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Neighborhood search approaches to non-coplanar beam orientation optimization for total marrow irradiation using intensity modulated radiation therapy

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Abstract

We consider the beam orientation optimization (BOO) problem for total marrow irradiation (TMI) treatment planning using intensity modulated radiation therapy (IMRT). Currently, IMRT is not widely used in TMI treatment delivery; furthermore, the impact of non-coplanar beam orientations is not known. We propose and implement two versions of a neighborhood search algorithm which solve the BOO problem effectively when gantry angles and couch translations are considered. Our work shows that the BOO problem for TMI cases can be solved in a clinically acceptable amount of time, and leads to treatment plans that are more effective than the conventional approach to TMI.

Keywords

beam orientation optimization, total marrow irradiation, intensity modulated radiation therapy, non-coplanar beam orientations.

1 Introduction

Total marrow irradiation (TMI) is a technique that involves the delivery of radiation to the entire body of a patient. The goal of TMI is to destroy the patient's bone marrow in preparation for a bone marrow transplant (BMT): transplants of this type are used to treat cancers of the blood or bone marrow, such as leukemia and lymphoma, as well as other diseases such as aplastic anemia and sickle cell disease. Currently, TMI is most commonly performed by irradiating the patient's entire body with a single beam of uniform intensity. As most of the patient's body receives the TMI dose intended for the bone marrow, this type of treatment is both unable at sparing healthy organs and limited by those same organs in how much it actually can irradiate and eliminate the diseased bone marrow.

One type of radiation therapy that could be better suited for this type of treatment is intensity modulated radiation therapy (IMRT), where each beam is made up of hundreds of smaller beams, called *beamlets*. The intensity (*fluence*) of each beamlet can be set arbitrarily, allowing the dose delivered by a beam to a structure to be finely controlled. The problem of determining how the fluences of a set of beams oriented in a certain way should be set to ensure that healthy organs receive as little dose as possible while the target structures (in this case, the bone marrow) receive an adequate dose is known as the *fluence map optimization* (FMO).

The problem we study is *beam orientation optimization* (BOO), which is concerned with determining how a set of beams should be oriented for optimal dose delivery. The optimal objective function value of the FMO problem for a set of beams can be used as a measure of the quality of those beams—that is, how capable the beams are of delivering the prescribed dose to the target structures while delivering as little dose as possible to critical organs. We formulate the BOO problem as the problem of optimizing this value over the set of all possible sets of beams.

There are have been some past studies into alternative methods of TMI delivery. For instance, [3] and [2] consider the delivery of TMI using IMRT and show that large reductions in dose to organs such as the liver, kidneys and heart can potentially be achieved. Unlike these and other studies, we consider consider the use of non-coplanar beam orientations obtained from altering both the gantry angle of the linear accelerator and the z–translation of the couch. In most TMI-IMRT studies, the patient is placed quite far from isocenter in order to cover as much of the patient's body

with radiation: as a result, there is a high degree of uncertainty in how much dose is delivered to the patient's body. We avoid this uncertainty by bringing the patient close to isocenter and using different couch z–translations to ensure coverage of the length of the patient's body.

To solve the BOO problem with non-coplanar beams we modify the Add/Drop (A/D) algorithm, a type of neighborhood search presented in [1], to address the need for non-coplanar beams. We implement the basic, sequential A/D algorithm and propose and implement a new, probabilistic version, which uses previous improvements in FMO value to randomly select the neighborhood to search in each iteration.

2 BOO problem formulation

Let Θ be a vector containing the orientations of k beams defined as $\Theta = (\theta_1, \theta_2, \ldots, \theta_k)^\top$. Each orientation θ is itself a vector of two components—the gantry angle (G) and the couch z-translation (z). We allowed the gantry angle to range from 0 to 350° in 10° increments and the couch z-translation to range from -160 cm (which places the isocenter near the patient's head) to -60 cm (which places the isocenter at the patient's pelvis), in 10 cm increments.

We represent the set of all possible sets of orientations for k beams with $\mathcal{B}^k = \mathcal{B} \times \cdots \times \mathcal{B}$, where $\mathcal{B}$ is the set of all possible orientations for a single beam. The BOO problem is formulated as the minimization of $\min\{\mathcal{F}(\Theta) : \Theta \in \mathcal{B}^k\}$ where the function $\mathcal{F}(\Theta)$ is the optimal FMO value that results from using the beams specified by Θ in the FMO problem. The function $\mathcal{F}(\cdot)$ is formulated in such a way that the lower the value of F is, the higher the quality of the beams. Our FMO formulation follows that used in [1] and [4]; we refer the reader to those studies for further details.

