

From cyclotrons to Cancer Therapy: A Physics-Based Simulation of Proton Beam Interactions in Human Tissue

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ABSTRACT

Since 1930, when Ernest Orlando Lawrence first conceived the device, the cyclotron has facilitated numerous achievements in nuclear and medical physics. This paper explores the physical principles behind the device, which uses a perpendicular magnetic field to deflect charged particles in a spiral trajectory and alternating electric fields across semicircular dees to increase their energy. The paper focuses on the applications of cyclotrons in proton beam therapy, where the Bragg Peak property makes protons highly effective at concentrating dose at the tumor and minimising damage to healthy tissue.

The paper presents a computationally light 3D python simulation modelling proton interactions with human tissue, with exploratory and optimising tracks. Fractionated treatment spread across multiple days, as well as one-time treatments can be modelled, helping discern the impact of various parameters such as beam energy, beam energy spread, and breathing motion on the beam range and the number of killed tumor and healthy cells. The optimiser found that 24 fractions, 1.6 Gy dose per fraction, 215 MeV beam energy, 1.2% beam energy spread, and 1.4 cm beam spot size results in maximum tumour cells killed (99.1%) and minimum healthy cells killed.

INTRODUCTION

The cyclotron has revolutionised nuclear and medical physics. The idea was conceived in 1929 by Ernest Orlando Lawrence, one of the founding fathers of the accelerator field (Lawrence, 1951). The device uses alternating voltages provided by an R.F. source and a uniform magnetic field perpendicular to the uniform electric field (Lawrence & Livingston, 1931). Although the notions of accelerating particles and bending their path already existed, Lawrence was the first to suggest combining the two. In 1931, the first cyclotron model was built by Lawrence and Livingston. It was 4.5 inches in diameter and protons could reach energies of 80 keV. Subsequent versions could reach 1 MeV while being 11 inches in diameter (Lawrence & Livingston, 1931).

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Particles' spiral motion in the cyclotron is what makes the cyclotron more advantageous than other particle accelerators: it can achieve high particle energies using relatively less space (Wiedemann, 2015). Cycles of acceleration of charged particles followed by centripetal motion inside semi circular dees creates a spiralling motion and allows the particle to gain enormous amounts of kinetic energy. Thus, the cyclotron helps use a relatively small voltage to impart large energies into charged particles.

As the velocity of the particle approaches the speed of light, however, relativistic effects, as per Einstein's theory of special relativity, lead to mass dilation. The increased mass reduces the orbital frequency; Eventually the particle falls out of phase with the oscillating RF source and is no longer able to accelerate. This necessitated new cyclotron devices that could deal with relativistic effects, such as the synchrocyclotron, isochronous cyclotron, synchrotron and the newest superconducting cyclotron.

The cyclotron has applications in the study of fundamental particles such as muons, atomic nuclei and nuclear reactions. Along with this, it finds greater uses for applied purposes. Cyclotrons are preferred over other particle accelerators for such applications due to their relatively less complicated production and operation, greater reliability, and high energies of the accelerated particle beam produced. The cyclotron has found applications in medical physics. In fact, the primary use of particle accelerators is in hospitals (Peach et al., 2011). Cyclotrons have been used to produce radioisotopes such as fluorine-18 and carbon-11 which are used in Positron Emission Tomography (PET) imaging. Cyclotrons are increasingly used in charged particle therapy (CPT), which uses protons and photons to treat cancer. Proton therapy, unlike other radiation therapy methods, is highly targeted to tumours and so is less damaging to surrounding tissues. Protons have a depth dose curve with a sharp peak known as the Bragg peak, allowing them to deposit most of their energy at the target tumour and minimise dose to surrounding tissues, called the exit dose (Hazem, 2023). Proton beam therapy is the use of protons, which have been accelerated to high velocities using particle accelerators, for delivering targeted doses that damage cancer cell DNA and lead to cancer cell death.

There exist many obstacles to the widespread implementation of cyclotron technologies for proton beam therapy. The primary limitation is range uncertainty, requiring conservative safety margins that hinder tumour coverage. Range uncertainty is the challenge of predicting exactly where the protons stop in tissue. Slight variations in tissue density, collisions with particles, and tumour movement could result in a beam that falls short or goes too deep. Another barrier to the widespread adoption of proton therapy is its high capital and operational cost. Multi-room centres, which are the common set up, require investments greater than \$100-200 million (Brodin et al, 2021; Huang et al, 2023).

Superconducting cyclotrons are a novel variation of the classical cyclotron. They are more compact and have lower cost, helping widen accessibility. Access to proton therapy is also uneven, most centres located in high-income countries. In lower and middle income countries, including regions in Africa, the primary barriers are high infrastructure costs and a lack of technical expertise due to various other healthcare priorities (Eki et al., 2026).

This paper focuses on the acceleration of protons in cyclotrons for cancer treatment applications specifically. The field of cyclotrons is well established and has witnessed minor advancements in the past decades. As a result, most existing literature is decades old. There is a need for a compilation of the concepts enabling the functioning of this device and of the newest advancements in this field. There is also a need for a lightweight, accessible and easy to use modelling software that simulates the interactions of high speed, cyclotron-accelerated protons with human tissue, based on accurate physics theory (Luo et al, 2025).

As its main contribution, the paper will describe a 3D Monte Carlo python simulation modelling the range and dose deposition of a large sample of protons to quantify range uncertainty in targeting protons to tumours of varying depths, as well as tumour coverage in terms of the number of killed tumour cells and healthy cells. It accounts for tissue heterogeneity (differences in density), tumour movement due to patient breathing, bones as obstructions to proton beam path, electronic stopping power, nuclear elastic collisions, as well as nuclear inelastic collisions. It is novel in its combining of modelling, 3D visual representations, and optimizing features on a single lightweight platform. It is also distinct in its ability to model fractionated treatment, considering the intrafraction cell repair. It accounts for tissue heterogeneity (differences in density), tumour movement due to patient breathing, bones as obstructions to proton beam path, electronic stopping power, nuclear elastic collisions, as well as nuclear inelastic collisions. The three main modes of energy loss considered are explained in Section 2, the literature review. Through the simulation, the research question this paper aims to test is: “Which source of uncertainty contributes most to range uncertainty and inefficient tumour coverage by the proton beam, and in what conditions can these limitations be minimised?”

The paper also aims to synthesise vast amounts of literature on cyclotrons, explaining the classical physics principles behind its working, derivations of key formulae, relativistic effects and how they necessitated innovations to the classical cyclotron, as well as a discussion of the properties of protons making them suitable for use in cancer treatment (Peach et al., 2011).

This paper is organised as follows. Section 2 works on the literature review of the paper in which we discuss the physics of classical cyclotrons, working principles of newer types of cyclotrons, properties of protons relevant to their use in proton beam therapy. Section 3 describes the aforementioned python simulation. Section 4 discusses results obtained from the 3D simulation. Section 5 evaluates the simulation. Section 6 concludes the paper with relevant takeaways.

LITERATURE REVIEW

Classical Physics of Cyclotrons

The cyclotron is composed of two hollow, circular metal containers called ‘Dees’ acting as electrodes (Figure 1). These dees are separated by a narrow gap. Next, there are two large dipole electromagnets on

either side of the circular dees, such that there exists a strong uniform magnetic field perpendicular to the plane of dees. Across the gap between dees, a radio frequency voltage is applied. Radio frequency voltage, which can alternate at a frequency from 200 kHz to 300 GHz, is used rather than standard alternating voltage, as its higher frequency enables it to remain ‘in phase’ with the accelerating particle and exert an electric force at the right time (Lawrence & Livingston, 1932).

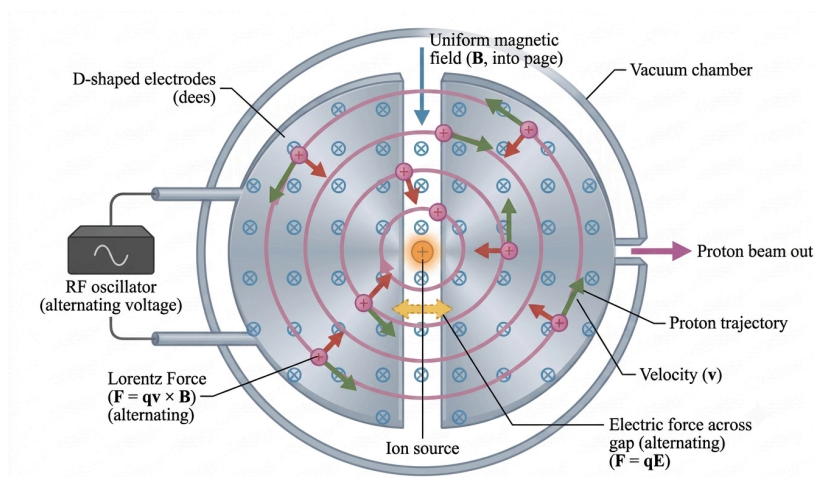


Figure 1 *The Internal Structure of a Cyclotron*

A charged particle, which is capable of facing electric field forces and deflecting under a magnetic field when moving, is injected at the centre of the narrow gap. The particle then faces an electric force, $\mathbf{F}=q\mathbf{E}$. A proton would, for example, accelerate in the direction of the electric field due to its positive charge. It is accelerated across the gap into one of the dees. The dees act as faraday cages, so the electric field inside them is effectively zero (Peach et al., 2011). The moving charged particle then faces a Lorentz force. This force acts perpendicular to the particle’s motion, causing circular motion. The dees and magnet are enclosed in a vacuum, to avoid collisions between the charged particles and air molecules which would lead to a loss of the charged particles’ energy.

Each time the particle reaches the narrow gap, the electric field reverses, and the particle is once again accelerated by the electric field towards the opposite Dee, gaining kinetic energy. It then travels a circular path of greater radius, resulting in a spiral-like trajectory. Once the particle’s path radius roughly equals that of the dees, the particle is extracted out of the device using magnetic deflectors (Lawrence & Livingston, 1932).

Description of formulae and physical concepts

Key formulae and concepts behind cyclotrons are described below. The Lorentz force is the resultant force faced by a particle in an electric and magnetic field. It is given by the sum of electric and magnetic forces (Lorentz, 1895).

F is the Lorentz force acting on the particle, perpendicular to its velocity and the magnetic field, **E** is the electric field acting across the dees, and **B** is the magnetic field between the electromagnets.

$$\mathbf{F} = q\mathbf{E} + q\mathbf{v} \times \mathbf{B} \quad (\text{Lorentz, 1895}) \quad (1)$$

Inside the dees, the charged particle faces no electric field. The Lorentz force faced by the particle of charge q , velocity v , and in uniform magnetic field B is given by:

$$\mathbf{F} = q\mathbf{v} \times \mathbf{B} \quad (2)$$

The force is therefore perpendicular to both the particle's velocity and the uniform magnetic field. For a uniform magnetic field B perpendicular to the particle's velocity, the Lorentz force causes uniform circular motion and centripetal acceleration.

The orbital radius is given by,

$$r = \frac{mv}{qB} \quad (3)$$

It is the radius of the particle's circular path. At non-relativistic speeds in the classical cyclotron, the orbital radius is influenced in a proportional manner only by the particle's velocity.

Equation 4 represents magnetic rigidity. It describes the difficulty in bending a particle's path in the presence of a magnetic field.

$$B\vec{r} = \frac{mv}{q} = \frac{p}{q} \quad (4)$$

with p being the momentum of the particle. This relation implies that particles with greater momenta require stronger magnetic fields to curve around a path of the same radius. In other words, in the classical cyclotron, as the particle gains speed, the radius of its path increases, explaining its spiral trajectory.

The angular frequency, which is the number of rotations of particle in a circular path per second, is given by:

$$\frac{qB}{m} = \frac{v}{r} = \omega_c \quad (5)$$

The frequency of the particle in Hertz is given by:

$$f = \frac{qB}{2\pi m} \quad (6)$$

This is called the cyclotron frequency. Both ω_c and f represent the same mathematical quantity; however, the cyclotron frequency is more useful for matching the cyclotron frequency (the number of turns the particle takes in a second) with the RF voltage across the dees.

Notably, the proton's orbital frequency in the cyclotron is independent of the radius of its path or its velocity when non-relativistic. This means an R.F. voltage of a constant frequency can be applied across the dees and the device would remain in phase with the particle.

Time taken for the particle to complete one rotation inside the dees is:

$$T_c = \frac{2\pi m}{qB} \quad (7)$$

Since the dees are semicircular, the particle completes a half-rotation before reentering the narrow gap in a time $\frac{T_c}{2}$, when the R.F voltage polarity must reverse. Therefore, R.F. voltage frequency is equal to the cyclotron frequency, f .

