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PHAS0097 Literature Review and Project Outline

Design of a Detector for Fast Treatment Plan Verification in Proton Radiotherapy

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1 Cancer: Biology, Diagnosis and Treatment

R. W. Ruddon defines cancer as an abnormal growth of cells caused by multiple changes in gene expression leading to a dysregulated balance of cell proliferation and cell death [1]. Cancer continues to serve as one of the most feared human diseases; according to Cancer Research UK [2], in 2016 there were 163,444 deaths from cancer in the UK and each year there are more than 360,000 new cancer cases. 1 in 2 people in the UK born after 1960 will be diagnosed with some form of cancer in their lifetime.

Biological cells naturally undergo division via mitosis or meiosis as part of their life cycle [3]. Mutations in cellular genetic code can be introduced in these delicate processes, typically as chromosomal mutations and point mutations [4]. With sufficient growth of such abnormal cells, a tumour develops, classed as either being benign or malignant [1]. Benign tumours are considered to be less dangerous than malignant tumours; as the latter is capable of disseminating mutated cells throughout the body, through metastasis. In 2000, Weinberg and Hanahan defined the six hallmarks of cancer, which were updated in 2011 with the addition of four others [5, 6]. These are:

1. Self-sufficiency in growth signals
2. Desensitisation to anti-growth signals
3. Evasion of apoptosis (cell death)
4. Angiogenesis
5. Indefinite cell division
6. Metastatic capacity
7. Abnormal metabolism
8. Evasion of immune system
9. Inflammation
10. Genomic instability

Diagnosis of cancer is typically done after indication of the disease from one or a combination of the following: screening tests, medical imaging and the appearance of symptoms [7]. Imaging can be performed in several ways: X-ray imaging, computerised tomography (CT) imaging, magnetic resonance imaging and nuclear medicine [8]. Treatment for cancer broadly falls into three categories: palliative, curative and preventative [9]. Palliative treatments seek to relieve the symptoms of cancer; curative treatment methods aim to eliminate the cancer completely; and preventative treatments attempt to reduce the risk of cancer recurrence. The main curative methods are:

1. Surgery – the excision of a solid tumour from the body. Whilst effective, it can only be used for tumours that are localised and accessible via surgical methods.

2. Chemotherapy – the use of cytotoxic agents to interfere with mitosis in non-specific cells [10]. An effective form of treatment, but significant side-effects occur in the vast majority of patients due to damage to both healthy and cancerous cells. This method is often used in conjunction with other, more localised treatments.

3. Radiotherapy – This treatment seeks to initiate apoptosis in cancerous cells by disrupting cell DNA with ionising radiation, and minimising the dose delivered to healthy cells. Whilst more localised than chemotherapy, the delivery of radiation to healthy cells can cause carcinogenesis [11]. As the method is non-invasive, it is highly useful for the treatment of inoperable tumours. Both internal and external methods exist, the latter is more typical and broadly comes in two forms: X-ray radiotherapy and proton radiotherapy.

2 X-Ray Radiotherapy

X-ray radiotherapy delivers ionising radiation with high energy photons. Although photons themselves possess no electric charge and therefore cannot ionise matter directly, they can deposit energy onto other particles, giving rise to free, energetic, charged particles along their path. Photons primarily lose energy via three mechanisms [12]:

1. The photoelectric effect: the excitation and liberation of electrons in atoms through direct collision with energetic photons.

2. Compton scattering: the deflection of photons off electrons, transferring energy in the process.

3. Pair production: at sufficient energies and in the electric field of an atomic nucleus, photons can produce electron-positron pairs.

Photon energy loss in a medium follows an exponential relation with the depth of the material:

$$I = I_0 e^{-\mu x} \tag{1}$$

where I is the intensity at depth x, I_0 is the initial intensity and μ is the attenuation coefficient, a description of the probability of interaction per unit length of a photon traversing a medium. This relation is visualised in Fig. 1. The dose is defined as the quantity of energy deposited by ionising radiation in

