MC simulations from the plan DICOM data and driving the GATE (v8.1) / GEANT4 (v10.3.3) environment. For simulations within the patient anatomy, LET and dose were scored in a 2 mm³ grid with the number of histories selected to achieve an approximate uncertainty of 1.2% GY$_{RBE=1.1}$ within the high dose region [144]. The clinical beam model for the Varian ProBeam delivery system at The Christie Proton Therapy Centre was used for simulation on patient anatomy [143].

Simulation settings for the simple geometries and PBT treatment plan were chosen to closely match the validated GATE settings applied in AUTOMC [143]. This includes the use of the ‘QGSP_BIC’ physics list with a sole non-default production cut specified for electrons (5 mm within the MC world and 0.1 mm within the patient). More information on MC settings can be found in [143]. All simulation output in the current study was processed using Python (v3.6) and the following python packages: NumPy [147] (v1.18.1), SciPy (v1.4.1), Suspect (edited v0.3.9), Nibabel (v3.0.0) and PyDicom (v1.3.0).

### 4.2.2 Scoring Parameters

#### 4.2.2.1 Absorbed Dose: Absorbed dose to water was obtained using the scorer within GATE to calculate absorbed dose to medium and the conversion method described in [94].

#### 4.2.2.2 LET: The LET scorer within GATE was used to obtain the LET scorings of LET$_d$, LET$_t$ and LET Spectra. This scorer uses the GEANT4 method ‘GetElectronicStoppingPowerDEDX’ as described in [82,83]. All LET values are scored to water and include only protons (primary and secondary) by using settings...
within the GATE scorer. Further details on LET definition can be found in previous work [157].

LET spectra was calculated in 49 bins by applying a series of energy filters to the LET actor within GATE. The LET-energy conversion was handled using the GATE lookup table. A higher resolution was selected between 1 - 8 keV μm⁻¹ to appropriately cover the greater change in frequency. The selection of the total number of bins was a compromise in the AUTOMC system between bin resolution and simulation time. In comparison to an averaged LET distribution, memory requirements were 50 times greater and the simulation time was approximately three times greater. However, an LET spectra scorer directly encoded within GATE may lead to significant improvement in computational requirements.

4.2.3 Patient Data and Consent.

The selected case is a PBT nasopharynx patient treated with four treatment fields and a target volume containing soft tissue, bone and cavities. This case was chosen as both the field arrangement and tissue inhomogeneity may result in complex LET spectra.

The PBT treatment plan in this work was previously treated at The Christie Proton Beam Therapy Centre as part of a nasopharynx patient’s treatment. This plan was designed following Christie clinical protocols with appropriate patient-specific QA.
4.3 Results

Figure 4.1: (A) Absorbed dose, dose-averaged LET ($\text{LET}_d$) and track-averaged LET ($\text{LET}_t$) for the pristine Bragg peak geometry. (B) Absorbed dose, $\text{LET}_d$ and $\text{LET}_t$ for the simple Spread Out Bragg Peak (SOBP) geometry. (C) Field arrangement schematic for complex Spread Out Bragg Peak (SOBP). (A1-A3) LET spectra at three depths in (A). (B1-B3) LET spectra at three depths in (A). (B1-B3) LET spectra at three depths in (B). (C1-C3) LET spectra at three depths in (C).

(A), (B): Absorbed dose, $\text{LET}_d$ and $\text{LET}_t$ are shown in black, blue and red, respectively. Dose is in the form of an Integral Depth Dose (IDD) with $\text{LET}_d$ and $\text{LET}_t$ averaged across the same area. Numbers on graphs relate to the position of the corresponding LET subfigure.