3 Add/Drop algorithm

The Add/Drop algorithm used for BOO is a deterministic local search procedure. A single iteration of the Add/Drop algorithm is performed by enumerating all of the solutions (and their corresponding FMO values) in some neighborhood of the current solution, and moving to a solution in the neighborhood if that solution improves the FMO value. The neighborhood that is searched is changed from iteration to iteration, and the algorithm stops when all of the neighborhoods of the current solution have been searched without leading to any improving solutions. Once the algorithm reaches a solution, it is executed again from a new starting point until a specific number of executions has been performed.

3.1 Neighborhood Definition

The Add/Drop algorithm in each iteration searches some form of neighborhood of the current solution. The neighborhood of a solution vector in our implementation of the algorithm is a neighborhood relative to a single beam and a single component/degree of freedom. An arbitrary degree of freedom (movable component of the linear accelerator) is represented by d; the set of all possible components is denoted by D. In our study, $D = \{G, z\}$, where G represents the gantry angle and z represents couch z-translation.
For clearer exposition, we will define the neighborhood in three steps. We first define the neighborhood for a single component of a single beam; we have

$$\begin{aligned} N_G(\theta_G) &= \{\theta'_G \bmod 360 \in \mathcal{S}_G : \theta_G - \delta_G \leq \theta'_G \leq \theta_G + \delta_G\} \\ N_z(\theta_z) &= \{\theta'_z \in \mathcal{S}_z : \theta_z - \delta_z \leq \theta'_z \leq \theta_z + \delta_z\} \end{aligned}$$

where $\mathcal{S}_d$ is the set of allowable values for component d. The δ variables specify the size of the neighborhood around the current value of the component. The use of the mod function in the gantry angle neighborhood definition is necessary due to the cyclical nature of angles (*e.g.*, 370° being equivalent to 10°).

The next step is to define the neighborhood of a solution vector of beam, relative to a single beam b and a single component d:

$$\mathcal{N}_{bd}(\Theta) = \{ \left(\theta_1, \theta_2, \ldots, \theta'_b, \ldots, \theta_k\right) \in \mathcal{B}^k : \theta'_{bd} \in N_d\left(\theta_{bd}\right) \wedge \theta'_{b\bar{d}} = \theta_{b\bar{d}},\ \forall \bar{d} \in D,\ \bar{d} \neq d\}$$

In other words, only one component of the bth beam is allowed to move. All other components of all other beams are

fixed.

3.2 Basic Add/Drop algorithm definition

The Add/Drop method, in its most general form, can be described as follows:

1. Generate initial starting point $\Theta^{(0)}$.
2. Set $\Theta^* = \Theta^{(0)}$ and $i = 0$.
3. Select $d \in D$ and $b \in \{1,\ldots,k\}$. Enumerate all values of Θ and their corresponding $\mathcal{F}(\Theta)$ values on the neighborhood $\mathcal{N}_{bd}(\Theta^{(i)})$. Find $\bar{\Theta}$ that minimizes $\mathcal{F}$ on $\mathcal{N}_{bd}(\Theta^{(i)})$.
4. If $\mathcal{F}(\bar{\Theta}) < \mathcal{F}(\Theta^*)$, set $\Theta^* = \Theta^{(i+1)} = \bar{\Theta}$ and set $i = i+1$.
5. If all points in $\bigcup_{b=1}^{k}\bigcup_{d\in D}\mathcal{N}_{bd}(\Theta^{(i)})$ have been sampled without improvement, stop with Θ^* as a local minimum; otherwise, go to Step 3.

The most basic form of the Add/Drop that we implement is the Simple Cycling Add/Drop (SCAD) algorithm. The SCAD algorithm cycles through all of the components for a particular beam before selecting the next beam and cycling through the components of the new beam. For instance, in the case where we have three beams and we are considering just the gantry angle and the couch z-translation, the order of neighborhoods, described as (beam number, degree of freedom), would be $(1,G)$, $(1,z)$, $(2,G)$, $(2,z)$, $(3,G)$, $(3,z)$, $(1,G)$, $(1,z)$, and so on.

