Unveiling the Role of Virtual Phantoms in Proton Therapy: A Computational Journey

Saidova Sevara, Mamayusupova Muqaddas, Abdukholiqov Fakhriddin

National University of Uzbekistan named after Mirzo Ulugbek, Faculty of Physics, Nuclear Physics Department

Abstract

This paper explores the current landscape of proton therapy, with a focus on the challenges and advancements in intensity-modulated proton therapy (IMPT). Three key areas are examined: treatment planning, delivery, and motion management. The discussion includes dose calculation uncertainties, emphasizing the importance of accurate computed tomography (CT) data and the potential of dual-energy CT scanners. The article delves into the critical aspect of Relative Biological Effectiveness (RBE) in IMPT, proposing strategies for optimizing treatment effectiveness. The simulation of proton interactions is explored, emphasizing the role of virtual phantoms in modeling complex processes like elastic and inelastic scattering, bremsstrahlung, and ionization. The anatomy of a virtual phantom is detailed, highlighting its role in representing the human body's intricacies for precise proton therapy simulations. The article underscores ongoing research and development efforts to overcome limitations, predicting significant improvements in IMPT in the coming years. Ultimately, the goal is to establish proton therapy as a premier treatment modality for various solid tumors.

Keywords: proton therapy, intensity-modulated proton therapy (IMPT), treatment planning, dose calculation uncertainties, Relative Biological Effectiveness (RBE), proton beam characteristics, Monte Carlo methods, Bragg peak, virtual phantoms

Introduction

The interest and enthusiasm for proton therapy (PT) in cancer management have grown significantly, evident in events such as the 2016 special issue on particle therapy in the International Journal of Radiation Oncology, Biology, Physics[1] and numerous publications like "Principles and Practice of Proton Beam Therapy" [2] and others [3]. According to the Particle Therapy Co-Operative Group (PTCOG), the number of proton therapy centers has risen by 40% in the last three years [4]). Protons, with their unique energy deposition characteristics, offer favorable dose distributions compared to photons, yet clinical data hasn't unequivocally demonstrated the increased effectiveness of PT [5,6,7,8]. Challenges include limitations in the current practice, particularly with passively scattered proton therapy (PSPT), which has constraints in tailoring dose distributions, especially proximally. Concerns about neutron dose in PSPT also exist, though the risk is lower than with photons [9,10,11,12,13].

The most advanced form of PT, intensity-modulated PT (IMPT), has only become widely available in the past five years [14,15,16]. Utilizing pencil beam scanning technology, IMPT provides dose modulation to balance distributions optimally for the target and various organs at risk (OARs). IMPT, a three-dimensional (3D) technique, optimizes the intensities of beamlets simultaneously across proton energies and beams, distinguishing it from intensity-modulated x-ray radiation therapy (IMRT), which modulates intensities in two dimensions.

With the increasing adoption of IMPT, research and development efforts are growing to address the limitations and uncertainties. Lomax et al. noted in 2015 that PBS proton therapy was in its infancy [17].

Predictions suggest substantial improvements in the next decade, paralleling the evolution of photon therapy with the development of IMRT and image-guided radiation therapy (IGRT). This article aims to discuss current limitations and uncertainties in IMPT, along with ongoing and future developments to overcome them, ultimately advancing PT as a premier treatment modality.

Three key areas of IMPT are examined: treatment planning, treatment delivery, and motion management. Treatment planning subtopics encompass uncertainties in proton range and dose computations, robust planning and optimization, adaptive treatment planning and delivery, and considerations of relative biological effectiveness (RBE) for protons. Treatment delivery subtopics include enhancing proton beam characteristics, in-room image guidance, contour-based beamlet scanning, and proton range determination during treatment. The impact of interfractional (e.g., tumor shrinkage, weight loss) and intrafractional (e.g., respiration-induced motion) anatomic variations and strategies to mitigate their effects are also discussed. The assertion is that technological and physical improvements in IMPT will significantly enhance clinical outcomes, establishing proton therapy as a standard for various solid tumor treatments.