(C): The SOBP direction and SOBP dose plateau is shown by the black arrow and the blue shaded area, respectively

(A1-A3), (B1-B3), (C1-C3): $\text{LET}_d$ and $\text{LET}_t$ are shown by dotted and dashed lines, respectively. Absorbed dose in each voxel is shown in the bottom right hand corner of each subfigure.
4.3.1 Radiobiology Experiment Geometries

Figure 4.1 shows absorbed dose, \( \text{LET}_d \) and \( \text{LET}_t \) for the pristine Bragg peak and simple SOBP geometries (Fig 1A & B) with the field arrangement shown for the complex SOBP geometry (Fig 4.1C). The absorbed dose is an Integral Depth Dose (IDD) with \( \text{LET}_d \) and \( \text{LET}_t \), averaged across the plane perpendicular to the beam direction for the same area. Three 2 mm\(^3\) CAX voxels are also shown for the pristine, simple SOBP and complex SOBP geometries in Fig 4.1 C1-C3, B1-B3 and C1-C3, respectively. These voxels are representative of their geometries as a whole and have been selected to demonstrate how similar averaged LET values may result in different underlying spectra.

For the pristine Bragg peak (Fig 1A), the change of LET spectra is caused by the initial monoenergetic protons reducing in energy, and thus increasing in LET, and energy straggling. This is seen from Fig1A1-A3, where the LET distribution at a depth of 60 mm is very narrow with low LET to the LET distributions at a depth of 154 mm where the LET had increased along with distribution spread.

The simple SOBP, shown in Fig 1B, is similar to the pristine case in initial depths despite a polyenergetic field of protons as the range of LET value is still low. This changes at greater depth as energies within the SOBP decrease to form the dose plateau. The two geometries then match each other at the end of range as both share a maximum proton energy of 150 MeV. The complex SOBP (Fig 1C) is formed of four identical SOBPs (shown in Fig 1B) with three arranged perpendicular to the fourth to overlap at a depth of 155 mm at three points. This is designed to produce irregular LET spectra, as expected to occur in patient treatments.

In comparing the LET spectra selected for each geometry, it is clear equal values of LET may have considerable differences in underlying LET spectra. This is seen for both averaging methods, \( \text{LET}_t \) and \( \text{LET}_d \). Before the end of range in the pristine Bragg peak and simple SOBP cases, the simple SOBP has a greater spread of LET for a matched LET value with a tail of higher LET values. It is this difference which is theorised to cause the different RBE-LET relationships between in vitro pristine and SOBP data [22,25]. This is demonstrated in Fig 1A2 and Fig 1B3 where the same \( \text{LET}_t \) (~2 keV \( \mu m^{-1} \)) is obtained with the pristine and SOBP obtaining a range of 1 – 3 keV \( \mu m^{-1} \) and 1 – 8 keV \( \mu m^{-1} \), respectively. The complex SOBP also obtains ~2 keV \( \mu m^{-1} \) with a bi-modal distribution of a similar range to the simple SOBP case. The same is demonstrated for \( \text{LET}_d \) in Fig 1 A3, B3 and C1, where \( \text{LET}_d \) is approximately 3.8 keV \( \mu m^{-1} \) for each geometry with a substantially different LET distribution. In this case, the pristine Bragg peak geometry has a greater range of LET values compared to the simple SOBP geometry (1.9 – 10 keV \( \mu m^{-1} \) vs 1.6 – 8 keV \( \mu m^{-1} \)). For the complex SOBP, a completely separately bi-modal distribution of a smaller range acquires a matched LET to the other 2 geometries.
As shown previously in the literature [72], the ratio between LET$_t$ and LET$_d$ is not monotonic and thus not an ideal single value measure of the LET distribution. This is also the case for the absolute difference between LET$_t$ and LET$_d$ value.

4.3.2 Patient Case

Figure 4.2 shows contours, absorbed dose and LET$_t$ for a nasopharynx PBT patient along with LET spectra at three selected voxels. The three selected voxels are representative of the LET spectra across the patient.