3.3 FMO algorithm starting points

In the implementation in [1], the projected gradient algorithm used to solve the FMO problem starts with all of the bixels set to a pre-defined constant. In this study, we instead set the starting bixel values to the optimal bixel values that were obtained for the optimal solution vector that was selected in the previous iteration. (For the beam which is translated or rotated in the current iteration, all of the bixels are set to the mean of the previous bixel values).

If we were to compare two beam sets which differ by only a small amount in the gantry angle or couch z–translation of a single beam, we would intuitively expect the FMO values of the two beam sets to be very similar and the optimal bixel values of the identical beams to be very close to one another. Therefore, by always warm starting the FMO evaluations from the optimal bixel values of the current beam solution, the FMO algorithm may take less time to converge to the new optimal bixels for each neighboring solution, leading to an increase in overall speed.

4 Probabilistic Add/Drop algorithm

The SCAD algorithm goes through the solution vector's neighborhoods sequentially, going through all the components of one beam before moving to the next. We now propose a different version of the algorithm which keeps track of the recent improvements in the FMO value that have been realized from the neighborhood of each beam-component pair, and uses these sets of improvements to construct probabilities which are then used to randomly select the next beam and component. Beam-component pairs which have recently led to higher improvements have a higher probability of being selected than pairs which led to lower improvements. The new algorithm thus has the potential to converge more quickly to a local minimum by having a tendency to explore promising neighborhoods first, rather than being constrained to go through the neighborhoods in a sequential fashion.

The probability schemes presented in this section are used to select beam-component pairs in Step 3 of the generalized Add/Drop algorithm in Section 3.2.

4.1 Selection based on historical improvements

The algorithm uses a joint probability mass function (PMF) which specifies the probability of selecting a particular beam-component pair, which is defined in its most general form as

$$\bar{p}(b,d) = \Pr(B=b, C=d) = \frac{1}{k|D|} + \frac{\alpha}{k|D|}\left(\frac{\Delta_{bdr} - \bar{\Delta}_m}{\bar{\Delta}_m}\right) \tag{1}$$

where the random variables B and C are the beam and the component to be sampled respectively; the variable Δ_{bdr} is the average of the r most recent improvement associated with beam b and component d; the variable $\bar{\Delta}_m$ is the average of the m most recent improvements; and the parameter α is a weighting parameter whose effect will be discussed momentarily. The formula assigns each (b,d) pair a uniform probability $(1/(k|D|))$ and then adds or subtracts an additional amount that depends on the improvement of each pair relative to the overall average improvement.

The parameter $\alpha \in [0,1]$ affects the degree to which the selection probabilities depend on the recent improvements. If α is set to 0, the probability of selecting any pair does not depend on the improvements at all, and each pair has an equal probability of selection $(1/(k|D|))$. If α is set to 1, the probability of selecting any pair exactly reflects the most recent improvement resulting from that pair.

After the adjustments to the probabilities $\bar{p}$ are performed, the probabilities are re-normalized so that the total of all probabilities sums to 1:

$$p(b,d) = \frac{\bar{p}(b,d)}{\sum_{b'=1}^{k} \sum_{d' \in D} \bar{p}(b',d')} \tag{2}$$

4.2 Exclusion of unlikely beam-component pairs

In the case that the algorithm selects a pair, searches through the neighborhood of that pair and finds no improving solutions, that pair should not be selected again until the iterate changes. Similarly, if the algorithm selects a pair and *does* find an improving solution in the neighborhood of that pair, it may be desirable to exclusively explore other pairs in the subsequent iterates. This is based on the intuition that once a beam component is improved, it may be unlikely to see significant further improvement in that beam component until the other beams and components are in new positions. For these reasons, we define the set C, which is the set of all pairs which are not to be sampled, and modify $\bar{\Delta}_m$ to be the average of all of the m most recent improvements of pairs not in C. We also appropriately adjust the denominators in equation 1 to reflect the number of available beam-component pairs ($k|D| - |C|$ instead of $k|D|$). In situations where $\bar{\Delta}_m$ is zero, the PMF for pairs not in C is undefined, so the selection probabilities are set uniformly (*e.g.* $p(b,d) = 1/(k|D| - |C|)$).

5 Results

The algorithms were tested on a single patient case from Princess Margaret Hospital, Toronto. The algorithms were executed on a 64-bit, 32-node CentOS cluster, with each node having 8GB of memory and eight 2GHz CPUs. Each algorithm was executed with 30 beams. The main reason for using such a large number of beams is that preliminary testing indicated that solutions with fewer beams were unable to control the degree of overdosage in the target structure.