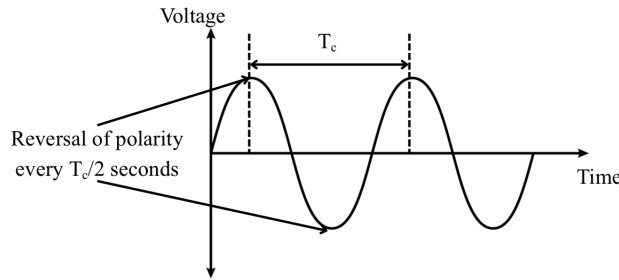


Figure 2 RF voltage over time applied across the dees of a classical cyclotron

The velocity acquired by the particle across the narrow gap is given by (refer to appendix A for derivation):

$$v = \sqrt{v_{initial}^2 + \frac{2qN|E| \cdot d}{m}} \quad (8)$$

Where $|E|$ is the magnitude of the electric field across the dees.

Voltage applied across the dees (V) is the product of the electric field and width of the narrow gap ($V = \vec{E} \cdot \vec{d}$). The cyclotron is designed so that the alternating electric field is perfectly in sync with the accelerating particle. This is such that the voltage of the radiofrequency alternating source is at its peak (V_{peak}) when the particle crosses the gap, providing the greatest possible increase in energy. Since the gap is narrow and the particle has a high speed, the voltage across the gap is effectively V_{peak} .

$$v = \sqrt{v_{initial}^2 + \frac{2qNV_{peak}}{m}} \quad (9)$$

The initial velocity can be assumed to be 0 ms^{-1} , as it would be minimal when injected out of the ion source. Therefore,

$$v = \sqrt{\frac{2qNV_{peak}}{m}} \quad (10)$$

The velocity can also be expressed in terms of magnetic field as:

$$v = \frac{qBr}{m} \quad (11)$$

The kinetic energy of a proton can also be expressed as,

$$T = \frac{q^2 B^2 r^2}{2m} = \frac{Z^2 e^2 B^2 r^2}{2Am_p} \quad (12)$$

The maximum kinetic energy attained by the charged particle inside the cyclotron is given by:

$$T_{max} = \frac{q^2 B^2 r_{max}^2}{2m} \quad (13)$$

Relativistic Effects

For proton beam therapy, a particle must have energies of the order 70-250 MeV (Mohan & Grosshans) to penetrate tissue, requiring speeds from 37% to 61% the speed of light (c). At velocities close to the speed of light, the above equations no longer accurately model the particle as relativistic effects must be considered.

Incorporating the Lorentz factor, the particle's total energy is given by:

$$E = \gamma m_0 c^2 \quad (14)$$

where m_0 is the rest mass of the particle and γ is the Lorentz scaling factor.

The Lorentz scaling factor is,

$$\gamma = \frac{1}{\sqrt{1 - \frac{v^2}{c^2}}} \quad (15)$$

where v is the velocity of the particle. (Lorentz, 1904) The Lorentz scaling factor is multiplied to any quantity carrying a time or space related dimension. The equations are now adapted to below:

The particle's kinetic energy:

The radius of the particle's path:

$$T = (\gamma - 1)m_0 c^2 \quad (\text{Einstein, 1905}) \quad (16)$$

$$r = \gamma \frac{mv}{qB} \quad (17)$$

The cyclotron frequency:

$$f_r = \frac{qB}{2\pi\gamma m} \quad (18)$$

The time taken by the particle to reach the narrow gap: $\frac{T_c}{2} = \frac{\gamma\pi m}{q\vec{B}}$ (19)

Thus, the cyclotron frequency decreases as the particle's velocity increases. This implies that, the R.F. voltage, with its fixed frequency, will no longer be in phase with the particle's motion, and the particle will soon decelerate.

Clearly, either the magnetic field must be increased or the R.F. voltage frequency must be decreased as the particle gains velocity. This necessitated the creation of new types of cyclotrons apart from the classical cyclotron, which can only reach energies up to 24 MeV (Kirsanov et al. 2019).

Newer Types of Cyclotrons

Synchrocyclotron

This type of cyclotron was the first solution to the problem of phase slippage, proposed in 1945 (McMillan, 1945). It decreases the RF frequency as a function of time to remain in phase with the cyclotron frequency. The R.F. frequency is given by:

$$f_{RF}(t) = \frac{f_0}{\gamma(t)} \quad (20)$$

where t is the time since the particle was injected into the device.

A limitation of the synchrocyclotron is that charged particles must be supplied to the device in batches to be in phase with the changing RF frequency, so a continuous beam is not produced (Wiedemann, 2015).

Isochronous Cyclotron

Isochronous cyclotrons are used commonly for proton beam therapy (Wiedemann, 2015). The magnetic field is designed such that magnetic field strength (B) increases with increasing radius (r). This helps maintain the isochronism condition, where a particle takes the same time to orbit one turn, allowing a constant RF voltage to be supplied.

$$B = \gamma(r)B_0 \quad (21)$$

A common way to achieve this is shaping the magnet poles to have hill and valley sectors. The hills allow for a stronger magnetic field due to smaller distance between poles, while valleys weaken the field.

The problem of vertical defocussing. Synchronised particles in a cyclotron have a velocity vector that is exactly perpendicular to the uniform magnetic field and will travel along the midplane for their entire trajectory. However, realistically, the charged particles in a cyclotron are injected with a distribution of directions and speeds. If a charged particle has an angle relative to the midplane, it will continue on that bearing until it collides with a ‘Dee’ as it faces no vertical force. (Figure 3).

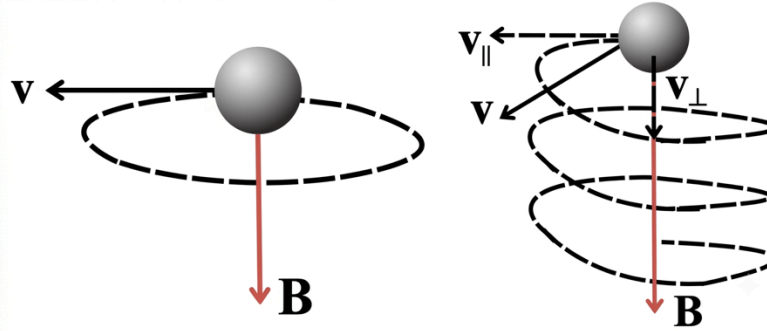


Figure 3 Left: The Path of a Synchronised Charged Particle in a Cyclotron. Right: The Helical path of a Deviating Charged Particle Moving in a Cyclotron.

To combat this, the magnetic poles in classical cyclotrons are slightly tapered on both sides to produce a radial magnetic field component that will lead to a vertical Lorentz force directed towards the midplane (Cyclotrons, 2023) (Figure 4).

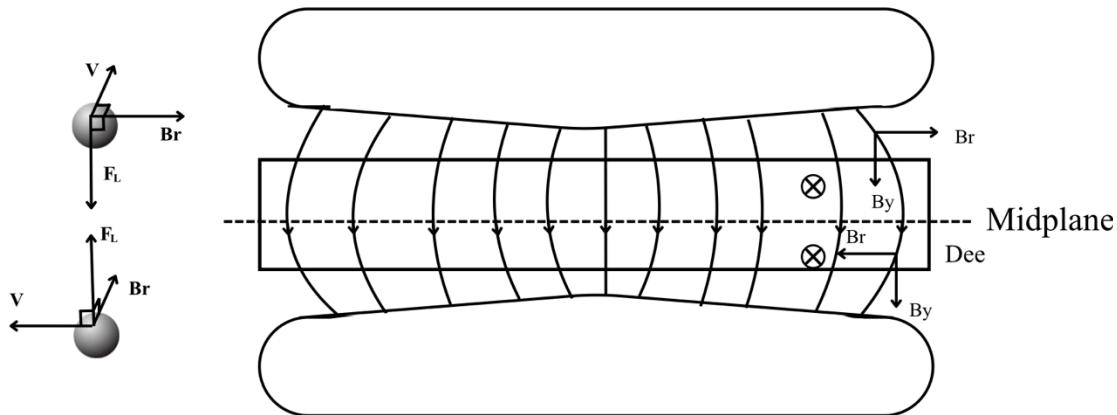


Figure 4 Lorentz Force (F_L) and Radial Magnetic Force (B_r) Felt by Particles Above and Below the Midplane Between Two Slightly Tapered Magnetic Poles of a Cyclotron. Note. The Vertical Lorentz Force, a Restoring Force, is Stronger the Farther a Particle Departs from the Midplane. This Magnetic Field is Known as the Weak Focussing Constant Gradient Magnetic Field.

The magnetic field index (n) describes the rate at which the vertical magnetic field B_z changes with increasing radius. In classical cyclotrons, $n > 0$ due to weak focussing.

$$n = - \frac{R}{B_z} \frac{dB_z}{dR} \quad (22)$$

Classical cyclotrons face a limitation due to vertical focusing. A slightly bent magnetic field means the magnetic field strength B and the vertical magnetic field component decrease with radius. This decreases the cyclotron frequency at non-relativistic speeds and decreases the cyclotron frequency two-fold at relativistic speeds. This therefore limits the speeds to which charged particles can be accelerated in the classical cyclotron before falling completely out of phase. Isochronous cyclotrons address the limitations of relativistic effects and vertical defocusing through a different technique known as strong focusing. Strong focusing helps achieve vertical focusing as well as increase magnetic field with radius to combat relativistic effects. Tapered poles would create a magnetic field that increases with radius ($n < 0$) but would lead to a strong vertical defocusing effect (Figure 5).

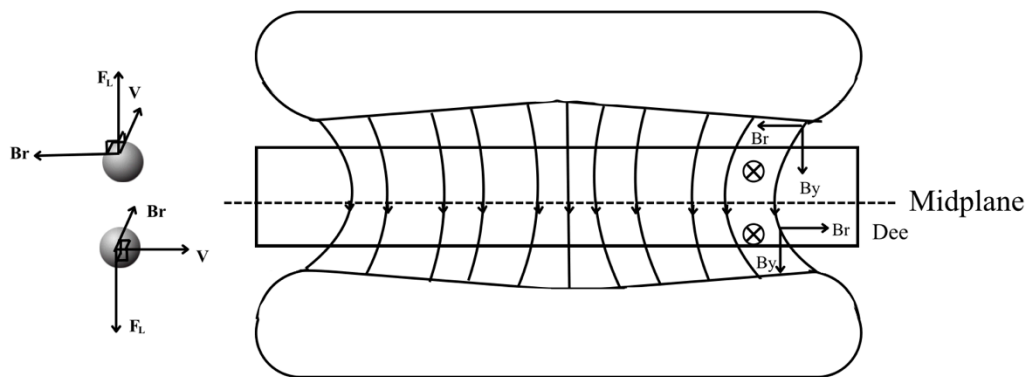


Figure 5 The Magnetic Field Between Two Tapered Magnetic Poles of a Cyclotron, Which Leads to Vertical Defocusing due to Increasing Magnetic Field with Radius.

Instead, azimuthally varying magnetic fields are produced using magnetic pole tips shaped with hills and valleys, creating areas of high and low magnetic fields (Figure 6).

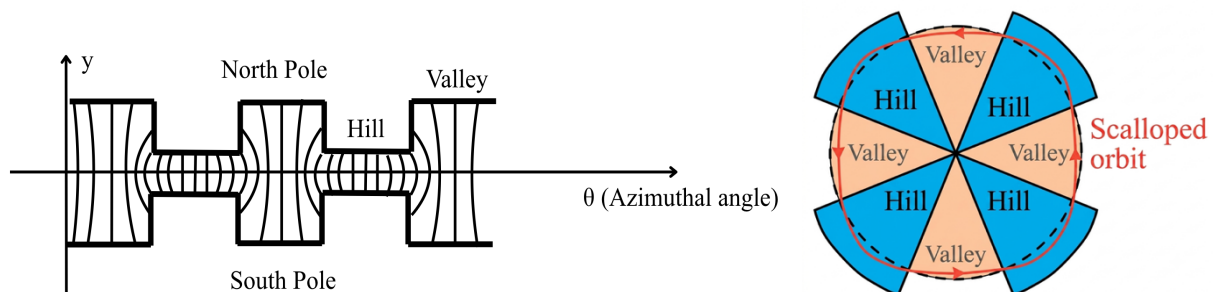


Figure 6 Left: A Diagram of Magnetic Pole Surface Vs Azimuthal angle, Revealing the Hills and Valleys Present and Resulting Magnetic Field Lines. Right: Top View of the Isochronous Cyclotron

As the radius increases, the azimuthal angle swept by each hill at that radius also increases, thus increasing the average magnetic field as a function of radius. The fringing (Figure 6) produces a vertical defocusing effect from hills to valleys, and a focussing effect from valleys to hills. Using spiral sectors introduces an additional transverse force that provides stronger vertical and horizontal focussing.

Synchrotron

Synchrotrons mitigate the limitations imposed by both the limited radius of the cyclotron as well as the relativistic cyclotron frequency. As the particle accelerates, both the magnetic field and voltage frequency are increased with particle velocity. Increasing the magnetic field proportionally to γv keeps the particle's trajectory radius constant, so the particle can be repeatedly accelerated along a loop and safely reach speeds near the speed of light (Peach et al, 2011). Like the synchrocyclotron, a limitation is that protons must be accelerated in pulses rather than continuously, producing a pulsed beam.