The LET spectra shown in Fig 2C1 is typical of the voxels within the entrance region around the target. It is similar to the entrance region of the pristine Bragg peak and simple SOBP geometries (Fig 1A1 & B1) except for a small tail of higher LET. This is caused by the end of range of fields travelling from the other side of the target. For this selected voxel, this tail extends from approximately 2 - 4 keV μm$^{-1}$ and is similar to the tail range seen in the entrance voxel of the complex SOBP, albeit without a bimodal distribution. The second selected voxel shown in C2 is typical of the spectra for the voxels within the PTV and higher dose regions (>80% of maximum dose). Here, the LET$_t$ is similar to the second point for the pristine Bragg peak (Fig 1A2) but with substantially different underlying spread of LET values (0.8 – 10 keV μm$^{-1}$ against 1.8 – 3.0 keV μm$^{-1}$). The third selected voxel, shown in Fig 2C3, is in a high LET area within the >10% isodose region. At this voxel and neighbouring voxels, the LET distribution is bi-modal and similar to those seen in the complex SOBP geometry (fig 1C). This occurs in a relatively high LET area where there are concerns over increased RBE.
Figure 4.2: Clinical proton beam therapy plan for a nasopharynx patient. (A) Contours. (B) Absorbed dose. (C) Track-averaged LET ($\text{LET}_t$). (C1-C3) LET spectra for selected voxels in (C).

(A): High dose and low dose target volumes are shown in dark and light red, respectively. The brainstem and temporal lobe contours are outlined in white. (A), (B), (C): Field directions are shown by white arrows and positions of selected voxels for LET spectra analysis are shown by numbers. (B), (C) Maps are windowed to 2% of the maximum dose in the plan.
4.4 Discussion

LET remains a focus within the PBT community after several decades of research on the RBE-LET relationship [158]. Currently, this research has only had a minor effect on clinical treatments with LET still not included in the routine practice of PBT treatments. This may change over the next decade as the clinical evidence for LET continues to build [42,43,47]. However, there are several issues to resolve before incorporating LET into clinical proton treatment planning. One issue is whether an averaged LET factor is sufficient or the LET spectra should be utilised in clinical practice as it is with heavier ion treatments [159].

In this work, LET spectra was calculated for a series of watertank geometries and a clinical proton treatment plan. The watertank geometries of differing complexity demonstrated that similar values of LET\(d\) and LET\(t\) may have considerably different underlying spectra (Fig 1). It has previously been postulated that underlying differences in LET spectra might cause different biological effects between Bragg peak and SOBP irradiations [22,25] and to cause LET\(d\) to cease to be a reliable predictor of biological effect [81]. Our results demonstrate how the LET distributions occurring in PBT treatment plans are substantially different to those in pristine and simple SOBP geometries. This is in both the spread of LET values and in spectral shape, with bi-modal distributions arising for the patient case. If the RBE-LET relationship is significantly non-linear, there may be a detrimental effect in applying an averaged LET instead of LET spectra when incorporating LET. Further to this, it was shown that similar complex distributions occurring in the patient plans can be produced in relatively simple setups (Fig 1 C-C3). Also, it appears a LET ratio (LET\(d\) / LET\(t\)) or LET subtraction may not work as a measure of LET distribution spread due to a non-monotonic relationship for either parameter.

From the literature, it is not yet clear whether an averaged LET is a sufficient parameter for predicting biological effect. It is likely its sufficiency will be based on the use case; a simple linear RBE model may be acceptable for optimising a treatment plan while a non-linear RBE model may be required for predicting biological effect, especially for different endpoints. Based upon these results, the authors suggest LET spectra is considered when LET is applied in constructing an RBE model intended to be used in complex fields such as those in clinical treatment plans. If radiobiological models are to be applied in clinical plans, they must ensure they can accurately predict biological effect outside of narrow LET distributions such as those seen in Fig 1 C1-3 and Fig 2 C3. To the authors’ knowledge, there are no current proton RBE models which have validated their results in cases such as those. An \textit{in vitro} experiment with a similar setup to the complex SOBP (Fig 1 C1) in this work may be able to achieve this.
4.5 Conclusion

This study has shown that while \textit{in vitro} data and proton patient plans may obtain similar values of averaged LET, the underlying LET spectra may be considerably different. We believe this work can contribute to the discussion regarding the use of averaged LET and LET spectra within clinical proton therapy. It is important proton RBE models are validated against ‘real world’ LET spectra rather than narrow LET distributions.
5. Other Related Work

5.1 Literature

Major co-author contributions to published literature in the course of the PhD are shown below with summary of contribution. This includes published literature as well as manuscripts currently in review or preparation.