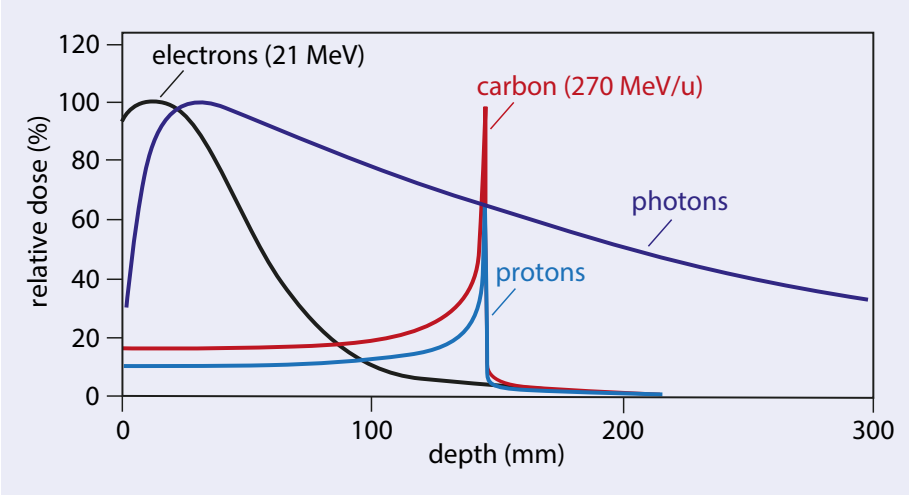

Figure 1: The variation of delivered dose with depth for several types of radiotherapy. The dose delivered by photons gradually decreases with depth, whereas the dose from protons culminates in a Bragg peak. Source: [13]

a medium, per unit mass, measured in grays (Gy) [11]. The purple line in Fig. 1 shows that, after a short initial build-up period, there is a peak in the dose deposition followed by an exponential fall off. Only a fraction of the full dose is delivered to the tumour itself, with a non-negligible amount delivered beyond the tumour. Such behaviour is undesirable: to deliver a sufficient dose to deep tumours, significantly more damage will have to be done to healthy tissues: if the tumour is close to sensitive organs (as is often the case with inoperable cancers), the non-negligible tail can result in serious side-effects for the patient post-treatment [14].

3 Proton Radiotherapy

Protons follow different mechanisms of energy loss within a medium, which gives rise to significantly different dose deposition properties when compared to photons. Protons primarily lose energy through electromagnetic interactions with the electrons of atoms in a medium. This is described by the Bethe-Bloch equation [15]:

$$\left\langle -\frac{dE}{dx} \right\rangle = Kz^2 \frac{Z}{A} \frac{1}{\beta^2} \left[\frac{1}{2} \ln \frac{2m_e c^2 \beta^2 \gamma^2 W_{max}}{I^2} - \beta^2 - \frac{\delta(\beta\gamma)}{2} \right] \tag{2}$$

where E is the energy, x is the depth, Z is the atomic number of the medium, A is the mass number of the medium, z is the charge of the incident charged particle,

I is the mean ionisation potential, W_{max} is the maximum kinetic energy transfer upon collision of a particle with an electron in the medium, c is the speed of light in a vacuum, m_e is the mass of the electron, $\beta = \frac{v}{c}$, where v is the velocity of the particle, and $\gamma = \frac{1}{\sqrt{1-\beta^2}}$ is the Lorentz factor. $K = 4\pi N_A r_e^2 m_e c^2$, where N_A is Avogadro's number and r_e is the classical electron radius. $\delta(\beta\gamma)$ is a density correction term.

Protons also interact via multiple Coulomb scattering (the deflection of protons from atomic nuclei) [16] and inelastic collisions (also with atomic nuclei, to create high energy ions, neutrons and protons as products) [17]. These processes are important in medical applications but contribute much less to the overall dose deposition than electron interactions. The $\frac{1}{\beta^2}$ term in (2) has the impor-

