Recent Advances in Intensity Modulated Proton Therapy Treatment Planning Optimization

Gino Lim†
Department of Industrial Engineering
University of Houston, Houston, USA
Tel: (+1) 713-743-4194, Email: ginolim@uh.edu

Wenhua Cao
Department of Industrial Engineering
University of Houston, Houston, USA
Tel: (+1) 713-743-4186, Email: wcao2@uh.edu

Radhe Mohan
Department of Radiation Physics
The University of Texas MD Anderson Cancer Center, Houston, USA
Tel: (+1) 713-563-2545, Email: rmohan@mdanderson.org

Abstract Radiation therapy is a non-invasive treatment modality for cancer patients. Radiation therapy treatment planning for cancer patients provides many challenging optimization problems. Various variables of a treatment plan need to be optimized so that the resulting plan can kill all cancerous cells while minimizing damage on the patient's normal tissues. Intensity modulated proton therapy (IMPT) has recently emerged as one of the most advanced radiation therapy modalities, and is being adopted by more and more cancer hospitals in the U.S. and the World. However, optimization methods that are specifically designed for IMPT treatment planning have not been well studied. Unlike conventional photon-based radiation therapies such as 3D conformal radiation therapy (3DCRT) and intensity modulated radiation therapy (IMRT), IMPT is highly sensitive to uncertainties and its optimization involves very large data sets. In addition, the biological effects of protons are greater in tissues. In this paper, we introduce recent advances in IMPT optimization methods and demonstrate how uncertainty incorporated models and efficient solution algorithms help selecting treatment variables including beam angles, proton energy levels, and intensity profiles. Furthermore, optimization models considering proton biological effects are discussed.

Keywords: radiation therapy, proton, IMPT, robust optimization

1. INTRODUCTION

The recent rapid development of proton therapy for cancer treatment has essentially relied on the physical property of protons and its resulting therapeutic benefits. The deposited dose of a proton beam, starting from a low entrance dose level, increases gradually along with the increasing depth, then suddenly jumps to a sharp peak known as Bragg peak. Dose deposition then sharply falls to zero a few millimeters beyond the Bragg peak (see Figure 1). Since a beam's energy determines the finite depth to which it can penetrate, proton beam delivery plan can be developed by controlling proton energy, such that the Bragg peaks are formed to cover the tumor target. Therefore, proton beams may deliver nearly no dose to regions beyond the target, which is typically infeasible for photon beams such as 3D

conformal radiation therapy (3DCRT) and intensity modulated radiation therapy (IMRT).

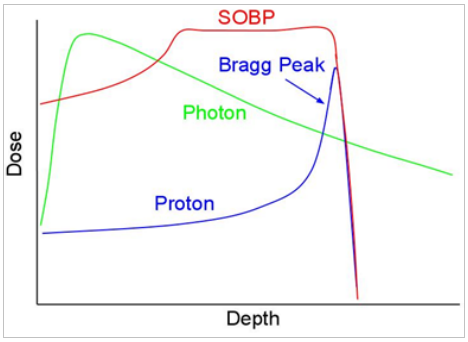


Figure 1: A comparison of the amount of radiation delivered with conventional photon beam radiation therapy versus proton therapy.

Intensity modulated proton therapy (IMPT) in which the intensity of all spots (Bragg peaks) can be modulated in three dimensions simultaneously is considered one of the most advanced cancer treatments available today. Increasingly more IMPT facilities have been developed and available to patients around world. However, most of the current procedures and parameter configurations for IMPT treatment planning are still based on limited clinical knowledge and operational evaluation. Research on IMPT treatment planning optimization is in a great need such that the clinical outcome and operational efficiency of IMPT can be fully exploited. In this paper, we review several key aspects of IMPT treatment planning optimization and relevant studies from the literature. Hence, there is ample opportunity to explore the true potential of using proton particles for treating cancer patients.

The rest of the paper is organized as follows. Section 2 describes the impact of uncertainty in IMPT delivery and treatment planning. Section 3 discusses the problem of optimizing important treatment variables, such as beam angle, energy level and spot profile. Section 4 presents the biological effects in IMPT and Section 5 concludes the paper.

