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Robust Proton Treatment Planning: Physical and Biological Optimization

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Accurate prediction of tumor control and toxicities in radiation therapy faces many uncertainties. Besides interpatient variability in the response to radiation, there are also dosimetric uncertainties, that is, differences between the dose displayed in a treatment planning system and the dose actually delivered to the patient. These uncertainties originate from several sources including imperfect knowledge of the patient geometry, approximation in the physics of radiation interaction with tissues, and uncertainties in the biological effectiveness of radiation. Generally, uncertainties are considered in the treatment planning process by applying margins. In intensity-modulated radiotherapy (IMRT), this leads to the planning target volume (PTV) concept. Intensity-modulated proton therapy (IMPT) is widely considered as the future of proton therapy. The treatment planning methods for IMPT and IMRT are similar and based on mathematical optimization techniques for both modalities. However, the PTV concept has fundamental limitations in IMPT. Therefore, researchers have developed robust optimization methods that directly incorporate uncertainties into the IMPT optimization problem. In recent years, vendors of commercial planning systems have started to implement these methods so that robust IMPT planning becomes available in clinical practice. This article summarizes uncertainties in proton therapy and the limitations of the PTV concept to deal with them. Subsequently, robust optimization techniques to overcome these limitations are reviewed.

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Uncertainties in Proton Therapy Planning

Treatment planning in proton therapy faces many uncertainties. The first uncertainty in the treatment planning chain is target delineation. Delineation of the gross tumor volume (GTV) based on CT, MR, and PET imaging is challenging, in part because all current imaging modalities only visualize surrogates for the presence of tumor, but do not visualize the tumor per se. Delineation of the clinical target volume (CTV), which aims to include microscopic tumor infiltration into normal tissues, faces even larger uncertainty[1] because microscopic tumor cannot be visualized with current imaging techniques. Following target delineation, there are also uncertainties in dose prescription. There is variability in tumor radiosensitivity between patients as well as heterogeneity within the individual patient's tumor related to genomic and physiologic factors. Concepts of biological target volume have been proposed to quantitatively consider tumor heterogeneity based on imaging information but are not being used routinely in the clinic.[2] Although these uncertainties may be the largest in the treatment planning chain, they are not specific to proton therapy and thus not the topic of this article. Instead this article will focus on the following:

- Uncertainties in predicting the physical dose distribution. Here, we focus on the particle therapy–specific problem of range uncertainty.
- Uncertainties in predicting the biological dose distribution, that is, the uncertainty in predicting the distribution of Relative Biological Effectiveness (RBE)-weighted dose.

Physics Uncertainties in Proton Therapy

Under the term physics uncertainties, we summarize all uncertainties in predicting the physical dose distribution

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delivered to the patient. Most physical uncertainties originate from an imperfect patient model. The most important input to treatment planning is the planning CT image, which has several limitations. First, the planning CT is only a snapshot of possible patient geometries which may not be reproducible in day-to-day treatment due to setup uncertainty and interfraction and intrafraction organ motion. Second, the Hounsfield numbers obtained from the planning CT, which from a physics perspective display photon attenuation coefficients, are an imperfect input for dose calculation algorithms. Not only is there statistical noise in CT images but also there are systematic uncertainties because there is no well-defined relationship between Hounsfield numbers and tissue properties. Most prominently, uncertainty in the conversion of Hounsfield numbers to stopping power for proton beams represents a type of uncertainty that is unique for charged particle radiotherapy.