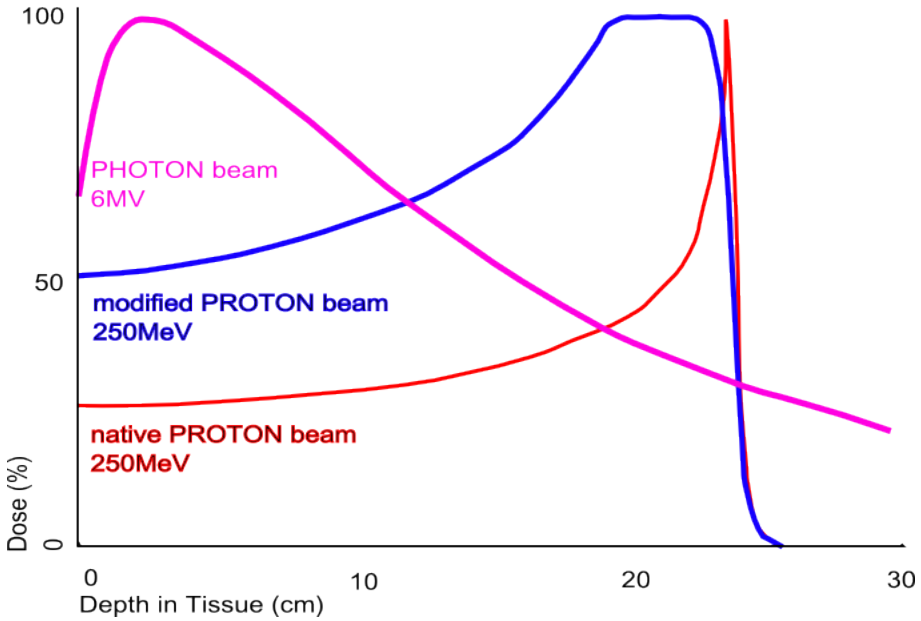

Figure 2: The delivered dose by superimposing several Bragg peaks from protons of different energies. Standard proton and photon dose variation is shown for comparison. Source: [18]

tant effect that the energy lost by the proton increases the slower the proton travels. Therefore, the finite range of protons allow for a highly concentrated dose to be delivered to a very specific region, i.e. wherever the proton stops in the medium. The depth the proton reaches before stopping can be controlled by adjusting the beam energy. Another attractive feature is the fast drop-off of the tail when the proton comes to a stop. This characteristic "Bragg peak" is visualised in Fig. 1 as the light-blue line. By utilising multi-energetic proton beams, several Bragg peaks can be superimposed to deliver consistently high

dosage to a localised area, whilst retaining the desirable low doses to other regions [19]: this is known as a "Spread Out Bragg Peak" (SOBP) and is shown in Fig. 2.

This behaviour makes proton therapy an attractive alternative to photon-based radiotherapy: a large dose can be delivered to a tumour, with significantly less collateral damage to healthy tissue. In addition, proton radiotherapy typically offers 60% less total integral dose compared to photon radiotherapy, thus making it optimal for treating paediatric patients, who are more susceptible to the side-effects of radiation [20]. However, this introduces new technical difficulties. The highly-localised nature of the dose deposition requires that the beam be delivered accurately, with very little margin for error. If the beam is delivered incorrectly, cancerous tissue may receive no dose at all (under-shooting), or healthy tissue may receive the full dose instead (over-shooting). Given that radiotherapy treatments are often used for tumours near vulnerable parts of the body, an incorrectly delivered dose could lead to devastating effects for the patient. This necessitates the need for treatment plan verification, otherwise known as patient-specific quality assurance (QA).

4 Treatment Plan Verification

A patient's treatment plan is defined as the sequence of proton beams that have been determined to be the best option for treating the patient. A patient will first undergo a CT scan to map the part of the body undergoing treatment. A treatment planning system then formulates the treatment plan by converting this CT scan into relative proton stopping powers, which is the energy lost by a charged particle per unit distance in a medium. This is typically done via analytic pencil-beam dose calculation algorithms to project the range of protons based on the water-equivalent depth in the patient [21]. The use of CT scans to formulate the treatment plan introduce an uncertainty of 1-3 mm in the location of the Bragg peak, due to the differences in the interactions of photons and protons in the medium [22]. Other uncertainties include those from CT noise, resolution and artefacts. Thus, a treatment plan must be verified to determine whether the range and dose predictions for the proton beams are correct within an acceptable uncertainty.

The calculation can be verified by repeatedly delivering the treatment plan to a water tank dosimeter, water phantom, or other detector formed of layers of ionisation chambers interspersed with water-equivalent material [23]. This process is typically very time- consuming, as the entire volume of the water phantom must be scanned piece-wise with measurements being made each time of proton energy and position. After each measurement, the dosimeter is moved to a new position within the water volume and the treatment plan is then redelivered. This process repeats until the entirety of the volume is scanned,

taking valuable time away from actual patient treatment. This project focuses on the development of a detector that is intended to significantly shorten the verification process from more than an hour to just a few minutes.