2. TREATMENT PLANNING OPTIMIZATION UNDER UNCERTAINTY

Although IMPT is proven to be effective in delivering more superior dose distributions than conventional external beam radiation therapy including IMRT, uncertainties affect IMPT to a greater degree than IMRT (Lomax et al. 2004a). Because the greatest energy release is at scanning spots or Bragg peaks of a proton beam (see Figure 1), the uncertainty in the depth of a proton beam may lead to serious overshoot or undershoot in dose distribution compared to what was designed prior to delivery. Thus, unanticipated overdose and underdose can be created in the dose distributions actually delivered. There are two major sources of uncertainties (Lomax 2008b, Lomax 2008a, Unkelbach et al. 2009). One of them is the *range uncertainty* of proton beams that can be caused by CT artifacts, the conversion from Hounsfield units to stopping powers, and geometric changes of the patients such as weight gain or loss. The *patient setup error* is another source of uncertainty. It can be caused by the misalignment of patient positions or tissue density heterogeneities.

2.1 Min-Max Model

One of the key optimization problems in IMPT treatment planning is to determine appropriate intensities or weights of scanning spots within the three-dimensional target volume with the objective of achieving the prescribed dose on the tumor volume with a minimum dose on the normal tissues. It is called the spot intensity optimization (SIO) problem.

Let $x \in \Re^n$ denote the spot intensity vector and $A' \in R$ denote the uncertainty scenario, where $R = \{A_1, A_2, \dots, A_n\}$ is the uncertainty set for dose contribution instance matrices. A min-max robust optimization model (Fredriksson et al. 2011) can be formulated as follows,

$$min_x\{max_{A' \in R}\{f(g(x, A'))\}, x \geq 0\}, \quad (1)$$

where the function g calculates the deposited dose for all voxels, commonly $g(x, A') = A'x$, and f is the penalty function which indicates the deviation between optimized and desired dose levels. Examples of the objective function, f, can be found in (Unkelbach et al. 2007, Cao and Lim 2011, Fredriksson et al. 2011).

Furthermore, the general stochastic model can be formulated by adding the probability of uncertainty scenarios, $p(A')$, i.e.,

$$min_x\{max\{\sum_{A' \in R} p(A') \cdot f(g(x, A'))\}, x \geq 0\}, \quad (2)$$

where $p(A') \in \Re^{|R|}$, $\forall A' \in R$, and $\sum_{A' \in R} p(A') = 1$. Either a range or a distribution can be used to define $p(A')$ according to the treatment planner's preference.

2.2 Worst-Case Dose Approach

In order to evaluate the robustness of an IMPT treatment, the worst-case dose distribution was introduced by (Lomax et al. 2004b). This is obtained based on different dose distributions according to different

uncertainty scenarios, e.g., different ranges of proton beams and setup errors. If a voxel is located within the target volume, the dose of this voxel is set as the minimum of all dose distributions in the worst-case dose distribution. If a voxel is located in the surrounding normal tissues, the dose of this voxel is set as the maximum of all dose distributions. Although the worst-case dose distribution is physically invalid, it provides a conservative lower bound of the uncertain plan quality.

A few recent studies adopted the concept of worst-case dose concept in their robust IMPT optimization models (Pflugfelder et al. 2008, Chen et al. 2012, Liu et al. 2012a, Liu et al. 2012b). The worst-case dose based robust IMPT optimization model can be formulated as follows,

$$min_x\{\lambda_{A_0}\{f(g_{nominal}(x,A_0))\}+ \lambda_{A'}\{f(g_{worst-case}(x,A'))\},x\geq 0\}, \quad (3)$$

where A_0 indicates the nominal scenario, and λ_{A_0} and $\lambda_{A'}$ are the weighting factors for the penalty functions considering nominal and worst-case dose, respectively.