5.1.1 Published Literature


Contribution: I selected the clinical patient case for relevance of the work and designed and ran the MC simulations needed to obtain the parameters for the model. I also provided advice on how to ensure the model can be scaled from the DNA level to the patient level. I read and provided feedback on the manuscript.


Contribution: I provided advice and discussion on the clinical relevance of the models and read and provided feedback on the work and manuscript.


Contribution: I formulated the Christie standard for LET featured in this paper (the stated LET definition preference made in Chapter 3 of this thesis). I designed and ran simulations for The Christie proportion of this work and contributed to guiding the direction of the article. I read and provided feedback on the manuscript.

   Contribution: I provided a clinical viewpoint on the state of proton beam therapy and which benefits may benefit from this emerging treatment. I read and provided feedback on the manuscript.


   Contribution: I wrote entries for the following sections in the Encyclopaedia of Medical Physics II Edition: Carbon Ion Therapy, Degraders, Distal Edge Tracking, Ionisation Density, Magnetic Beam Steering, Pion Therapy, Track Structure. The contribution for Track Structure was highlighted in this article. I read and provided feedback for the article before publication.

5.1.2 Under Review Literature


   Contribution: I selected the patient case appropriate for the work and designed and ran the patient MC simulations required for the work. I provided feedback on the design of the study and provided feedback on the manuscript.


   Contribution: I designed and ran MC simulations required for all PBT plans in the work. I gave guidance from the beginning on study design including patient selection, RBE model selection and presentation of results. I read and provided feedback during the manuscript writing process.
5.2 Major Presentations

Major presentations given in the course of the PhD are shown below with summary of contents. These include both oral and poster presentations and are defined as those given outside of University of Manchester and The Christie Hospital, UK.

5.2.1 Completed Oral Presentations


Title: Biologically Relevant Predictions for Proton Beam Therapy from In-Silico Modelling and the Relevance to Treatment Planning

Summary: This conference is aimed at researchers using the GEANT4 software for medical applications. This 15-minute presentation covered early work on applying the MM model at the patient level. This work is detailed in Chapter 2.


Title: ‘Biologically Relevant Predictions for Proton Beam Therapy from In-Silico Modelling and the Relevance to Treatment Planning’

Summary: This workshop is aimed at researchers working on subjects related to PBT with a focus on work occurring within the UK. This 15-minute presentation covered early work on applying the MM model at the patient level. This work is detailed in Chapter 2.

[3] Rigshospitalet Lecture, 2020, Copenhagen (Denmark)

Title: ‘LET in Proton Beam Therapy’

Summary: This two-part one hour invited talk was delivered at the Rigshospitalet in Copenhagen to medical physicists and clinicians involved in PBT. The first part covered applying RBE models in proton therapy including the work detailed in Chapter 2 on using the MM model at the patient level and how it compares to common proton phenomenological models. The second half of this lecture covered the variation in LET definitions at use and how they affect proposed clinical metrics. This second half outlined the early work detailed in Chapter 3.
[4] Öresund Workshop on Radiotherapy, 2020, Helsingborg (Sweden)

Title: ‘Biological uncertainties for pediatric patients with mediastinal Hodgkin lymphoma treated with proton therapy’

Summary: This workshop is held annually for Danish and Swedish researchers, clinicians and clinical medical physicists working in radiotherapy. This 15-minute talk was co-delivered and presented the early work on the implications of variable RBE on paediatric patients with mediastinal Hodgkin Lymphoma. My portion of the talk covered the RBE model, MC simulations and LET in the work. This work is detailed in the manuscript ‘Proton LET and variable RBE for pediatric patients with Hodgkin lymphoma’ which is currently in preparation for submission.

[5] ART-NET Proton Monte Carlo Conference, 2020, Online

Title: ‘Different LET Flavours in Clinical Proton Beam Therapy’

Summary: This online conference was aimed for those working involved with ART-NET, a CRUK funded network of eight radiotherapy research institutions. This 15-minute talk covered work on the different LET definitions at use in PBT. It partially covered the work detailed in Chapter 3.