Superconducting Cyclotron

The electromagnets are made of superconducting wire cooled to near absolute zero temperatures using liquid helium, reducing electrical resistance. The electromagnets in this device require a low power input to produce a very large magnetic field with strength between 2.4 to 3.8 Teslas. Due to a large magnetic field, particles travel small radii, so the superconducting cyclotron takes significantly less space (JM Schippers, 2015). Common versions are the superconducting synchrocyclotron and the superconducting isochronous cyclotron, fitting into smaller clinical spaces.

Applications of Cyclotrons

Cyclotrons are predominantly used in nuclear physics and medicine. They are used to produce compounds for diagnostic imaging, for example for the production of Fluorine radioisotopes to act as tracers for Positron Emission Tomography (PET) (Braccini, 2017), Computed Tomography (CT) and in single photon emission computed tomography (SPECT) (Schmor, 2011). Cyclotrons have also been applied in nuclear research. High intensity beams are directed at thick materials to produce particles such as pions and muons, helping study nuclear structure (Gelbeke, 1999). They are also used for radiation therapy to treat cancer, known as Proton Beam Therapy (PBT).

Proton Beam Therapy

Proton therapy, the use of high energy protons to treat tumours, was first proposed by Robert Wilson in his 1946 paper. The first individual was treated at the Lawrence Berkeley Laboratory in 1954 (Lawrence et al, 1958). The world's first hospital dedicated to proton beam therapy was established in 1990 at Loma Linda University in the United States (Slater et al, 1992). As of 2024, there were 120 proton therapy centres worldwide with more than 450 thousand treated (Zhang et al., 2026).

Traditional proton beam therapy prefers isochronous cyclotrons and in some cases, synchrotrons, as opposed to classical cyclotrons or synchrocyclotrons. Isochronous cyclotrons produce a continuous beam of fixed energy, which is especially useful in pencil beam scattering (described in Structural components). To create spread out Bragg peaks by modulating intensity, energy degrading materials are used. Synchrotrons can produce beams of varying energies without such equipment, by adjusting the magnetic and electric field of the device (Liu & Chang, 2011).

The Bragg Peak Advantage

The primary advantage of proton therapy over other radiation therapy, such as photon therapy, is its ability to deliver highly conformal doses, sparing healthy tissue while depositing the maximum of their dose to tumour tissue. This is due to a property of protons known as the Bragg Peak. The Bragg Peak phenomenon, governed by the Bethe-Bloch equation, states that the energy loss of a heavy charged particle moving through a stopping medium is inversely proportional to the square of its velocity (Figure 7). As charged particles slow down, they spend more time in contact with surrounding electrons and thus transfer a larger momentum to electrons due to coulombic electrostatic forces. Due to the square proportionality of momentum to kinetic energy, the kinetic energy transferred to electrons is inversely proportional to the square of the proton's velocity.

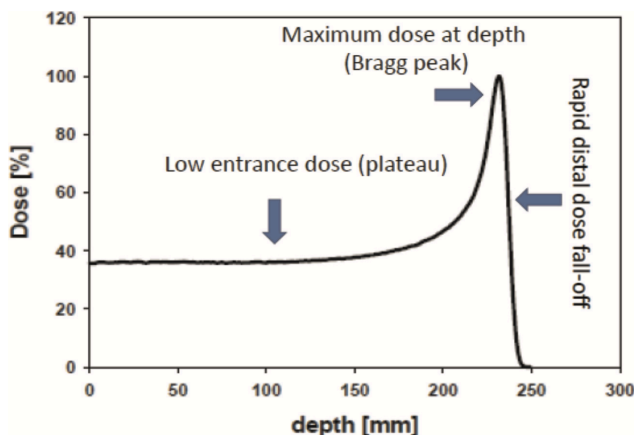


Figure 7 A General Depth vs. dose Curve for a Proton in a Stopping Medium. Reproduced from "Interaction of Proton Beam with Human Tissues in Proton Therapy" by Rafik Hazem, used under CC BY 4.0. (Hazem, 2023)

The tissue-sparing advantage of proton therapy is of increasing relevance today. The incidence of second cancers, fertility complications and other side effects is high for cancer survivors as per recent studies (Demoor-Goldschmidt & de Vathaire, 2018; Di Tucci et al., 2022). This is especially important because, as of 2021, more than 50% of cancer patients receive radiation therapy as part of cancer treatment. (WHO, 2021)

In terms of patient outcomes, proton beam therapy is comparable to advanced photon therapy (Verma et al., 2016; Mohan, 2022; Zhang et al., 2026) in terms of survival outcome, but is advantageous due to its ability to spare healthy tissue and deliver conformal doses (Alme et al., 2020). This makes it the radiation therapy treatment of choice where repeated treatment is likely, the tumor is near critical organs and structures (Nácher et al., 2024), and in pediatric cases to reduce long term radiation effects (Choi et al., 2024; Zhang et al., 2026).

The Bragg Peak of a single proton is known as a pristine Bragg peak. Realistically, tumours span from 1-10+ centimeters (National Cancer Institute (US), n.d.), so Bragg Peaks need to be spread across the entire thickness instead of targeted at a point. A spread out bragg peak (SOBP) is the superimposed result

of multiple pristine Bragg peaks of different depths, produced by protons of different energies (Figure 8). These proton energies are precisely calculated and obtained through passive scattering and active scattering.

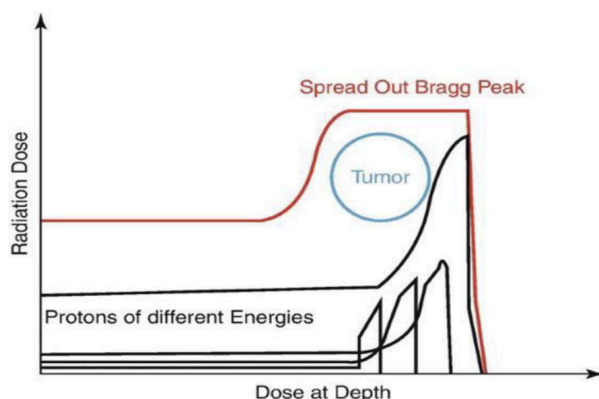


Figure 8 A general depth vs dose curve showcasing the Superimposed Spread-Out Bragg Peak (SOBP). Reproduced from "Interaction of Proton Beam with Human Tissues in Proton Therapy" by Rafik Hazem, used under CC BY 4.0. (Hazem, 2023)

Structural components of cyclotrons in proton beam therapy

Penning Gauge Ion Source

The ion source is placed in the centre of the cyclotron, in a uniform magnetic field. Neutral hydrogen gas is supplied into a grounded chamber. Each end of the chamber has a cathode connected to a negative high voltage power supply. Electrons are emitted from the cathodes with high kinetic energy and are attracted to the grounded chamber walls. However, due to the magnetic field, they move in a spiral motion back and forth between cathodes, stripping off electrons from hydrogen gas atoms. The positively charged ions leave through an aperture connected to a dee, and are attracted to the aperture when the RF voltage is negative (Cyclotrons, 2023).

Rotating Gantries

Gantries are large, often 3 story high mechanical supports that can target the proton beam at a tumour from a range of angles due to its 360 degree turning capacity. The gantry is made of supporting structures, bending magnets, quadrupole magnets, and a treatment nozzle. Due to the proton's bragg peak quality, it is crucial to rotate the gantry precisely around an isocentre - a fixed coordinate where the rotational axis of the gantry and the proton beam intersect (Collings et al., 2022).

Treatment Delivery Methods

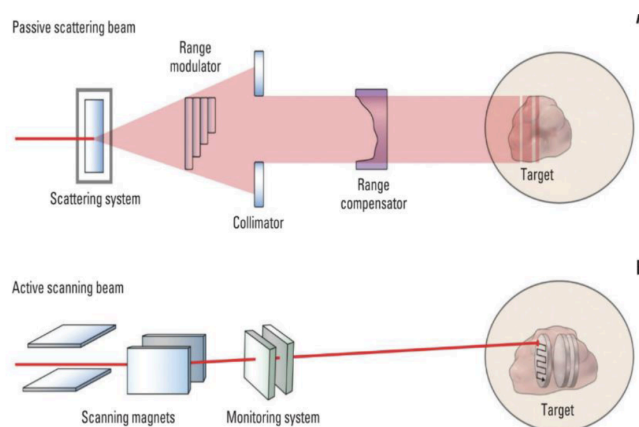


Figure 9 Diagram showcasing Treatment Delivery Methods Used In Proton Beam Therapy. Note. From “Schematic designs of passive scattering...”, by Byun et. al, 2021, CC BY-NC 4.0.

Protons travel from cyclotrons to vacuum beam lines to prevent energy loss by colliding with gases. Mechanisms are used to modulate the proton beam’s range and energy to target the tumour and minimise dose to surrounding tissue.

Passive Scattering. A beam of fixed energy is modulated to have varying intensities using various components. The beam is passed through a scatter foil, where electrostatic repulsion causes spreading out (Figure 9). Single scatterers are uniform and produce beam intensity with gaussian distribution. Double scatterers flatten the energy distribution by scattering protons in the center more strongly. Next, a range modulator, a spinning device with steps of varying thicknesses, produces a SOBP by modulating the energies of protons reaching a given region of the tumour. It spreads the bragg peak across the depth of the tumor. The aperture is a stencil that matches the tumor’s outer contour. Finally, range compensators are stationary devices with regions of varying thicknesses, which shape the distal edge of each proton’s dose-depth curve. This ensures the dose does not pass beyond the tumor contour into surrounding tissue. While this method is simple and safe, it is inefficient as many protons are lost. Further, many protons collide with the various devices and undergo nuclear collisions, producing radiation and secondary particles. Secondary neutrons are highly destructive and contribute to unwanted dose in healthy tissue (Liu & Chang, 2011).

Pencil Beam Scattering. A magnetic scanning mechanism is used to deflect an unscattered, pencil proton beam spot by spot across the tumor (Figure 9). X magnets create vertical magnetic fields while Y magnets create horizontal magnetic fields, producing Lorentz forces that steer the beam in the x and y directions respectively. Scattering foils, range compensators, and apertures are not required. Monitor units measure total charge through current produced by the ionisation of gases by the proton beam, in chambers. The last chamber of the monitoring unit determines the beam diameter and position by detecting ionised gas molecules. Tumour motion due to breathing is a challenge in pencil beam

scattering, as a target 'spot' may shift. A solution is to trace the tumour multiple times to increase the average dose (Liu & Chang, 2011).

Interactions between protons and human tissue in Proton Beam Therapy

As a proton enters tissue, it encounters coulombic inelastic collisions with electrons (Hazem, 2023), however is not deflected due to its higher rest mass (1836 times an electron's rest mass (Mohr et al., 2025)). The proton's kinetic energy and momentum is transferred to electrons, causing it to slow down gradually. The proton also experiences elastic coulombic interactions with nuclei due to a repulsive force. The proton's path is heavily deflected due to its lower mass. Inelastic collisions with nuclei occur when a primary proton is absorbed by nuclei, releasing secondary particles such as secondary protons, neutrons, and gamma rays. Bremsstrahlung radiation, the photon released when a charged particle is rapidly decelerated or deflected by an electric field, has negligible effect on dose deposited.

In proton beam therapy, coulombic inelastic collisions with electrons determine protons' range in the tissue and the dose deposited by them. Elastic coulombic interactions with nuclei results in a less sharp lateral penumbra (the amount of dose spillover outside the tumour contour). Inelastic collisions with nuclei result in stray secondaries which deposit their own dose (Newhauser et. al, 2015).

Modelling Coulombic Inelastic Collisions Between Protons and Electrons: The Bethe-Bloch Equation and the Bragg Kleeman Rule

The Bethe-Bloch equation (Bethe, 1930; Bloch, 1933) models the stopping power, S , (average energy lost per unit of path length) of matter for charged particles having mass greater than an electron and kinetic energies 0.1-10 times the particle's rest energy.

The equation, with shell, Barkas, density shell and Bloch corrections is given by:

$$s = \frac{4\pi Z_1^2 e^4}{m_e v^2} NZ \left\{ \ln \ln \left(\frac{2m_e v^2}{I_0} \right) + \ln \ln (\gamma^2) - \beta^2 + \frac{1}{2} f(\gamma) - \frac{C_0(\gamma)}{Z} - \frac{1}{2} \delta_F + \Delta L_{Bloch} + \Delta L^B(\gamma) \right\} \quad (23)$$

Adapted from Salvat (2022, p. 032809-24)

The variables, descriptions of corrections, and formulae of correction terms are defined in appendix B. At very low velocities, $\beta \ll 1$, the formula reduces to:

$$s = \frac{4\pi Z_1^2 e^4}{m_e v^2} NZ \left\{ \ln \ln \left(\frac{2m_e v^2}{I_0} \right) - \frac{C(v)}{Z} + \Delta L^{LS} + \Delta L^B(a) \right\} \quad (24)$$

The linear stopping power is

$$S = - \frac{dE}{dx} \quad (25)$$

To express energy loss as independent of mass density, the mass stopping power is often defined by:

$$\frac{S}{\rho} = - \frac{dE}{\rho dx} \quad (\text{Hazem, 2023}) \quad (26)$$

The Bethe-Bloch equation is an accurate model as it accounts for relativistic and quantum mechanical effects (Newhauser et. al, 2015).