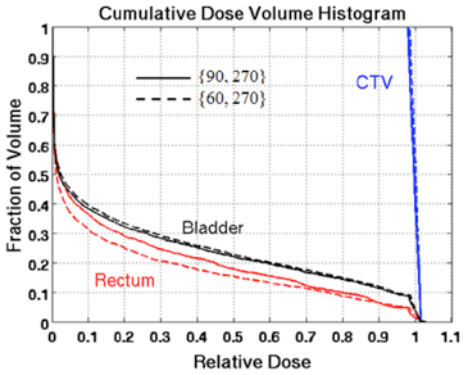
3. OPTIMIZING TREATMENT DELIVERY PARAMETERS

In addition to spot intensities, other important variables can be optimized for an IMPT treatment plan, such as beam angles, proton energies and spot positions. The selection of beam angles, proton energies and spot positions essentially affects both the resulting treatment quality and the delivery efficiency. For example of prostate cancer cases, an IMPT plan using two parallel-opposed beam angles and a plan with two orthogonal beams may react very differently towards uncertainties, even though the same delivery time is needed (Tang et al. 2012). However, a three-beam plan is generally more robust than a two-beam plan, while the three-beam plan requires more time in delivery (Cao et al. 2011).

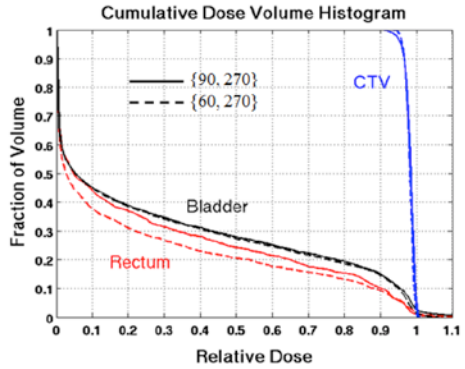
3.1 Beam Angle Selection

A typical IMPT treatment employs two to four beam angles from which radiation doses are delivered, whereas four to nine beams are often used for IMRT treatment. The selection of beam angles plays an even more important role in designing an IMPT treatment plan than IMRT. Extensive research has been published in the literature regarding beam angle optimization for IMRT (Djajaputra et al. 2003, Wang et al. 2004, D. Bertsimas 2012, Lim and Cao 2012, Rocha et al. 2013a, Rocha et al. 2013b, Zhang et al. 2013, Lim et al. 2014). However, those studies may not be useful for IMPT planning unless treatment uncertainties are considered in the optimization model.

An uncertainty incorporated beam angle optimization method was recently reported by (Cao et al. 2012b). In this study, a local neighborhood search heuristic was used to find local optimal solutions that minimize a worst-case dose based objective function (see Figure 2). It was also compared with other global solution approaches including simulated annealing and genetic algorithm in terms of computational efficiency.



(a) Nominal dose distribution



(b) Worst-case dose distribution

Figure 2: Dose-volume comparison of IMPT plans with conventional (90,270) and optimized (60,270) beam angles for a prostate cancer patient.

Although such proof of principle study has shown that efficient solution algorithms for this combinatorial problem were able to find quality beam angles for IMPT treatment in practical computational times, the modeling of IMPT uncertainties was not close to reality. In order to limit the complexity, only several (nine in this study) uncertainty scenarios were included in a deterministic manner. In addition, to find the optimal number of beams for various

cancer types is another important area for future research.

3.2 Proton Energy Selection

In current IMPT facilities, the slow energy switching is the bottleneck when one tries to reduce the treatment delivery time (Gillin et al. 2010). An IMPT treatment requires tens to hundreds of energy levels to be delivered based on various tumor sizes. The time spent on switching proton energy from one level to another takes a non-negligible portion of the total treatment delivery time.

An initial investigation of optimizing proton energies in IMPT treatment planning can be found in (Cao et al. 2013b). A mixed integer linear programming based iterative optimization approach was developed to find optimal proton energies from a given set of energies. Dose volume measures of treatment plans with optimized proton energies were compared with ones with conventional energy setups using real patient data including prostate, lung and mesothelioma cancer cases. With a reduction of approximately 11.0% to 26.5 % of total energies, they observed that there was no degrading effect on treatment plan quality compared with an all-energy plan based on dose volume measures (Cao et al. 2013b).