Title: ‘LET in Proton Therapy: An Overview of My Work’

Summary: This 40-minute online invited lecture was given to clinical scientists and clinicians at the UCLH proton centre. This talk detailed my work on the MM model, LET definitions and LET spectra. This covers Chapter 3, 4 and 5 of this thesis.

[7] PTCOG 59 Taipei / Online, 2021, Online (Due to COVID)

Title: ‘Potential effects due to variation in linear energy transfer definition and calculation method’

Summary: PTCOG 59 was the 2021 annual conference Particle Therapy Co-Operative originally to be held in Taipei, Taiwan but held online due to COVID
travel restrictions. I originally won a travel award to attend this conference. This 15-min presentation covered the early stages of the work detailed in Chapter 3.

5.2.3 Completed Poster Presentations

[8] PTCOG 58, 2019, Manchester (United Kingdom)

Title: ‘Biologically Relevant Predictions for Proton Beam Therapy from In-Silico Modelling and the Relevance to Treatment Planning’

Summary: PTCOG 58 was the 2019 annual conference Particle Therapy Co-Operative held in Manchester, UK. This poster covered work detailed in Chapter 2.

5.2.2 Future Presentations

[9] Engineering and Physical Sciences in Medicine (EPSM), 2022, Adelaide (Australia)

Title: ‘Potential effects due to variation in linear energy transfer definition and calculation method’

Summary: EPSM is the Engineering and Physical Sciences in Medicine conference held annually in Australia. This work will be presented as a poster.

[10] Engineering and Physical Sciences in Medicine (EPSM), 2022, Adelaide (Australia)

Title: ‘Relevance of Linear Energy Transfer Spectra in Models of Biological Effect for Clinical Proton Beam Therapy’

Summary: EPSM is the Engineering and Physical Sciences in Medicine conference held annually in Australia. This work will be presented as an oral talk.
6. Conclusion

6.1 Summary of Work

Despite sustained interest in variable RBE within the PBT community, there has been little movement in incorporating variable RBE into clinical practice over the last few decades. A constant RBE of 1.1 is still applied in the proton clinic even with a substantial body of in vitro data and a growing body of in vivo studies. This lack of movement is partially due to no definitive clinical evidence that a constant RBE is causing a detrimental effect and also a lack of consensus on how variable RBE should be handled. To move towards replacing the use of a constant value, further clinical and transitional research is required to properly study the clinical impact and develop radiation biology modelling. In the meantime, incorporating the physical parameter of LET, with its ease of calculation and strong in vitro evidence base, may provide a stepping stone to a fuller account of variable RBE.

The work in this thesis aims to aid the introduction of LET into standard PBT treatment planning as part of a larger process of a full account of variable RBE. This aim includes studying how different approaches to RBE models may vary in their predicted biologically-weighted dose, how the different definitions of LET may affect the outcome of variable RBE models and other proposed clinical metrics, and to build a consensus for a type of LET.

In Chapter 2, we extend previously published correlations on residual and misrepaired DSBs to RBE correlations and, for the first time, apply these to a clinical PBT plan. These results are compared against common methods of estimating variable RBE in PBT; the LQ-based McNamara model and the LET-weighted dose model. We found the models to be generally comparable with the MM model predicting higher doses. A roadmap is plotted for improvements for the MM model to reach more clinically relevant endpoints.

In Chapter 3, we gathered from the literature a range of common LET definitions in categories such as averaging, particle inclusion, scoring and hit type / MSS settings. These LET definitions were calculated on a range of clinical PBT plans for a range of common sites and processed through proposed clinical metrics such as LVHs, qualitative analysis and maximum and mean values. Our results highlighted the need for careful understanding of the type of LET to use and the need to achieve a greater consensus on which LET to select. This work concluded by advocating a LET standard of dose-averaged LET scored to water for primary and secondary protons with a random hit type and automated MSS.