The Bragg-Kleeman rule is an empirical and simplified, yet accurate formula used to approximate stopping power. It is given by

$$\frac{S}{\rho} = - \frac{dE}{\rho dx} \approx \frac{E^{1-p}}{\rho \alpha p} \quad (27)$$

where ρ is the mass density of the material, α is a material specific constant and p depends on the accelerating particle. The values of α and p are found empirically. While the Bragg-Kleeman rule allows for quick, accurate calculations in the energy range used in proton beam therapy, the Bethe-Bloch equation has corrections to correctly estimate stopping power for a broader range of energies. The Bethe-Bloch is more complex to compute and can depict unphysical behaviour at low energies (Ashby et al., 2024).

Modelling Elastic Coulombic Interactions With Nuclei: Highland Approximation

To model such interactions, Molière scattering, gaussian, or highland approximations are used (Santos et al., 2021). Highland approximation is a simplified, easier to implement formula as compared to Molière scattering, determining the root mean square of angles at which a charged particle in a medium is scattered.

$$\theta_0 = \frac{13.6}{\beta c p} z \sqrt{\frac{x}{x_0}} [1 + 0.038 \ln \ln \left(\frac{x}{x_0} \right)] \quad (28)$$

where x_0 is the radiation length, a material dependent property, x is thickness of material, z is particle charge, βc is the particle's velocity, and p is particle momentum when it is incident on the surface.

Multiple coulomb scattering describes the jagged path of a charged particle due to deflections by multiple elastic nuclear collisions. Therefore, the highland approximation predicts the root mean square of all angles to which the charged particle passing through the medium is deflected. The root mean square is likely chosen as a useful quantity as compared to mean, as the mean would cancel to a value close to zero, because particles are equally likely to scatter below than they are above. By squaring angular deflections, the RMS reports the magnitude of scattering.

Modelling Inelastic Collisions With Nuclei

The probability of a nuclear inelastic collision occurring for a given path length is given by:

$$P_{coll} = 1 - e^{-\sum_{in} \Delta x} \quad \text{where } \sum_{in} = \sigma_{in}(E) \cdot \frac{\rho \cdot N_A}{A_t} \quad (29)$$

This is a commonly used formula in Monte Carlo modelling of nuclear collisions between accelerated particles entering a medium (Brown & Martin, 2001).

METHODS

A literature review was conducted using Google Scholar. Keywords searched were “cyclotrons”, “proton beam therapy”, and “proton beam therapy modelling”, prioritizing recent papers while retaining seminal works. A 3D python simulation focusing on proton beam and tissue interactions was created. It presents range uncertainty, spillover of dose, the number of killed healthy and tumour cells, and other parameters.

It models a general case of soft tissue liposarcoma, a type of cancer that develops in deep fat tissue. An irregular-shaped tumour spanning ~5 cm is modelled, located 20 cm within a 40x40x40 cm tissue block. 2-centimetre-thick femur bone spans along the z axis as an obstacle in the proton beam’s path.

It offers two tracks: an ‘exploratory’ and ‘optimising’ track. For both, the general flow is as follows. The simulation calculates the energy a proton loses per step size (0.01 cm) based on the material it is in, using the Bethe Bloch equation. The angular deflection of each proton at a given depth along the x-axis is calculated using the Highland approximation. The probability of an inelastic nuclear collision occurring at the position is calculated using the nuclear reaction probability formula. A random number generator generates a number between 0 and 1, and if it is greater than the probability of nuclear reaction, the interaction occurs. For each collision, about 15% of the primary proton energy is deposited in tissue as a result of the nuclear reaction, and 1-3 secondaries are randomly generated. The dose deposited in each voxel by the protons is updated in an array, and each proton’s current energy (initial energy - total deposited energy) is tracked. When the proton’s energy is below a threshold (0.5 MeV) or if the proton exits the tissue, it is considered stopped. Based on the linear quadratic formula, the probability of a cell surviving given the dose in the voxel is found. This is multiplied to the number of cells per voxel to represent the number of living cells. An array is updated to track the number of living healthy and tumor cells.

In the exploratory track both, a one-time proton beam treatment and a fractionated proton beam treatment delivered over the course of weeks can be modelled.

In the regular proton beam treatment route, 7 parameters that affect tumour coverage and proton ranges can be adjusted, namely, beam energy (after intensity modulation), beam energy spread (variation in the energies of protons of the beam), beam angular spread, beam entry spot size (thickness of the beam at tissue entry), number of protons to simulate, breathing amplitude (which impacts the tumour location), and breathing period. A single proton beam with 300 protons is simulated.

The fractionated proton beam treatment route can be used to model a more realistic cancer treatment. In addition to the 7 parameters, the dose delivered per fraction and the interfraction gap in hours for weekdays and the weekend can be varied.

Since healthy cells repair faster than tumour cells, fractions help reduce the damage inflicted on healthy cells. A usual fraction delivers 2 Grays of dose, and a liposarcoma requires 28-33 such fractions. One fraction is delivered 5 days a week, 24 hours apart, with a 2 day break over the weekend.

For clinically realistic results, 1-2 billion protons had to be simulated. Since modelling individual protons would make the simulation time consuming and heavy, a coarse graining approach was used. Instead of tracking individual protons, the average dose deposited per voxel is tracked. An initial run of 20,000 protons tracks each proton's individual path and energy loss. An array sums the dose deposited in each voxel by all protons that crossed that voxel. An average 'dose deposited per proton' for each voxel in the x,y,z position is calculated. This is a 'kernel' of dose ($K(x,y,z)$). The dose deposited per voxel ($D(x,y,z)$) in each treatment session is the fluence (ϕ) multiplied by the kernel dose, where fluence is the number of protons crossing a region. Fluence was calculated based on the roughly 2 Gy of dose that should be deposited in voxels.

The Lea-Catcheside factor (G) determines the probability of a cell repairing the damage done to DNA by the first dose before a second dose is provided. It is used in the extended linear-quadratic model, where S is the fraction of cells surviving.

$$S = e^{-(\alpha D + \beta G D^2)} \quad (30)$$

While the linear quadratic (LQ) model, given by

$$S = e^{-(\alpha D + \beta D^2)} \quad (31)$$

estimates the cell survival fraction for a one-time dose with cell repair (Nilsson et al., 1990), the extended LQ model is used when dose is delivered in fractions with incomplete cell repair between them and some cell repair during fractions (McMahon 2019).

Alpha and beta parameters describe the radiosensitivity of the cell, with alpha representing the impact of single high-energy particles and beta representing cell death due to multiple 'hits' by particles (McMahon, 2019).

The Lea-Catcheside factor is calculated using:

$$G = \frac{n + 2 \sum g(\Delta t)}{n^2} \quad (\text{Dale, 2018}) \quad (32)$$

where n is the number of fractions delivered.

The damage that is carried over from previous fractions to the next one is

$$g(\Delta t) = e^{-\mu \Delta t} \quad (33)$$

ΔT is the time difference between any two radiation fractions so far (i.e. the time difference between the n th fraction and the 1st fraction, between the n th fraction and the 2nd fraction, and so on).

μ (hours^{-1}) is given by:

$$\mu = \frac{\ln(2)}{T_{\frac{1}{2}}} \quad (34)$$

$T_{\frac{1}{2}}$ is the time for a cell to repair half of the DNA damage inflicted, and T is the length of the fraction (hours).

This formula was adapted by Roger G. Dale (Dale, 1985) from the Thames Incomplete Repair Model (Nillson et al., 1990). G is calculated after each fraction and substituted into the LQ model to find the number of living healthy and tumor cells.

The optimising track

The optimizing track uses reinforcement learning to find optimal parameters for the aforementioned variables that lead to maximum number of killed tumor cells and a minimum number of killed healthy cells. A CMA-ES (Covariance matrix adaptation evolution strategy) evolutionary optimization is used, as the number of parameters being optimized is only 4-8. The optimising track has two options, a beam parameter optimiser and a fractionation schedule optimiser.

The beam parameter optimiser optimises for the following parameters: beam energy, energy spread, angular spread, and beam spot radius. It randomly generates a set of parameters, runs the simulation for them, calculates a score based on a reward function, and continues for a set number of generations. The parameters providing the greatest score is the final output. The linear reward function is as follows:

$$W_1 * \text{No. of killed tumour cells} - W_2 * \text{No. of killed healthy cells}, \quad (35)$$

where W_1 corresponds to the weight given to killing tumour cells, and W_2 corresponds to the weight for killing healthy cells. Both W_1 and W_2 have been set to 1 to equally penalise killed healthy cells and reward killed tumour cells.

The fractionation schedule optimiser optimises for following parameters: the number of fractions, dose per fraction, gap hours on weekdays, gap hours on weekends, beam energy, energy spread, angular spread, and beam spot radius.

The linear reward function is:

$$W_{\text{tumour}} * (\% \text{ tumour cells killed by end of course}) - W_{\text{healthy}} * (\% \text{ healthy cells killed by end of course}) \\ - W_{\text{duration}} * (\text{Course duration, days}) \quad (36)$$

where W_{Tumour} is set to 1, $W_{Healthy}$ is 4, to penalise killed healthy cells as they may be near critical organs, and reward killed tumor cells slightly less. $W_{Duration}$ is set to zero as it is an optional parameter if shorter course durations are preferred, as tumour cells eventually repopulate if the course duration is long (Refer to appendix C for additional features of the simulation).

RESULTS

The simulation is available on GitHub for public use. ParaView is required for viewing animations. The 3D simulation maintains a level of accuracy through its use of accurate physical modelling, combining exploratory and optimising tracks in one single software, while being relatively lighter than existing modelling software used in proton beam therapy such as GEANT4 or TOPAS.

The 3D simulation models the latter part of proton beam therapy, interactions between protons and tissue after cyclotron-acceleration. It models a roughly five centimetre wide tumour with an irregular, discoidal shape using a spherical harmonic perturbation function, centred around the 20 cm depth mark. It splits the 40x40x40 cm tissue into voxels 0.01 cm³ carrying the properties of the region it is present in (irregular tumor, healthy tissue, and bone) to simplify computations. The simulation also models natural heterogeneity in tissue density, using a normal distribution centered around clinically established density values for the tissue, bone and tumour. It also accounts for oscillatory movement of tumours due to breathing.

Simulation Outputs

For the exploratory track, various results are output, so that the impact of changing parameters on measures such as range, range uncertainty, dose spill over or lateral penumbra, and dose deposition can be quantitatively and visually assessed. Firstly, a histogram of Bragg peak depths of all primary protons - the horizontal depth along tissue at which a proton's Bragg peak occurs is generated. A histogram of Bragg peak depths of all primary protons and secondary protons is also created. A 3D heatmap is generated. It showcases the tumor, the bone and tissue in 3D, and the dose deposited by the entering proton beam. The intensity of the red color of each voxel represents the total dose in each voxel relative to other voxels. Total dose is the sum of doses deposited by all protons that passed through that voxel. For the fractionated route, 3D diagrams showcasing the number of living tumor cells and the number of killed healthy cells after each fraction are also produced.

3-dimensional frontal and sagittal cross sections help qualitatively view the spillover of dose around the tumor's outline at each depth. Further, a depth-dose curve is created, representing the total dose of all voxels at a depth as a function of depth into the tissue. The R90 and R50 ranges are also marked on this diagram. R90 and R50 are commonly used parameters in the proton beam therapy, representing the depth at which dose drops to 90% and 50% of the maximum deposited dose respectively (Schuemann et al., 2014).

Animation files are generated and can be viewed on ParaView. They showcase the accumulation of dose in the tissue as the proton beams enter it. The motion of the tumor as the patient breathes is also depicted if the option for breathing is selected.

In the local terminal, the following statistics are provided: the number of primary protons (protons that did not undergo inelastic nuclear collision) and the mean, median, standard deviation and IQR of their ranges in tissue. Similarly, the number of protons that underwent nuclear inelastic collisions and their range statistics. For the fractionated treatment route, the number of living healthy and tumour cells is reported after each fraction.

As for both the optimiser routes, the reward function score and living tumour and healthy tissue cell counts for each generation are reported in the terminal. 3D diagrams showcasing the number of living tumour cells and the number of killed healthy cells are produced. Finally, the optimal parameters found are reported in the local terminal.

Data Collection

Sample data produced by the model for each track can be seen in figure 10, figure 11, figure 12 and table 1 and 2. Further, the optimisation results and convergence graph can be viewed in figure 13 and 14, respectively.