The next step of the proton energy studies will have to include robustness against uncertainty into the cost function during optimization. In addition, the impact of reducing proton energy levels on savings in total treatment delivery time and improvement in patient throughput needs to be analyzed for proton facilities.

3.3 Spot Allocation

There are thousands of proton pencil beam scanning spots, or Bragg peaks, distributed in 3D volume to create a desired dose distribution. Degenerate solutions often exist for the spot intensity profile (Albertini et al. 2010). Differently allocated spots, together with or without different intensities, may yield identical nominal plan quality, e.g., target coverage, normal tissue sparing, and tumor dose homogeneity, but result in different properties in plan robustness, deliverability, and delivery efficiency, etc.

The recent study by (Cao et al. 2013a) illustrated that an L1-based SIO model can automatically optimize spot intensities with a sparse non-uniform spot arrangement when compared to an L2-based BIO model which inherently selects all predetermined (uniformly located) spots. Figure 3 shows the spot locations on the same energy layer of the L1 and L2 optimized plans, respectively. Those two plans exhibits the same dose volume measures but have very different spot allocations. Regarding delivery efficiency, the sparse spot allocation requires less delivery time. Moreover, unlike the L2-based model, the L1-based model is capable of incorporating specific machine delivery constraints without cause additional computational burden (Cao et al. 2013a).

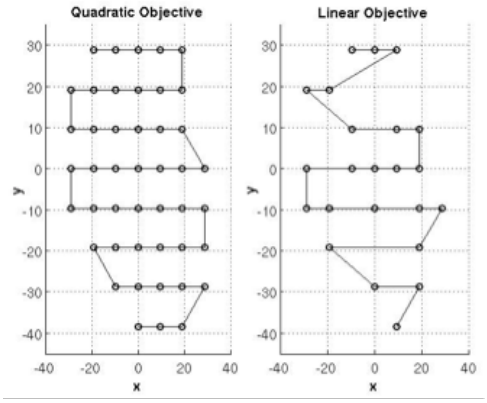


Figure 3: Comparison of spot allocation from IMPT plans based on quadratic and linear optimization models for a prostate cancer case.

In another study (Cao et al. 2012a), it was found that the use of smaller spot spacing, i.e., denser spot allocation, could improve target coverage and normal tissue sparing. It also suggests that spot spacing less than a threshold value, 4 mm for the prostate cancer cases, could not achieve pronounced dosimetric improvements.

It is also important to investigate the problem of delivering sequence of spots, i.e., scanning path, in IMPT treatment planning. The travelling salesman model has been proposed to find optimal scanning path for a set of pre-selected spots (Kang et al. 2007). It will be more interesting to consider the delivery/transportation cost in the spot position selection and spot intensity optimization model in future works.

4. BIOLOGICAL EFFECTS

The biological effects of protons are greater in tissues than photons (Wilkens and Oelfke 2004). A constant value of relative biological effectiveness (RBE) for protons, 1.1, is used in current clinical practice. However, due the highly heterogeneous spot intensities in a typical IMPT plan, the actual RBE may deviate significantly from the constant value and vary extremely from one voxel to another. Therefore, it is clinically beneficial to use a variable RBE in IMPT optimization. The first study on RBE incorporated

IMPT optimization can be found in (Wilkens and Oelfke 2005). A more recent study investigated the variable RBE planning with organ-specific biological parameters (Frese et al. 2011). In future research, robust RBE-based IMPT optimization is an important development towards fully maximizing the therapeutic ratio. In addition to uncertainties in proton range and patient setup, the variations in biological effects should also be taken into account. In contrary, given the current lack of knowledge in tissue dependent RBE values, the relationship or trade off between RBE optimized plan and physical dose optimized plan should also be examined.

5. CONCLUSION

Proton therapy in specific and particle therapy in general are considered as the next generation radiation therapy. More important findings by medical researchers and operations research experts are yet to come. In this paper, we presented some optimization problems existing in current IMPT treatment planning practice. The current research and future directions were discussed.

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