Dose calculations

Calculation of dose distributions and associated parameters is a critical aspect of intensity-modulated proton therapy (IMPT), and inherent uncertainties in the current treatment planning systems pose a potential challenge to its efficacy. The literature has extensively highlighted the impact of uncertainties in dose computation on treatment outcomes [11,12], and addressing these uncertainties represents an area where notable improvements can be made with a relatively modest effort.

Dose distributions, derived from computed tomography (CT) data, form the foundation for treatment planning in IMPT. The accuracy of these computed dose distributions is influenced by various factors, including both random and systematic uncertainties in CT numbers, the conversion of CT numbers to stopping power ratios (SPRs) as discussed in the section on range uncertainty, and assumptions made in semiempirical models and algorithms used for dose computations. Additionally, limitations in imaging systems, particularly in accurately imaging high-Z materials like dental fillings, can introduce errors in CT numbers and generate artifacts that may obscure tissue boundaries. These uncertainties related to CT numbers and imaging artifacts have a more significant impact on proton therapy compared to photon therapy. Dual-energy CT (DECT) scanners offer a potential solution by reducing systematic errors and minimizing high-Z artifacts compared to conventional single-energy CT scanners.

Practical considerations, such as the need for efficient treatment planning on affordable computers, lead to the use of analytic semiempirical models for proton dose computations. However, these models often involve numerous assumptions and approximations, such as ray tracing to correct for tissue heterogeneities, assuming slab geometry for estimating lateral spreading of proton beamlets in heterogeneous media, neglecting scattering from apertures or multileaf collimators (MLCs), and simplifying the nuclear component of beams at the end of calculations. Monte Carlo techniques, or their accelerated variants, are crucial to overcome the limitations inherent in these approximations and assumptions. Monte Carlo methods are also essential for calculating physical quantities like linear energy transfer (LET), necessary for computing relative biological effectiveness (RBE).

Several academic institutions and vendors are actively developing and investigating Monte Carlo methods. These methods employ statistical techniques to track a large number of protons and their secondary progeny, simulating their dose deposition through the treatment delivery system and the patient's anatomy represented by the CT image. Despite advancements, Monte Carlo methods are not yet sufficiently fast for routine proton dose calculations, partly due to the additional dimension of proton energy, significantly increasing CPU time requirements. To address this speed issue, accelerated Monte Carlo

methods, such as the "track repeating algorithm," are being developed. These methods, while nearly as accurate as full-fledged Monte Carlo, are two or more orders of magnitude faster by tabulating proton tracks and their interactions for reuse in subsequent simulations.

In addition to accelerating Monte Carlo, the utilization of specialized hardware, such as graphical processing units (GPUs), offers a significant boost in speed. GPU implementations, however, may necessitate certain approximations due to current hardware limitations. In a typical Monte Carlo or accelerated Monte Carlo process for dose and LET distribution computation, beamlet phase spaces (proton positions, directions, and energies) are precomputed in a plane normal to the beamlet direction. These phase spaces serve as a starting point for tracking particles in the patient during IMPT dose calculations. The integration of accelerated Monte Carlo systems and specialized hardware holds promise for advancing the state of IMPT technology[15].

Proton therapy harnesses the physical properties of protons, leveraging their ability to deposit the majority of their energy precisely at the target site—known as the Bragg peak. This focused delivery reduces collateral damage to surrounding healthy tissues, making proton therapy an increasingly preferred choice for cancer treatment.

Relative Biological Effectiveness (RBE) in proton therapy

Understanding proton RBE becomes even more crucial in the context of Intensity-Modulated Proton Therapy (IMPT), where each beam exhibits a highly heterogeneous dose distribution, magnifying the complexities associated with RBE. On the flip side, IMPT's inherent flexibility provides an opportunity to leverage the high RBE around the Bragg peak by incorporating this information into optimization processes, thereby enhancing treatment effectiveness[16].

To unequivocally demonstrate the advantages of IMPT, a comprehensive understanding of the clinical effects arising from the variability of RBE on treatment response is imperative. It is crucial to address other sources of uncertainties and incorporate residual uncertainties into computed dose distributions to reveal the clinical consequences of RBE. This knowledge could pave the way for the development of more reliable models predicting RBE as a function of dose, Linear Energy Transfer (LET), and the α and β values of tissues. Existing models are often simplistic, leading to proton RBE that is a linear function of LET, which contradicts recent high-precision experiments [17,18,19].