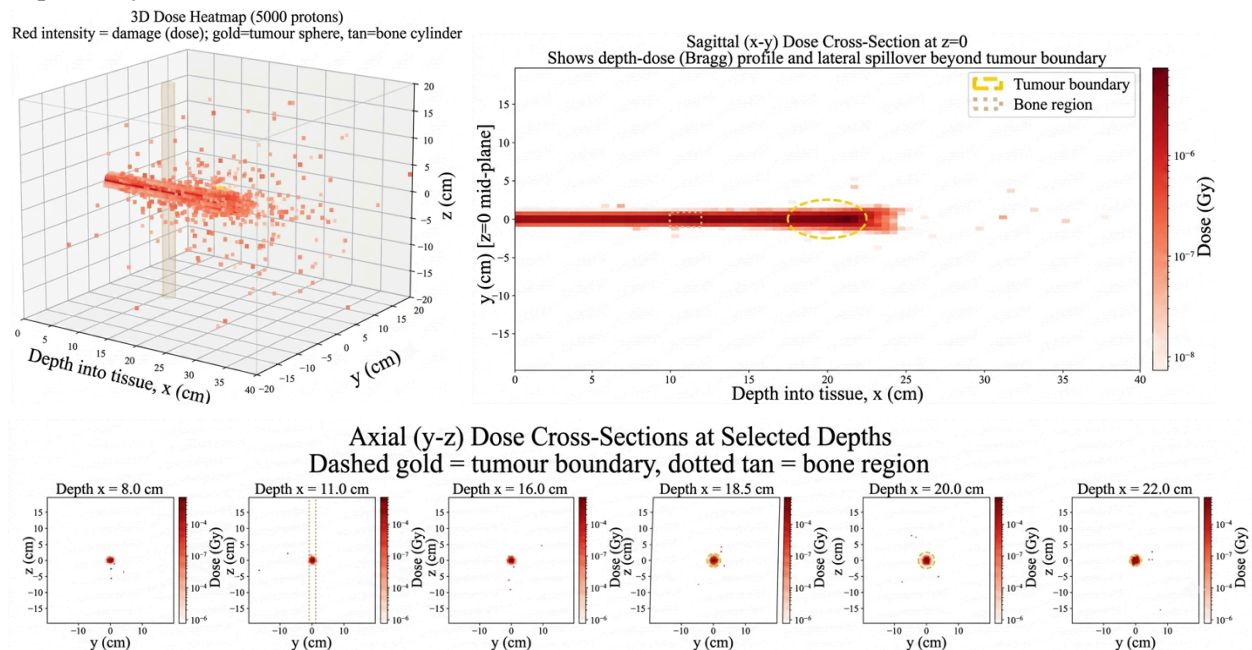


Figure 10 Sample 3D Heatmap (top right), Sagittal Cross Section (top left), and Frontal Cross Sections (bottom) Showcasing the Amount of dose Deposited per Voxel by the Proton beam, Denoted by the

Intensity of red. Note. The Scatter of Dose in the Sample 3D Heatmap is Explained by Secondary Particles and Angular Deflection of Protons.

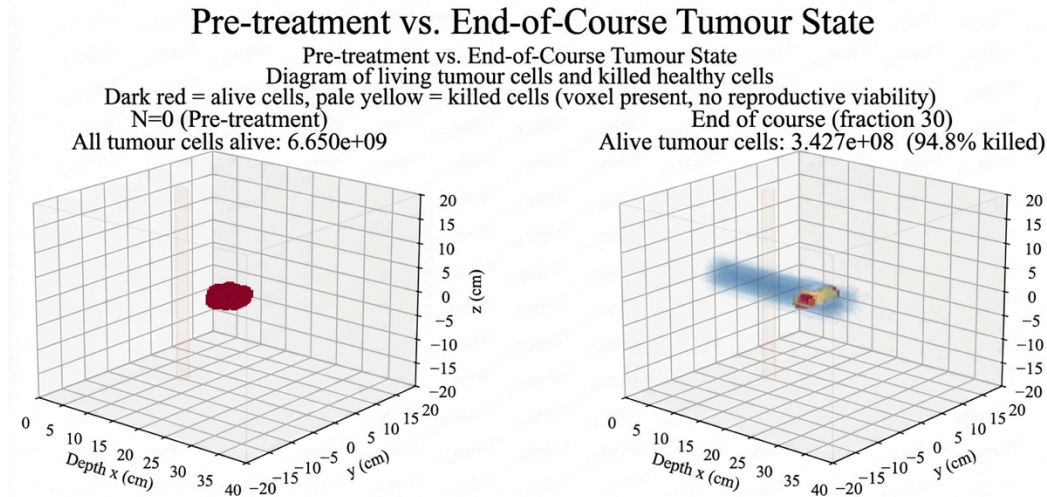


Figure 11 3D Diagram of 30-Fraction Treatment Result. Shrinkage of the Tumor by 95% is Visible.

A heatmap diagram was chosen as it aids in visualising the effects of the proton beam on the entire tumour, tissue and bone arrangement in three dimensions. The range of the beam (Figure 12), beam spot size, dose deposition due to Bethe-Bloch interactions, scattering due to secondary particle production and angular deflection can be viewed. Compared to 2D visualisations, it helps gain more information about the impact of adjusting one or more parameters on therapy provided by the proton beam.

Table 1:

Impact of Varying Beam Energy on the Range of Protons in Tissue.

Beam Energy (MeV)	Mean Range (cm)	σR =Standard deviation of Range (cm)	Range Uncertainty (%)
150	12.37	0.82	6.63
160	14.04	1.13	8.05
170	15.80	1.44	9.11
180	17.61	1.72	9.77
190	19.43	1.98	10.19
200	21.31	2.20	10.32
210	23.25	2.48	10.67
220	25.29	2.78	10.99

Note. The range of protons is defined as the depth at which the Bragg Peak of each proton occurs. The Bragg Peak depth quantity was introduced as it can be useful in representing where protons deposit their maximum energy and damage. The Bragg Peak depth histogram then is directly representative of areas where maximum dose is deposited in the tissue (Figure 12). Beam energies impact the proton's entering velocity, which impacts energy loss (inverse proportionality to velocity squared) and the position of the Bragg peak.

Table 2:
Impact of Angular Spread on Range.

Angular Spread	Mean Range (cm)	σ_R =Standard deviation of Range (cm)	Range Uncertainty (%)
0.1°	21.29	2.21	10.38
0.2°	21.29	2.21	10.38
0.5°	21.32	2.22	10.41
1.0°	21.40	2.24	10.47
2.0°	21.35	2.36	11.05

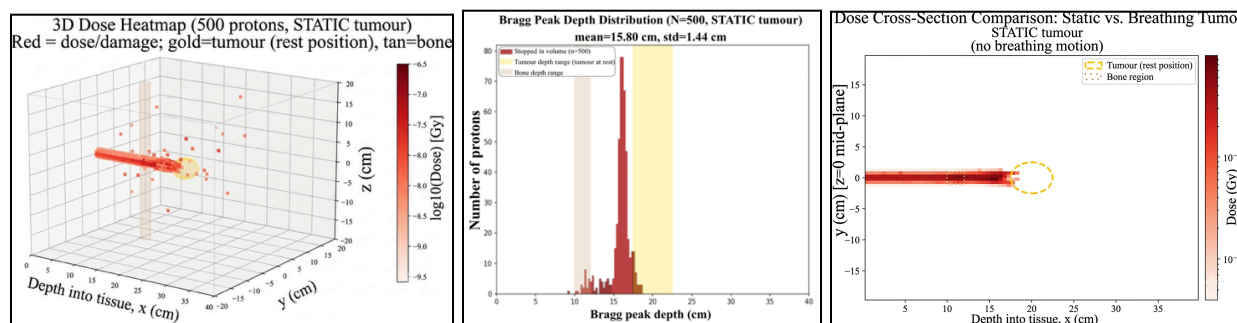


Figure 12 The Range Histogram and Heatmap (Proton beam energy of 170 MeV) Suggest the Bragg peak of Most Protons Fell Short of the Tumour.

The fractionation schedule optimiser found that 24 fractions, 1.6 Gy dose per fraction, 36 hours of ‘weekday’ gap, 63 hours of ‘weekend’ gap, 215 MeV beam energy, 1.2% beam energy spread, 0.44 degree angular spread, and 1.4 cm beam spot size results in maximum tumour cells killed (99.1%) and minimum healthy cells killed (Figure 13).

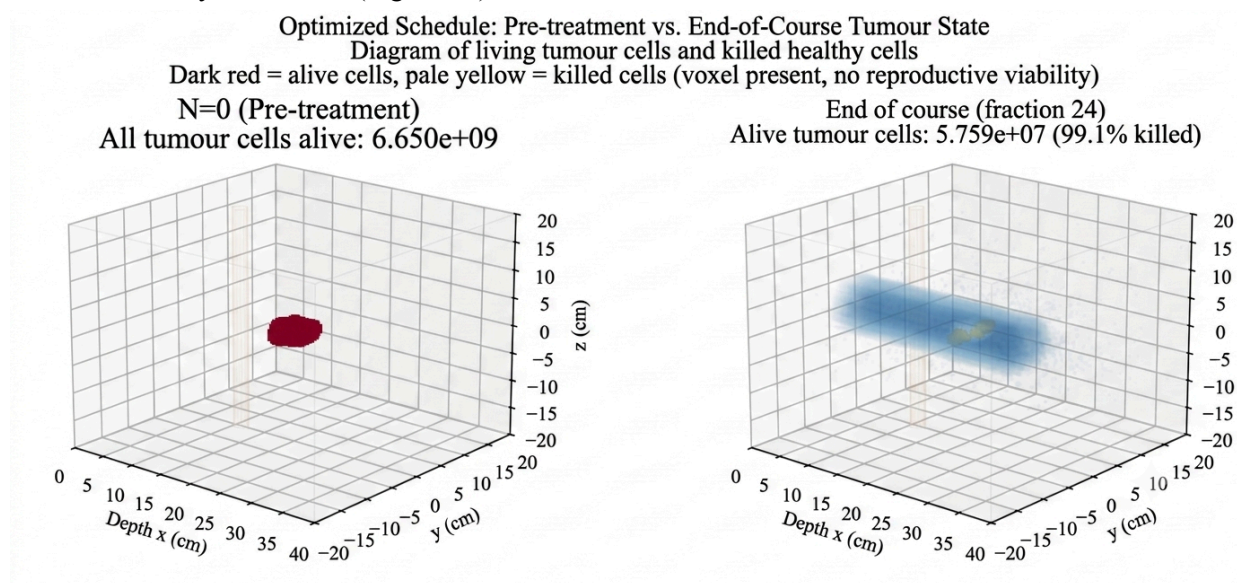


Figure 13 3D Diagram of Fractionated Treatment Optimiser Tumour Shrinkage Result (99.1% killed).

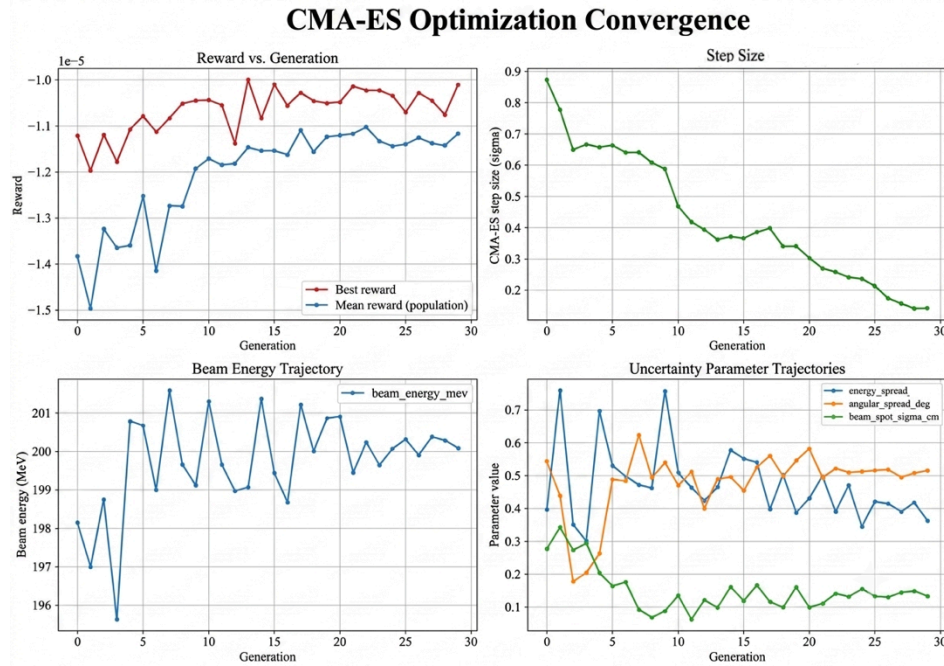


Figure 14 Optimiser (Non-Fractionated Route) Convergence Graph. Note. Convergence graphs plot the reinforcement learning model's reward function score over generations. This helps view the model's performance in finding an optimal set of parameters. An initially fluctuating graph that steeply increases and gradually plateaus is ideal. It suggests the model has found a stable, optimum state. The convergence graphs produced are discussed in the Discussion section.