Besides uncertainties that arise from an imperfect patient model, additional approximations are being made. For example, pencil beam algorithms are being applied because of their computational efficiency at the cost of lower accuracy compared to Monte Carlo methods. Many of these uncertainties lead to errors in predicting the range of protons in a patient and thus the location of the distal dose fall-off. These can be on the order of several millimeters in water equivalent path length caused by the conversion from CT image to tissue properties, underestimation of scattering by analytical algorithms, and interfaces from low- to high-density tissues parallel to the beam affecting scattering.[3,4] The effect of uncertainties related to imaging, setup, or dose calculation algorithms in proton therapy has been extensively studied.[5-7] Consequently, an additional range margin needs to be considered in proton therapy to ensure tumor coverage.[8]

Treatment planners have long been aware of uncertainties in proton therapy planning and delivery, and consequently devised heuristics to ensure that tumor dose prescriptions and organ dose constraints are fulfilled despite errors in planning and delivery. Examples of such methods are as follows:

- Choice of beam directions. Typically, it may be possible to minimize potential effect of range uncertainties by using a larger number of beam directions. In addition, carefully selecting beam angles not to go through regions of day-to-day anatomical variations or region with large anatomical density variations results in more robust plans.
- In treatment planning for passively scattered proton therapy, range and modulation of the spread-out Bragg peak is increased to account for range uncertainty. Widening of the aperture and compensator smearing is used to account for setup uncertainty.[9,10]

Pencil beam scanning is gradually replacing passively scattered proton therapy.[11,12] IMPT is seen as the future of proton therapy by many researchers and practitioners. IMPT uses treatment planning methods that are very similar to those used in IMRT planning.[13] For both modalities, clinical planning goals are formulated mathematically in terms of objective functions. Subsequently, mathematical optimization algorithms are used to determine pencil beam intensities that minimize the objective function value and, in that sense, best meet the planning goals.

At first glance, it may appear logical to also use the same concept for handling uncertainty. Delivery uncertainties in IMRT are typically considered by a margin used to create a Planning Target Volume (PTV) or, in the case of moving targets, an Internal Target Volume (ITV). These margin assignments depend on the treatment site and tumor location although general recipes have been suggested.[14] However, the PTV concept has significant limitations and shortcomings in IMPT.[7,15] The fundamental assumption behind the PTV concept is that the shape of the dose distribution is largely unaltered by the underlying changes of the patient geometry. Hence, it is assumed that, as long as the CTV moves within the boundaries of the PTV, and the PTV is irradiated to the prescribed dose, the CTV is guaranteed to receive the prescribed dose. Although this is an acceptable assumption in IMRT, it is no longer valid for protons.

This issue is illustrated in Figures 1A and 2A for an ependymoma patient, in whom the target contains parts of the brainstem. The treatment plan consists of 3 coplanar beams and was created using conventional IMPT planning aiming at a prescription dose of 50 Gy physical dose (corresponding to 55 Gy [RBE] for a constant RBE of 1.1); 5% overdose was allowed in those parts of the CTV that do not overlay the brainstem. Additional planning objectives were conformity as well as minimizing dose to the brainstem and the surrounding healthy tissues. A 2 mm CTV to PTV margin was added for IMPT planning. Figure 1A shows the dose distribution (right panel) as well as the contributions of the 3 individual fields. Figure 2A shows the deviation from the prescription dose for the nominal scenario (no range error), a range overshoot scenario, and a range undershoot scenario. Range errors were modeled by upscaling and downscaling the Hounsfield numbers of the planning CT by 4.6%. Figure 2A illustrates that the range errors do not simply lead to underdose at the edge of the CTV that could be compensated for by larger margins. Instead, range errors lead to hot spots and cold spots inside the target volume. The reason becomes apparent in Figure 1A. A range error leads to a relative shift of the dose contributions, which consequently do not add up to the planned homogeneous target dose. For a range undershoot, an over-proportionate amount of dose is shifted back into the CTV. This leads to hot spots, which may be undesirable in those parts of the CTV that contain critical normal tissues such as the brainstem. For a range overshoot, an over-proportionate amount of dose is shifted out of the CTV, which causes cold spots in the CTV. The cause of such degradations of the dose distribution lies in the steep dose gradients in the dose contributions of individual fields. These are not influenced by adding larger margins, illustrating the need for new approaches to account for uncertainty.

In addition to this fundamental limitation, there are other shortcomings of the PTV concept in IMPT. For example, range