5 The Project

It is proposed that the development of a sufficiently small, sufficiently fast, single module calorimeter attached to the nozzle of a proton beam can yield fast, accurate measurements of proton energy (and therefore depth). If coupled with a 2D tracker, providing the positions of proton hits in 2D, complete information required for treatment verification of the dose distribution of proton beams could be obtained. As energy is directly correlated to depth, a 3D dose distribution could be provided by matching hits recorded in the tracker and the calorimeter. In such a device, the plastic scintillator serves as the water equivalent material and if mounted onto the nozzle of the proton beam, the detector would rotate with the clinic gantry, eliminating the need for realignment. This method could significantly improve the time taken to complete patient-specific QA as the treatment plan would not have to be delivered repeatedly between piece-wise measurements.

The University College London (UCL) Proton Beam Therapy Group is currently developing a single-module calorimeter using technology from the SuperNEMO experiment, which is seeking evidence for neutrino-less double-b decay. Such an experiment requires highly accurate and sensitive apparatus in order to detect low-energy electrons against a strong background of g-rays, fulfilling the requirements of fast, accurate data collection. The apparatus was also designed with cost-effectiveness and longevity in mind, both of which are highly desirable for medical applications [24]. The single module calorimeter prototype consists of a 3 cm $\times$ 5 cm $\times$ 5cm plastic scintillator block, a Hamamatsu R13089 photomultiplier tube (PMT), powered by a Caen NDT1470 high voltage power supply, with data collection performed by a Teledyne LeCroy HDO6104 oscilloscope.

This project is conducted in partnership with the Proton Radiotherapy, Verification and Dosimetry Applications (PRaVDA) consortium, who have developed solid-state silicon-based trackers capable of simultaneously detecting several protons in 2D at beam rates of 2.5 MHz to high precision [25]. While primarily intended for use in the development of proton CT techniques to improve treatment planning for proton therapy[1], the tracker can be utilised in conjunction with a calorimeter for treatment plan verification measurements. The tracker, developed by Birmingham University, consists of three layers of

[1]If protons were used instead of photons in mapping treatment areas for patients, many of the uncertainties associated with the differences in particle interactions could be overcome, giving more accurate treatment plans.

silicon strip detectors in each module, that are offset by 60 degrees to each other to form a *x*-*u*-*v* coordinate system, to allow unambiguous 2D measurements of position. Experimental runs will be conducted at Birmingham University using a test proton beam, where a PRaVDA tracker is made available.

The goals of the project are two-fold:

1. Development of analysis tools: Code written by the previous MSci student exists for the analysis of the data output from the LeCroy oscilloscope. Written in C++ and utilising CERN's ROOT data analysis framework, the code is designed to extract the energy spectrum of thousands of protons recorded in the calorimeter. Extensions to the code have been made to allow analysis of tracker data from PRaVDA and (unsuccessfully) match tracker events to calorimeter events. The planned work seeks to repackage and improve this code to make it more efficient, more powerful, and easier to use.

2. To provide proof-of-principle of the use of a calorimeter and tracker simultaneously to reproduce dose deposition distributions by successfully matching calorimeter and tracker events. Experiments will be held at Birmingham University using a test proton beam to fire protons at the calorimeter and tracker, placed in line of each other and the beam. Collected data will be analysed to extract the energy spectrum of recorded protons, and to pair tracker and calorimeter events to reproduce dose deposition maps. Work conducted by the previous MSci student attempted to do this but was unsuccessful due to a failure to sync clocks between the tracker and calorimeter. Planned work intends to overcome shortcomings by operating detectors on a single clock.

The intended scheme of work is as follows:

1. Learn necessary background and complete literature review (4 weeks).

2. Use sample data to perform basic data analysis, ensuring existing code is functional, and implement new features and improvements (4 weeks).

3. Familiarise with and test UCL single-module calorimeter.

4. 2 or 3 trips to Birmingham university to run experiments with proton beam and take data with single-module calorimeter and tracker.

5. Analyse data taken in experiments (12 weeks including hardware testing and trips).

6. Write final report and prepare presentation (4 weeks).

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