Interpretation of Results

Six beam parameters - beam energy, beam energy spread, angular spread, breathing amplitude, beam entry spot size and breathing period - were independently varied while keeping other parameters constant at their default. A local sensitivity analysis was conducted to determine which parameter has greatest impact on range uncertainty and answer the research question. In addition, a standard regression analysis was conducted. Both help quantify the impacts of individual parameters on each dependent variable, range, range uncertainty, and range uncertainty %, however standard regression analysis assumes a linear correlation between each parameter and each dependent variable, while local sensitivity analysis applies to non-linear models. The results of each test are provided in appendix D.

The local sensitivity analysis results suggest that beam energy is the variable with the most impact on range, range uncertainty %, and range standard deviation, with relative impacts of 60.63%, 42.25% and 89.09%, respectively. Angular spread, beam spread, and breathing amplitude had no significant impact on range. The minimal impact on range by altering angular spread is likely attributable to unaffected proton energies. Although varying angular spread changes the directions of protons, impacting measured displacement in the x-direction and the range, the overall effect on range remains negligible. In terms of

range standard deviation and uncertainty percentage, beam energy spread is the second major contributor. range is unaffected by beam energy spread as range is averaged, while effect on uncertainty is explained by the variation in particle energies and the resulting variation in individual ranges. Standard regression analysis suggests that a strong positive correlation exists between all independent variables and range, range standard deviation and uncertainty percentage, supporting that each independent variable linearly correlates with each dependent variable. When evaluated individually, beam energy displays the strongest linear relationship with absolute range and range standard deviation, while beam energy spread holds the greatest impact on relative range uncertainty percentage. A sensitivity analysis was also conducted, where combinations of 2 parameters were varied (Results in appendix E).

Figure 11 showcases a shrinkage of tumour by 95% after a 30-fraction treatment of the liposarcoma tumour with consideration of intrafraction cell repair, produced through the exploratory track. Figure 13 showcases 99.1% of tumour cells killed using optimised conditions found through the fractionated schedule optimiser, displaying the simulation's ability to effectively maximise tumour kill.

Model validation:

Simulation range values were compared against PSTAR ranges at different beam energies. Simulation values in table 1 deviate from PSTAR striated muscle (ICRU density 1.04 g/cm²) values due to the presence of femur bone and variation in tissue density. Mean range values were adjusted into water-equivalent ranges, by adding 1.37 cm to each mean range, using the procedure for water-equivalent thickness detailed by Newshauser et. al (Newshauser et al., 2015), using 1.85 g/cm³ mass density (Blanton & Biggs, 1968) and 0.91 mass stopping power ratio obtained using PSTAR.

Table 3:

Comparison of water equivalent adjusted ranges and PSTAR ranges at different beam energies.

Beam Energy (MeV)	Mean Water-equivalent Range (cm)	PSTAR Range (cm)	Absolute Diff ΔR (cm)	Relative Diff % ΔR (%)	Standardized Diff (Z-score)
150	13.74	15.28	-1.54	-10.08%	-1.88
160	15.41	17.10	-1.69	-9.88%	-1.50
170	17.17	19.00	-1.83	-9.63%	-1.27
180	18.98	20.97	-1.99	-9.49%	-1.16
190	20.80	23.03	-2.23	-9.68%	-1.13
200	22.68	25.14	-2.46	-9.79%	-1.12

210	24.62	27.34	-2.72	-9.95%	-1.10
220	26.66	29.60	-2.94	-9.93%	-1.06

The remaining difference between the simulation ranges and PSTAR ranges can be attributed to the model's consideration of variations in tissue density as compared to PSTAR's modelling of a uniform material. The data showcases that simulation and PSTAR data align with a margin of deviation of 10%.

The water-equivalent ranges were compared against the Bragg-Kleeman rule which accurately approximates empirical ranges of protons. The linearised rule was fitted to simulation outputs on Microsoft Excel, producing $\alpha=0.0024$ cm/MeV^p and $p=1.7274$ (appendix D). p value matches the clinical range of 1.7-1.8, while α is slightly greater than the experimentally determined 0.0022 cm/MeV^p value for beam energies less than 200 MeV (Sobhy et al., 2025).

DISCUSSION

Model Novelty

In the presented simulation, all three significant interaction types between protons and human tissue have been modelled, a feature absent in foundational python-based simulations like the one presented by Luo et. al (Luo et al, 2025). Such simulations also employ water-phantom as a model for the tumor, while the presented simulation models human tissue and considers natural density variations, biological structures such as the 2 cm bone in front of the tumour, as well as the density and shape properties of the tumour.

Advanced Monte Carlo radiation tracking or medical physics simulations such as GEANT4, TOPAS, and FLUKA use more comprehensive physics principles as well as real-time 3D visuals rather than post-computation 3D visuals. GEANT4 models electromagnetic, strong and weak interactions between particles and media, while the presented simulation models three electromagnetic interactions that are significant for protons. TOPAS, a wrapper for GEANT4 in medical physics applications, can model treatment components such as patient specific compensators, a variety of treatment configurations such as passive scattering and pencil beam scattering, as well as real time movement of objects such as tumor. While preexisting models are specially designed for clinical planning, and hence configure the tumour and surrounding structures based on CT scan data, the presented simulation is for exploratory and educational purposes, and hence models a single case of an irregular tumour in heterogenous tissue with thin bone in front of it.

The simulation is distinct from existing proton beam therapy radiation simulations in its combining of modelling, 3D visual representations, and optimizing features on a single lightweight platform. It is programmed in Python, making it portable and lightweight as compared to GEANT and FLUKA which require compilation of code. Unlike tools such as GEANT4, which necessitates expertise in programming, and TOPAS, which requires foundational knowledge of Monte Carlo techniques, the proposed simulation

eliminates programming prerequisites, using a simple interface that allows users to input parameters through textual inputs.

GEANT4/TOPAS, and other existing simulations model solely one-time dose and its biological effects, while the proposed simulation - in its 'fractionated treatment route' - models radiation treatment spread across multiple fractions, simulating cell repair between fractions, tumor movement due to breathing, as well as approximations of the number of killed healthy and tumor cells after each fraction, in one platform. matRad models fractionated treatment by scaling the dose of a single treatment with the number of fractions, while the presented simulation considers intrafraction cell repair and damage carried over between fractions.

Evaluation

The simulation has several advantages over existing models used in proton beam therapy. It is lighter and faster than software such as Geant4, using only 510 MB of disk space, producing exploratory data in 1-8 minutes and completing optimising in 20-30 minutes. Unlike models such as the python model by Luo et al. (2025), the simulation incorporates the full Bethe-Bloch equation with its corrections. The simulation also models all significant proton and tissue interactions.

A strength is its handling of uncertainty in tumour position by modelling oscillatory breathing motion, thus allowing users to directly quantify and compare the range uncertainty and tumour coverage with and without breathing motion.

According to our knowledge, this is the only proton beam therapy simulation which combines exploratory parameter analysis with reinforcement learning in a single lightweight platform. A 3D animation of the proton beam impacting the tissue is produced and can be viewed on ParaView software.

Limitations of the model include: Secondary particles produced as a result of nuclear inelastic collisions were not individually or fully tracked to prioritise computational efficiency. Instead, their dose was deposited in voxels locally surrounding the point of collision and it was assumed a fixed proportion of neutrons and secondary protons were produced after each collision. The simulation also does not model intensity modulation (creation of SOBP). Although the presented simulation employs a single beam configuration rather than pencil-beam scanning, the findings clearly demonstrate the therapeutic potential of a fixed-position proton beam targeted at the tumor volume. Due to limited computational resources, the number of optimiser generations run were reduced to 10. The optimiser convergence graph has a non-ideal, jagged pattern. This is due to the linearity of the reward function, which uses raw, absolute metrics (number of killed cells) and the number of generations run.

Future work could extend to conducting a sensitivity analysis where all parameters are varied, for example through latin hypercube sampling, modelling the asymmetry in breathing as the time of exhale is longer realistically, and refining the optimiser's reward function. Furthermore, current data analysis

measures the impact of one or two parameters, such as beam energy and angular spread, on range, range uncertainty, and tumour kill. An extension would be to vary multiple parameters in order to examine multi-factor interactions and how they impact range uncertainty and tumour kill (treatment effectiveness). Additionally, the presence and location of the bone obstacle can be made adjustable, and critical structures such as veins and organs can also be modelled. While the model balances computational efficiency with physical considerations, additional Further improvements, one can use the simulation to answer a pertinent question in the field, “Which source of uncertainty contributes most to range uncertainty and inefficient tumour coverage, and in what conditions can these limitations be minimised?”

CONCLUSION

The paper reviews the physics of cyclotrons in proton beam therapy in a coherent manner. It also presents a computationally light 3D python simulation that models the interactions of protons with human tissue. These interactions are highly stochastic and consist of multiple steps, making them difficult to analytically predict and visualise or experimentally determine. This easily deployable, easy to use, and fast 3D model helps visually present the results of such interactions, displaying range, range uncertainty, lateral penumbra, the number of healthy and tumour cells killed. Compared to GEANT4 models, this is a code free platform, and parameters values simply need to be typed. This is intended for educational and exploratory use rather than clinical use, helping users understand the parameters most affecting range uncertainty and tumour coverage and by how much, as well as optimal combinations of parameters.

The Model is available at [github.com](https://github.com/piyaarora1020-oss/Proton-Beam-Therapy-3D-Python-Simulation-Modelling-proton-beam-interactions-with-human-tissue) in piyaarora1020-oss/Proton-Beam-Therapy-3D-Python-Simulation-Modelling-proton-beam-interactions-with-human-tissue-, or using the link <https://zenodo.org/records/21238457>.

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APPENDIX

A. Derivation of velocity acquired by a charged particle across the narrow gap between dees in a cyclotron

The electric force applied on the particle is given by:

$$\vec{F} = q\vec{E} \quad (\text{A.1})$$

Where q is the proton charge (in coulombs) and $\vec{E}$ is the electric field (in Newton per Coulomb).

The work done on the particle every time it passes through the narrow gap between the dees:

$$W = q\vec{E} \cdot \vec{d} \quad (\text{A.2})$$

Where d is the length (in meters) of the gap.

The particle loses electrical potential energy as electric force does work on it, gaining kinetic energy. As per the law of conservation of energy, the potential energy lost by the particle is converted to kinetic energy (T). Thus, the increase in kinetic energy (ΔT) is given by:

$$\Delta T = q\vec{E} \cdot \vec{d} \quad (\text{A.3})$$

The kinetic energy of the particle after crossing the narrow gap between dees N times, is given by:

$$T = T_{initial} + N\Delta T \quad (\text{A.4})$$

Where $T_{initial}$ accounts for its initial energy when injected into the cyclotron.

$$\frac{mv^2}{2} = \frac{mv_{initial}^2}{2} + qN\vec{E} \cdot \vec{d} \quad (\text{A.5})$$

Therefore, the particle's velocity is:

$$v = \sqrt{v_{initial}^2 + \frac{2qN|\vec{E}| \cdot \vec{d}}{m}} \quad (\text{A.6})$$

Where $|\vec{E}|$ is the magnitude of the electric field across the dees.

B. Bethe Bloche Formula variables and corrections - Complete definitions and description

Z_1 is the atomic number of the charged particle; Z is the atomic number of the stopping medium; m_e is the mass of an electron; v is the velocity of the charged particle; $\mathcal{N}$, the atomic number density of the target medium, is given by

$$N = \frac{\rho \cdot N_A}{A_M} \quad (\text{Cember \& Johnson, 2008}) \quad (\text{B.1})$$

where N_A is the avogadro number, ρ is the mass density of the medium, and A_M is the molar mass of the medium; I'_0 is the empirical mean excitation energy; $\beta = \frac{v}{c}$; $\frac{C'_0(\gamma)}{Z}$ is the shell correction, which considers target electrons' velocities when the charged particle is moving at a relatively low speed, correcting the assumption that electrons are at rest as the charged particle traverses; δ_F is the fermi density effect correction, which considers the shielding of far away electrons due to dielectric polarisation of the medium by a charged particle at relativistic speeds, introducing the fermi plateau; ΔL_{Bloch} is the

Bloch correction, which corrects differences between coulomb scattering and quantum scattering; and $\Delta L^B(a)$ is the Barkas-Andersen correction, which introduces polarity with through Z_1^3 (Ashley et al., 1972), correcting the assumption that the stopping power for a particle and the antiparticle is the same; and

$$f(\gamma) = \ln \left(\frac{1}{1 + 2\gamma \left(\frac{m_e}{M} \right) + \left(\frac{m_e}{M} \right)^2} \right) + \frac{W_{\max}^2}{4\gamma^2 M^2 c^4} \quad (\text{B.2})$$

(Salvat, 2022, p. 032809-6)

where

$$W_{\max} = \frac{2m_e c^2 (\gamma^2 - 1)}{1 + 2\gamma \left(\frac{m_e}{M} \right) + \left(\frac{m_e}{M} \right)^2} \quad (\text{B.3})$$

represents the maximum energy transfer in a head-on collision between the charged particle and an electron, c is the speed of light in a vacuum, and M is the mass of the charged particle.