In Chapter 4, LET\_t, LET\_d and LET spectra were calculated for a series of watertank geometries and a clinical PBT plan. The simple geometries in the watertank cases demonstrated that similar values of LET\_d and LET\_t could be obtained with considerably different underlying spectra. It was shown that while in
vitro data and proton patient plans may obtain similar values of LET$_d$ and LET$_t$, the underlying LET spectra may be different with no unique single value parameter describing it.

In Chapter 5, the contribution to co-authored publications related to the use of LET or variable RBE in PBT, as well as conference communications, are detailed. This work helps to increase consensus on LET and RBE in the wider proton therapy community. In the end, to reach a consensus within the field, and to eventually reach the widespread introduction of LET and RBE into the clinic, the community at large needs to work together.

6.2 Overall Contribution

Overall, the chapters in this thesis can be viewed as a practical attempt to resolve some of the major issues blocking the use of a variable RBE model in proton treatment planning. These models have been proposed for nearly two decades but still find no routine use in clinical proton therapy. With growing clinical evidence and substantial in vitro evidence, the PBT community is in need of both practical shorter-term approaches and also wider approaches towards the ideal, a multi-parameter multi-endpoint variable RBE model.

Chapter 2 focuses on the latter longer-term approach by comparing a mechanical model to the more common phenomenological RBE models. This is the first known work to compare these different types of models directly on clinical proton plans and to highlight the potential advantages the lesser common mechanical models have. Via a ‘proof of concept’, this work aims to increase interest in mechanical models as path to a more comprehensive variable RBE model.

Chapter 3 is orientated towards the practical steps of including some component of variable RBE within the treatment planning process. There is a multitude of choice in LET definition and clinical methodology with little knowledge in the community of how this affects clinical application. While the paper does not introduce a new definition, metric or technique, it is the first known work to compare the most common LET types and methodology on the wide range of clinical proton plans. This may serve as an educational resource as well as an important step towards needed consensus on how to apply these metrics.

Chapter 4 aids both short- and long-term approaches to variable RBE. Averaging of LET is applied in the vast majority of literature with limited studies investigating the underlying LET spectra. An understanding of LET spectra is important to applying LET to clinical plans as well as building complex variable RBE models. To the author’s knowledge, this is the first work in the literature highlighting the LET spectra differences in the radiobiology experiments used to create RBE models and the treatment plans in which they aim to be applied in.
These chapters are not a complete solution to an improved account of biological effect in PBT. However, combined with the co-authored papers and conference communications outlined in Chapter 5, they may contribute to the body of literature and increase knowledge in the community.

6.3 Further work

There are multiple routes to extend the work in this thesis and further aid the introduction of LET and variable RBE into routine PBT clinical practice. Currently in the uncommon cases of necrosis, clinicians at The Christie Proton Centre request retrospective analysis for any correspondence between the location of the necrosis and any region of high dose and/or LET. However, this analysis is not routine for patients without toxicity. Ideally, an automated system would calculate the advocated LET definition (Chapter 4) on each PBT patient plan and the LET distribution would be stored as part of the patient record. This work would naturally lead to an image change study, as discussed in ‘1.3.3 In Vivo Evidence’. Despite the existence of other image studies, it is important to run studies locally to account for differences between centres for standards of care and protocols, population differences and delivery methods. With the severity of brainstem necrosis, ependymoma and similar sites would be the first target for such work.

In tandem with the automated LET calculation and image change study, further work is required to reach a standard protocol and statistical analysis across the PBT centres around the globe. One recent review found that after accounting for differences throughout the literature, clinical evidence for variable proton RBE remains statistically weak at present with larger patient cohorts required [160]. Patients from multiple centres will need to be pooled together to reach the required patient cohort sizes. Before the image study at The Christie is formulated, care should be taken to standardise with other proton centres on physical parameters, statistical analyses, imaging and patient site.

Finally, once LET is routinely calculated, there are many studies on the practicalities and effect of doing so. Currently, without LET calculation, planners are often mindful of its existence when placing fields and optimising dose distributions. An analysis on the effect of giving LET distributions to treatment planners would be welcome to understand if and how clinical decision-making has changed. This extends to how LET fits in with other key research areas in PBT such as robustness, range uncertainty and interplay.
7. References


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