Robust RBE models are not only vital for assessing the potential clinical impact of IMPT dose distributions but also for optimizing these distributions to maximize the biological effect, particularly in the tumor target. The characteristic Bragg curve of protons, with the RBE-weighted dose at the Bragg peak potentially 30% to 40% higher than the entrance dose compared to the physical dose, suggests that utilizing a variable RBE should result in an even greater differential between the tumor target and normal tissue biologically effective dose than assuming a constant RBE. Strategies for achieving this include IMPT optimization based on a variable RBE model or criteria defined in terms of RBE-weighted dose, similar to approaches used in carbon therapy [10]. Other strategies involve optimizing based on dose $\times$ LET to minimize LET in critical normal tissues [16] or placing constraints on LET and optimizing spot placement. However, significant research gaps exist in our understanding of RBE, necessitating further studies analyzing clinical outcomes data with RBE and LET information. Additionally, refining or developing new models to predict RBE and intercomparing approaches for incorporating biological effect models into the evaluation and optimization of IMPT is essential. Lastly, evaluating the impact of factors like interfractional and intrafractional anatomy variations on biological consequences, particularly in regions affected by distal edge degradation, is crucial to fully exploit and demonstrate the true potential of IMPT.

Simulation of proton interactions

Simulation of proton interactions is a crucial aspect in the realm of proton therapy, and virtual phantoms serve as indispensable tools for these simulations. These simulations involve the consideration of various intricate processes, each playing a pivotal role in understanding how protons behave when traversing through different tissues. Here, we delve into the multifaceted nature of proton interactions within virtual phantoms, exploring processes such as elastic and inelastic scattering, bremsstrahlung, and ionization.

In the simulation of proton interactions, elastic scattering is a fundamental process where protons change direction without any change in energy. This phenomenon is essential to model accurately, as it influences the trajectory of protons within the tissue, ultimately impacting the dose distribution. Understanding elastic scattering is vital for predicting how protons navigate through different anatomical structures within the virtual phantom[14].

Contrastingly, inelastic scattering involves a change in both direction and energy of protons as they interact with atomic nuclei. This process is significant in capturing the complex interactions that occur within tissues, influencing the energy deposition patterns. Accurate modeling of inelastic scattering within virtual phantoms enhances the precision of dose predictions, contributing to the optimization of proton therapy treatment plans.

The phenomenon of bremsstrahlung, or braking radiation, occurs when protons experience acceleration or deceleration in the vicinity of atomic nuclei, emitting photons in the process. In the context of proton therapy simulations, bremsstrahlung is a crucial aspect to consider, as it contributes to the overall energy loss of protons and influences the dose distribution. Virtual phantoms enable the comprehensive modeling of bremsstrahlung events, allowing for a more realistic representation of the radiation interactions.

Ionization involves the removal of electrons from atoms, leading to the creation of positively charged ions. In proton therapy simulations, ionization is a central process, as it directly influences the biological effects of radiation[17]. Accurate modeling of ionization events within virtual phantoms contributes to a better understanding of how protons deposit energy along their path, affecting both tumor and healthy tissues. This information is crucial for predicting the biological response to the radiation delivered during proton therapy.

These simulations collectively contribute to predicting the energy deposition and dose distribution within the virtual anatomy represented by phantoms. While providing a virtual environment for these interactions, phantoms play a pivotal role in advancing our understanding of proton therapy and refining treatment plans[12].

Anatomy of a Virtual Phantom

Virtual phantoms serve as intricately detailed replicas of the human body's geometry, capturing the diverse array of tissues and organs. The faithful representation of anatomical details is critical for accurately predicting the interactions of protons during the course of treatment.

In the context of EGS simulations, the geometry of virtual phantoms is defined through constructs like boxes or cylinders within the simulation's input file. These constructs outline the spatial distribution of various tissues, enabling a three-dimensional depiction of the anatomical structure.