The Barkas-Andersen correction is given by:

$$\Delta L^B(a) = \frac{Z_1 \alpha}{\gamma^2 \beta^3 m_e c^2} \frac{1}{Z} \int_0^{W_{\max}} dW \frac{df(W)}{dW} \times W \left[I_1(\xi) + \frac{1}{\gamma^2} I_2 \right] \quad (\text{B.4})$$

(Salvat, 2022, p. 032809-12)

where α is the Sommerfeld constant, W is the kinetic energy transferred to an electron in a collision, whose formula was established by Bethe and Ashkin (1953), $\frac{df(W)}{dW}$ is the generalised oscillatory function whose equations were established by Fernandez-Varea et al. (1993), and $I_1(\xi)$ and $I_2(\xi)$ are integral functions that are calculated using the equations established by Ashley et al. (1972). The Bloch correction is given by:

$$\Delta L_{\text{Bloch}} = \psi(1) - \Re \psi \left(1 + i \frac{Z_1 v_0}{v} \right) \quad (\text{B.5})$$

where Ψ represents the digamma function, $\Re$ represents the real part operator, v is the velocity of the incoming particle, and

$$v_0 = \frac{e^2}{\hbar} \quad (\text{B.6})$$

(Sigmund & Schinner, 2020)

C. Features of the model

#1 The tumour has an irregular, discoidal shape. Its surface is modeled as a smooth trigonometric radius perturbation on an oblate ellipsoid.

The oblate ellipsoid has a C semi-axis that is 60% less than the A semi-axis. A given position (x,y,z) is normalised to (nx, ny, nz), where $nx = \frac{x}{a}$, $ny = \frac{y}{a}$, and $nz = \frac{z}{c}$. The normalized radius is

$$r_{norm} = \sqrt{nx^2 + ny^2 + nz^2} \quad (C.1)$$

Angular coordinates are then computed, where the azimuthal angle ϕ is $\arccos\left(\frac{ny}{r_{norm}}\right)$ and polar angle theta is $\arccos\left(\frac{nz}{r_{norm}}\right)$.

The perturbed surface is created using the function:

$$Perturbation = A_i \sin\left(f_{\theta_i} + Phase_i\right) \cos(f_{\phi}, \phi) \quad (C.2)$$

A_i represents the amplitude, and it is capped at 0.12, so the maximum perturbation is 12% of the original ellipsoid radius. f_{θ_i} and f_{ϕ} control the number of bumps, while $Phase_i$ shifts the positions of the bumps.

For a given θ and ϕ , the perturbation function is run 6 times with different values, and 1+total perturbation is the multiplier for the oblate ellipsoid's radius at a given position (Figure5). This method was used for its computational efficiency.

#2. Natural heterogeneity/variation in tissue density is modelled using a monte carlo generator that picks values from a normal gaussian distribution.

3#. Breathing is modelled as an oscillatory sine wave in the y-z direction to cause misalignment between the proton beam and tumor. This allows one to estimate the impact of tumor motion on the number of damaged healthy and tumour cells.

$$center(t) = center_0 + A \sin\left(\frac{2\pi t}{T}\right) \cdot axis \quad (C.3)$$

The $center_0$ is the (20,0,0) position, A is breathing amplitude and T is breathing period. Axis represents a normalised vector, [0.05, 0.848, 0.528]. The y and z components of the normalised vector are greater than the x, helping direct tumour motion in the y-z axis.

The time of arrival of each proton is divided equally between all protons of the beam. It is assumed that each proton enters the tumour one at a time, and that all protons pass through the tumor in 3 breathing cycles.

$$t_{arrival} = \frac{i}{n_{protons}} \cdot (3T) \quad (C.4)$$

For a given arrival time, the tumour center position is calculated using equation (C.3) and it is checked whether the proton is present in the tumour. It is considered that the proton instantaneously travels through the tumour due to its high velocity.

D. Results of Standardised Regression and Local Sensitivity Analysis, and Linearised Bragg-Kleeman Fitting.

Table D.1

Standard regression analysis on range

Independent Variable	Unstandardized Slope (b)	sX	sY	Standardized Coefficient (β)	Linear Trend (R²)
Beam Energy	0.1843 cm/Mev	24.49	4.517	0.9996	0.999
Beam Energy Spread	0.0322 cm/%	1.133	0.0366	0.9973	0.995
Breathing Amplitude	0.0207 cm/cm	1.204	0.0361	0.6910	0.477
Angular Spread	0.0386 cm/deg	0.777	0.0464	0.6457	0.417

Table D.2

Standard regression analysis on range standard deviation

Independent Variable	Unstandardized Slope (b)	sX	sY	Standardized Coefficient (β)	Linear Trend (R²)
Beam Energy	0.0274 cm/MeV	24.49	0.6716	0.9990	0.998

Breathing Amplitude	0.0134 cm/cm	1.204	0.0164	0.9855	0.971
Beam Energy Spread	0.1215 cm/%	1.133	0.1407	0.9784	0.957
Angular Spread	0.0790 cm/deg	0.777	0.0638	0.9618	0.925

Table D.3

Standard regression analysis on range uncertainty %

Independent Variable	Unstandardized Slope (b)	sX	sY	Standardized Coefficient (β)	Linear Trend (R²)
Beam Energy Spread	0.5512 %/%	1.133	0.6394	0.9765	0.954
Breathing Amplitude	0.0521 %/cm	1.204	0.0661	0.9485	0.900
Angular Spread	0.3502 %/deg	0.777	0.2886	0.9423	0.888
Beam Energy	0.0568 %/MeV	24.49	1.4781	0.9405	0.884

Table D.4

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Local sensitivity analysis test on range

Independent Variable	Tested Range	Min	Max	Absolute Range (ΔY)	Relative Impact ($\% \Delta Y$)	Impact Rank
Beam Energy	150 – 220 MeV	12.37 cm	25.29 cm	12.92 cm	60.63%	1
Angular Spread	0.1° – 2.0°	21.29 cm	21.40 cm	0.11 cm	0.52%	2
Beam Energy Spread	0.1% – 3.0%	21.29 cm	21.38 cm	0.09 cm	0.42%	3
Breathing Amplitude	0 – 3.0 cm	21.26 cm	21.35 cm	0.09 cm	0.42%	4

Table D.5

Local sensitivity analysis test on range standard deviation

Independent Variable	Tested Range	Min	Max	Absolute Range (ΔY)	Relative Impact ($\% \Delta Y$)	Impact Rank
Beam Energy	150 – 220 MeV	0.82 cm	2.78 cm	1.96 cm	89.09%	1

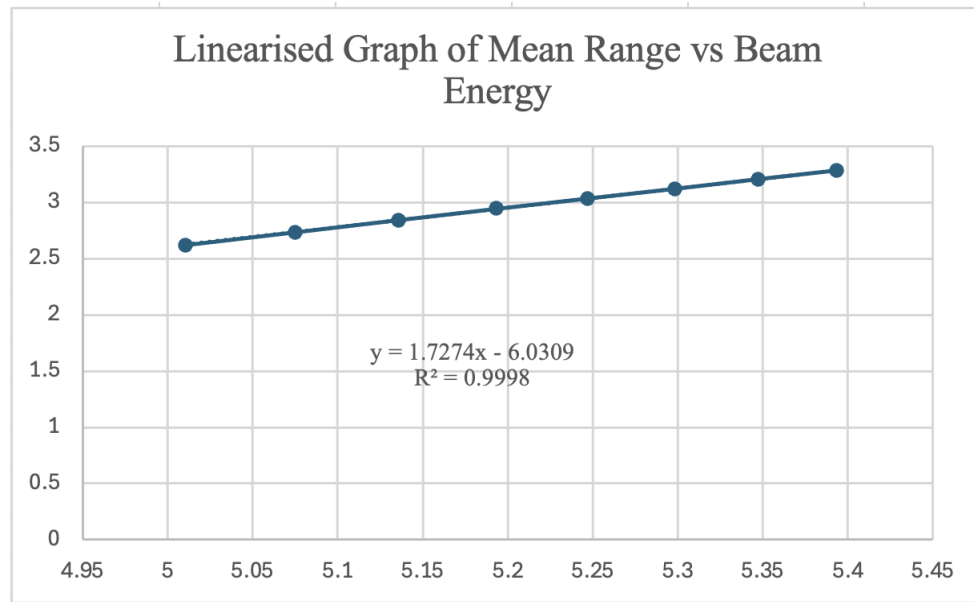
Beam Energy Spread	0.1% – 3.0%	2.19 cm	2.54 cm	0.35 cm	15.91%	2
Angular Spread	0.1° – 2.0°	2.21 cm	2.36 cm	0.15 cm	6.82%	3
Breathing Amplitude	0 – 3.0 cm	2.20 cm	2.24 cm	0.04 cm	1.82%	4

Table D.6

Local sensitivity analysis test on range uncertainty %

Independent Variable	Tested Range	Min	Max	Absolute Range (ΔY)	Relative Impact ($\% \Delta Y$)	Impact Rank
Beam Energy	150 – 220 MeV	6.63%	10.99%	4.36%	42.25%	1
Beam Energy Spread	0.1% – 3.0%	10.29%	11.88%	1.59%	15.41%	2
Angular Spread	0.1° – 2.0°	10.38%	11.05%	0.67%	6.49%	3
Breathing Amplitude	0 – 3.0 cm	10.32%	10.49%	0.17%	1.65%	4

Figure D.1: Linearised Graph of Mean Range vs Beam Energy



E. Subset of data collectible using the simulation

Table E.1: Effect of varying Beam Energy

beam_ energy_ mev	energy_ spread_ pet	angular_ spread_ deg	beam_ sp_ ot_ sigma_ cm	breathing_ amplitude_ cm	breathi_ ng_ peri_ od_ s	n_ fr_ ac_ tio_ ns	dose_ per_ fraction_ Gy	gap_ h_ ours	wee_ ken_ d_ g_ ap_ hou_ rs	R_ 9_ 0	R_ 5_ 0	media_ n_ bragg_ all	std_ bragg_ all	median_ bragg_ cl_ can	std_ bragg_ cl_ can	pct_ nuclea_ r_ interacti_ ons	lateral_ penumbra_ gaussian_ sigma_ cm	tumour_ k_ illed_ pct_ lfx	healthy_ k_ illed_ pct_ lfx
160.00	0.60000	0.30000	0.30000	0.00000	4.0000	30	2.0000	24.000	60.000	1.34	1.45	14.190	1.1193	14.260	0.70519	12.133	0.063217	4.4475	0.18396
170.00	0.60000	0.30000	0.30000	0.00000	4.0000	30	2.0000	24.000	60.000	1.56	1.67	16.090	1.4034	16.170	0.70159	13.467	0.27502	12.418	0.12980
180.00	0.60000	0.30000	0.30000	0.00000	4.0000	30	2.0000	24.000	60.000	1.78	1.89	17.960	1.6656	18.060	0.68992	14.700	1.0480	14.653	0.068367
190.00	0.60000	0.30000	0.30000	0.00000	4.0000	30	2.0000	24.000	60.000	2.00	2.11	19.840	1.9204	19.950	0.71085	16.067	0.45692	21.714	0.049155
200.00	0.60000	0.30000	0.30000	0.00000	4.0000	30	2.0000	24.000	60.000	2.22	2.33	21.810	2.1849	21.960	0.74905	17.567	0.44678	26.225	0.043802
210.00	0.60000	0.30000	0.30000	0.00000	4.0000	30	2.0000	24.000	60.000	2.44	2.55	23.940	2.4767	24.110	0.77834	18.867	0.44036	25.599	0.057598

beam_energy_mev	energy_spread_pct	angular_spread_deg	beam_spot_sigma_cm	breathing_amplitude_cm	breathing_period_s	n_fraction	dose_per_fraction_gy	gap_hours	weekend_gap_hours	R90	R50	median_bragg_all	std_bragg_all	median_bragg_clean	std_bragg_clean	pct_nuclear_interactions	lateral_penumbra_gaussian_sigma_cm	tumour_killed_pct_ifx	healthy_killed_pct_ifx
220.00	0.60000	0.30000	0.30000	0.0000	4.0000	30	2.0000	24.000	60.000	2.95	2.56	26.070	2.7623	26.270	0.79081	20.667	0.43400	25.327	0.074186
230.00	0.60000	0.30000	0.30000	0.0000	4.0000	30	2.0000	24.000	60.000	2.88	2.58	28.260	3.0585	28.490	0.80034	22.000	0.42736	25.034	0.089409

Table E.2: Effect of varying Beam Energy Spread

beam_energy_mev	energy_spread_pct	angular_spread_deg	beam_spot_sigma_cm	breathing_amplitude_cm	breathing_period_s	n_fraction	dose_per_fraction_gy	gap_hours	weekend_gap_hours	R90	R50	median_bragg_all	std_bragg_all	median_bragg_clean	std_bragg_clean	pct_nuclear_interactions	lateral_penumbra_gaussian_sigma_cm	tumour_killed_pct_ifx	healthy_killed_pct_ifx
200.00	0.05000	0.30000	0.30000	0.0000	4.0000	30	2.0000	24.000	60.000	2.410	2.12	21.810	2.1712	21.940	0.71069	17.567	0.44592	26.106	0.043651
200.00	0.3000	0.30000	0.30000	0.0000	4.0000	30	2.0000	24.000	60.000	2.410	2.12	21.810	2.1752	21.950	0.72010	17.600	0.44657	26.131	0.043699
200.00	0.60000	0.30000	0.30000	0.0000	4.0000	30	2.0000	24.000	60.000	2.410	2.12	21.810	2.1849	21.960	0.74905	17.567	0.44678	26.225	0.043802
200.00	1.0000	0.30000	0.30000	0.0000	4.0000	30	2.0000	24.000	60.000	2.410	2.12	21.800	2.2072	21.980	0.81405	17.533	0.44696	26.410	0.044041
200.00	2.0000	0.30000	0.30000	0.0000	4.0000	30	2.0000	24.000	60.000	2.410	2.12	21.760	2.3059	22.010	1.0716	17.400	0.45180	26.667	0.045516
200.00	3.0000	0.30000	0.30000	0.0000	4.0000	30	2.0000	24.000	60.000	2.410	2.12	21.710	2.4633	22.025	1.3985	17.467	0.45180	26.720	0.047699

Table E.3: Effect of varying Angular Spread

beam_energy_mev	energy_spread_pct	angular_spread_deg	beam_spot_sigma_cm	breathing_amplitude_cm	breathing_period_s	n_fraction	dose_per_fraction_gy	gap_hours	weekend_gap_hours	R90	R50	median_bragg_all	std_bragg_all	median_bragg_clean	std_bragg_clean	pct_nuclear_interactions	lateral_penumbra_gaussian_sigma_cm	tumour_killed_pct_ifx	healthy_killed_pct_ifx
200.00	0.60000	0.05000	0.30000	0.0000	4.0000	30	2.0000	24.000	60.000	21.706	22.287	21.810	2.1858	21.950	0.74651	17.533	0.43824	25.800	0.043280

200.00	0.60000	0.30000	0.30000	0.00000	4.00000	3.00000	2.00000	24.00000	60.00000	21.713	22.297	21.810	2.1849	21.960	0.74905	17.567	0.44678	26.225	0.043802
200.00	0.60000	0.50000	0.30000	0.00000	4.00000	3.00000	2.00000	24.00000	60.00000	21.752	22.303	21.820	2.1854	21.970	0.75417	17.567	0.46070	26.997	0.044621
200.00	0.60000	1.00000	0.30000	0.00000	4.00000	3.00000	2.00000	24.00000	60.00000	21.776	22.351	21.840	2.2046	22.000	0.78697	17.567	0.49978	29.509	0.048097
200.00	0.60000	1.50000	0.30000	0.00000	4.00000	3.00000	2.00000	24.00000	60.00000	21.791	22.398	21.880	2.2359	22.040	0.85180	17.600	0.54869	32.338	0.052976
200.00	0.60000	2.00000	0.30000	0.00000	4.00000	3.00000	2.00000	24.00000	60.00000	21.809	22.463	21.940	2.2669	22.100	0.92883	17.600	0.59995	35.177	0.059152

Table E.4: Effect of varying Beam Spot Size

beam_energy_mev	energy_spread_pct	angular_spread_deg	beam_spot_sigma_cm	breathing_amplitude_cm	breathing_period_s	n_fractions	dose_per_fraction_gy	gap_hours	weekend_gap_hours	R_90	R_95	median_bragg_all	std_bragg_all	median_bragg_clean	std_bragg_clean	pct_nuclear_interactions	lateral_penumbra_gaussian_sigma_cm	tumour_killed_pct_1fx	healthy_killed_pct_1fx
200.00	0.60000	0.30000	0.050000	0.0000	4.0000	30	2.0000	24.0000	60.0000	2.41065	2.215	21.715	2.1373	21.840	0.51024	17.633	0.35181	19.436	0.028109
200.00	0.60000	0.30000	0.10000	0.0000	4.0000	30	2.0000	24.0000	60.0000	2.41065	2.215	21.720	2.1221	21.850	0.51358	17.533	0.35817	20.108	0.028453
200.00	0.60000	0.30000	0.30000	0.0000	4.0000	30	2.0000	24.0000	60.0000	2.41065	2.215	21.810	2.1849	21.960	0.74905	17.567	0.44678	26.225	0.043802
200.00	0.60000	0.30000	0.50000	0.0000	4.0000	30	2.0000	24.0000	60.0000	2.41065	2.215	22.030	2.3315	22.230	1.0632	17.633	0.57477	33.615	0.071256
200.00	0.60000	0.30000	1.0000	0.0000	4.0000	30	2.0000	24.0000	60.0000	2.41065	2.215	22.970	2.5393	23.380	1.4461	17.367	0.95244	44.720	0.12462
200.00	0.60000	0.30000	1.5000	0.0000	4.0000	30	2.0000	24.0000	60.0000	2.41065	2.215	23.780	2.5760	24.340	1.4743	17.600	1.3620	47.608	0.20896

Table E.5: Effect of varying Breathing Amplitude

beam_energy_mev	energy_spread_pct	angular_spread_deg	beam_spot_sigma_cm	breathing_amplitude_cm	breathing_period_s	n_fractions	dose_per_fraction_gy	gap_hours	weekend_gap_hours	R_90	R_95	median_bragg_all	std_bragg_all	median_bragg_clean	std_bragg_clean	pct_nuclear_interactions	lateral_penumbra_gaussian_sigma_cm	tumour_killed_pct_1fx	healthy_killed_pct_1fx
200.00	0.60000	0.30000	0.30000	0.0000	4.0000	30	2.0000	24.0000	60.0000	2.41065	2.215	21.810	2.1849	21.960	0.74905	17.567	0.44678	26.225	0.043802

200.00	0.60000 0	0.30000	0.30000	0.50000	4.0000	30	2.0000	2 4. 0 0 0	60.000	2 1 2 . 7 8 2	2 2 . 2 . 5	21.860	2.4 784	21.960	0.756 14	16.800	0.45962	25.191	0.045221
200.00	0.60000 0	0.30000	0.30000	1.0000	4.0000	30	2.0000	2 4. 0 0 0	60.000	2 1 2 . 9 2	2 2 . 7 5	21.860	2.4 816	21.970	0.758 00	16.800	0.45941	25.215	0.045216
200.00	0.60000 0	0.30000	0.30000	1.5000	4.0000	30	2.0000	2 4. 0 0 0	60.000	2 1 2 . 8 1	2 2 . 3 8	21.880	2.4 881	21.995	0.761 53	16.800	0.45937	25.258	0.045213
200.00	0.60000 0	0.30000	0.30000	2.0000	4.0000	30	2.0000	2 4. 0 0 0	60.000	2 1 2 . 8 3 6 5	2 2 . 3 6 2	21.910	2.4 969	22.029	0.763 43	16.733	0.46045	25.333	0.045185
200.00	0.60000 0	0.30000	0.30000	2.5000	4.0000	30	2.0000	2 4. 0 0 0	60.000	2 1 2 . 8 4 6 6 8	2 2 . 4 4 1 8	21.930	2.5 077	22.070	0.766 90	16.733	0.46069	25.397	0.045151

Table E.6: Effect of varying Breathing Period

beam_ener_gy_mev	energy_spread_deg	angular_spread_deg	beam_spot_sigma_cm	breathing_amplitude_cm	breathing_period_s	n_fraction	dose_per_fraction_gy	gap_hours	weekend_gap_hours	R0	R5	median_bragg_peak_all	std_bragg_peak_all	median_bragg_peak_clean	std_bragg_peak_clean	pct_nuclear_interactions	lateral_penumbra_gaussian_sigma_cm	tumour_killed_pct_1fx	healthy_killed_pct_1fx
200.00	0.60000 0	0.30000	0.30000	0.0000	2.0000	30	2.0000	2 4. 0 0 0	60.000	2 1 2 . 7 9 3	2 2 . 5 7	21.810	2.1 849	21.960	0.749 05	17.567	0.44678	26.225	0.043802
200.00	0.60000 0	0.30000	0.30000	0.0000	3.0000	30	2.0000	2 4. 0 0 0	60.000	2 1 2 . 7 9 3	2 2 . 5 7	21.810	2.1 849	21.960	0.749 05	17.567	0.44678	26.225	0.043802
200.00	0.60000 0	0.30000	0.30000	0.0000	4.0000	30	2.0000	2 4. 0 0 0	60.000	2 1 2 . 7 9 3	2 2 . 5 7	21.810	2.1 849	21.960	0.749 05	17.567	0.44678	26.225	0.043802
200.00	0.60000 0	0.30000	0.30000	0.0000	5.0000	30	2.0000	2 4. 0 0 0	60.000	2 1 2 . 7 9 3	2 2 . 5 7	21.810	2.1 849	21.960	0.749 05	17.567	0.44678	26.225	0.043802
200.00	0.60000 0	0.30000	0.30000	0.0000	6.0000	30	2.0000	2 4. 0 0 0	60.000	2 1 2 . 7 9 3	2 2 . 5 7	21.810	2.1 849	21.960	0.749 05	17.567	0.44678	26.225	0.043802
200.00	0.60000 0	0.30000	0.30000	0.0000	8.0000	30	2.0000	2 4. 0 0 0	60.000	2 1 2 . 7 9 3	2 2 . 5 7	21.810	2.1 849	21.960	0.749 05	17.567	0.44678	26.225	0.043802

Table E.7: Two Parameter analysis sample (Beam energy and angular spread are varied)

beam_energy_mev	energy_spread_deg	angular_spread_deg	beam_spot_sigma_cm	n_fraction	dose_per_fraction_gy	gap_hours	weekend_gap_hours	R0	R5	median_bragg_peak_all	std_bragg_peak_all	median_bragg_peak_clean	std_bragg_peak_clean	pct_nuclear_interactions	lateral_penumbra_cm	tumour_killed_pct_1fx	healthy_killed_pct_1fx
180.00	0.60000	0.10000	0.30000	30	2.0000	24.000	60.000	17	18	17.960	1.6677	18.055	0.68756	14.733	0.0000	14.398	0.067779

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200.00	0.60000	2.0000	0.30000	30	2.0000	24.000	60.000	2 1	2 2	21.940	2.266 9	22.100	0.92883	17.600	0.50000	35.177	0.059152
								8 0 9	4 6 3								
210.00	0.60000	0.10000	0.30000	30	2.0000	24.000	60.000	2 3	2 4	23.930	2.478 8	24.110	0.77731	18.800	0.50000	25.237	0.056888
								8 5 5	4 8 8								
210.00	0.60000	0.57500	0.30000	30	2.0000	24.000	60.000	2 3	2 4	23.940	2.473 4	24.120	0.78334	19.000	0.50000	26.772	0.059640
								8 7 0	5 0 0								
210.00	0.60000	1.0500	0.30000	30	2.0000	24.000	60.000	2 3	2 4	23.970	2.493 5	24.140	0.82550	18.967	0.50000	29.213	0.065017
								8 8 8	5 3 1								
210.00	0.60000	1.5250	0.30000	30	2.0000	24.000	60.000	2 3	2 4	24.010	2.517 6	24.180	0.88211	19.000	0.50000	32.079	0.072261
								8 9 5	5 7 3								
210.00	0.60000	2.0000	0.30000	30	2.0000	24.000	60.000	2 3	2 4	24.040	2.542 7	24.240	0.94967	19.067	0.50000	34.842	0.080410
								9 2 4	6 3 2								
220.00	0.60000	0.10000	0.30000	30	2.0000	24.000	60.000	2 5	2 6	26.070	2.764 3	26.280	0.78978	20.667	0.50000	24.943	0.073145
								9 6 6 7	6 3 4								
220.00	0.60000	0.57500	0.30000	30	2.0000	24.000	60.000	2 5	2 6	26.080	2.761 8	26.290	0.79506	20.667	0.50000	26.557	0.077014
								9 7 6	6 5 1								
220.00	0.60000	1.0500	0.30000	30	2.0000	24.000	60.000	2 5	2 6	26.110	2.775 0	26.310	0.83219	20.667	0.50000	29.032	0.084247
								9 9 0	6 6 4								
220.00	0.60000	1.5250	0.30000	30	2.0000	24.000	60.000	2 6	2 6	26.140	2.799 1	26.350	0.88837	20.600	0.50000	32.074	0.093677
								0 1 3	7 0 2								
220.00	0.60000	2.0000	0.30000	30	2.0000	24.000	60.000	2 6	2 6	26.190	2.820 7	26.400	0.95234	20.800	0.50000	35.011	0.10427
								0 2 2	7 5 6								

Figure E.1: Grid map of effect of variation of beam energy and angular spread on various metrics.