To facilitate the simulation of proton interactions at a microscopic level, virtual phantoms undergo voxelization, a process where the continuous anatomical structure is discretized into small, uniform volumes known as voxels. This voxelized representation forms a grid structure, allowing for precise modeling of proton transport and dose deposition.

EGS simulations utilize this voxelized grid structure to simulate the passage of protons through discrete volumes, enabling the calculation of energy deposition at a localized level within the phantom.

Each voxel within the virtual phantom is assigned specific material properties corresponding to the biological tissues it represents. Material properties include parameters such as density, elemental composition, and atomic number, which influence the behavior of protons as they traverse through different tissues.

EGS simulations incorporate these material properties to accurately model the stopping power and energy loss of protons in various tissues, contributing to the realism of the virtual phantom[18].

Virtual phantoms often integrate computed tomography (CT) imaging data to enhance the accuracy of their anatomical representation. Real patient CT scans provide valuable information about tissue density variations, aiding in the assignment of material properties and ensuring a more realistic simulation[19]. In EGS simulations, CT data can be incorporated to refine the voxelized structure, aligning the virtual phantom closely with the actual patient anatomy and improving the precision of proton interaction predictions. Beyond general anatomy, virtual phantoms can delineate specific biological structures and target volumes relevant to proton therapy. This includes defining tumor volumes, critical organs, and other anatomical features crucial for treatment planning.

EGS simulations consider these delineated structures when modeling proton interactions, allowing for a targeted analysis of dose delivery to the tumor while minimizing exposure to surrounding healthy tissues[13]. Some virtual phantoms incorporate dynamic elements such as motion and deformation modeling. This is particularly relevant in scenarios where anatomical structures undergo changes over time, such as respiratory motion or deformation due to organ motion. EGS simulations can account for these dynamic factors, enabling a comprehensive understanding of how proton therapy interacts with moving or deforming anatomies within the virtual phantom. The comprehensive anatomy of a virtual phantom, encompassing geometric fidelity, voxelized structures, material properties, CT data integration, delineated biological structures, and dynamic modeling, forms the foundation for accurate and insightful simulations of proton therapy interactions. These virtual representations play a pivotal role in advancing the understanding and optimization of proton therapy treatments.

Summary

In summary, the growing interest in proton therapy (PT) for cancer treatment is evident, with advancements such as intensity-modulated proton therapy (IMPT) marking significant progress. Despite the potential benefits of protons, challenges persist in demonstrating their superiority over traditional photon therapy. The current state of IMPT reflects a technology in evolution, analogous to the early stages of photon therapy before the development of advanced techniques like intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT).

The three major areas of focus in IMPT—treatment planning, treatment delivery, and motion management—underscore the need for addressing uncertainties and limitations. Treatment planning involves considerations of proton range, dose computations, and factors influencing relative biological effectiveness (RBE). Treatment delivery aims to enhance proton beam characteristics and optimize dose distributions. Motion management addresses the impact of anatomical variations during treatment.

Dose calculations in IMPT are crucial, and efforts to improve accuracy involve advancements in computed tomography (CT) data utilization, Monte Carlo methods, and specialized hardware like graphical processing units (GPUs). These developments contribute to refining treatment plans and optimizing the therapeutic potential of proton therapy.

The recognition of uncertainties in the assumed constant RBE of protons prompts a closer examination of the variability of RBE along the proton beam path. Understanding the complexities of RBE is particularly critical in IMPT, where each beam exhibits a highly heterogeneous dose distribution. Optimizing IMPT dose distributions based on a variable RBE model or criteria defined in terms of RBE-weighted dose offers potential avenues for more effective treatments. However, substantial research gaps exist, necessitating further studies analyzing clinical outcomes with RBE and linear energy transfer (LET) information.

In conclusion, while proton therapy, especially IMPT, shows promise in providing precise and effective cancer treatment, ongoing research and technological advancements are vital to address current limitations and uncertainties. The evolution of IMPT over the next decade is anticipated to significantly enhance its clinical outcomes, potentially establishing proton therapy as a standard and preferred treatment modality for various solid tumors.

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