The use of a large number of beams is also justified because IMRT may not be appropriate for a problem of this scale. A more viable approach may be arc therapy, where the beam is constantly on as the gantry and couch are rotating and translating continuously. An arc therapy approach could be more potent because the number of beam orientations effectively becomes unrestricted; unfortunately, the associated optimization problem suffers from increased dimensionality, as it would be necessary to solve for the orientation and the beam fluences as functions of time. Due to the large number of beams used, the methods proposed in this study could be used as a starting point for solving arc therapy treatment planning problems for TMI.

5.1 FMO and BOO execution results

The average time required to evaluate a single FMO value using the moving FMO starting point method on the cluster was approximately 17.1 minutes. This average was calculated from a sample of 752 FMO evaluations, obtained from six A/D executions with 30 beams. In contrast, the average time required to evaluate the first FMO value (which was not warm started) for the same six executions was 57.8 minutes. This significant reduction in run time highlights the importance of warm starting the FMO algorithm with the bixel values of the current beam solution.

Each execution of the A/D algorithm was started with a randomly generate starting set of beams. Each execution was also allowed to run for a maximum of 12 hours, as this amount of time is the most an optimization algorithm of this kind would have in an actual clinical setting. For both the SCAD and the probabilistic A/D, δ_G and δ_z were

both set to 20; the probabilistic A/D variant was tested with r and m both set to 5 and α values of 0, 0.25, 0.5, 0.75 and 1.

The plots of FMO value versus time suggest that the SCAD is slower to converge to its final FMO value than the probabilistic A/D. This may be because the SCAD in each execution samples approximately the same number of beams, while the probabilistic A/D is not constrained in this way and has the potential to change more beams in the solution over the course of one execution. Also, SCAD will check both the gantry angle and the couch-z neighborhood for the same beam, which may be unnecessary – if one beam does change and yields a better solution, it is questionable how much improvement we can get by attempting to change the same beam again in a different way.

5.2 Treatment Plan Quality

Due to the relative absence of treatment planning in total marrow irradiation, there is a lack of clear criteria on what level of underdosage and overdosage is acceptable in the bone marrow and in the patient's healthy organs. To address this we developed some new treatment plan criteria, which we outline below:

- At least 95% of the volume of the bone marrow must receive 12Gy or more;
- The bone marrow may receive at most 25Gy;s
- At most 20% of the bone marrow can receive 20Gy or more; and
- The majority of each organ should receive less than 8Gy.

The constraint on the level of overdosage in the bone marrow is necessary because if the dose exceeds 30 Gy, fibrosis can occur, preventing the new bone marrow from successfully integrating in the bone and being able to function normally. To account for uncertainties, the maximum dose for the bone marrow was restricted to 25 Gy.

The DVHs obtained from SCAD and the probabilistic A/D variants in general met all of the constraints and from our testing, do not appear to exhibit significant differences in organ sparing and marrow elimination. One representative DVH, obtained from an execution of the probabilistic A/D with $\alpha = 0.75$, is shown as Figure . From this DVH we can see that our methods are able to attain acceptable dose levels within the bone marrow. We can also see that for most organs, the majority of the volume receives less than 8Gy, suggesting that our methods lead to an improvement over conventional TMI (where most of the organs would receive around 12Gy). Although some studies, such as [3], appear to show better organ sparing, it should be noted that our study and other studies differ in which organs are considered. For instance, the bowel, spinal cord, bladder, saliva glands and oral cavity were not explicitly taken into account as organs at risk (OARs) in [3], but are taken into account here; at the same time, [3] consider the brain which is not considered here. If the bowel, spinal cord and other additional organs were to be taken out of consideration in the FMO algorithm, better sparing to the other organs would certainly be attained. To our knowledge, there are no other studies which consider as many organs as we do.

Currently, the main problem with the treatment plans obtained from these methods is the high level of overdosage to the bone marrow, which results in high overdosage in healthy organs. More testing is needed to bring down this level of overdosage while still allowing the algorithm to operate within the timeframe of 12 hours.

6 Conclusions and future directions

From our tests, the SCAD and the probabilistic A/D algorithms are both capable of obtaining solutions that meet our treatment plan criteria in 12 hours from a single execution and do not differ significantly in solution quality. More testing on the current patient data and other patient data is required to reduce overdosage to the bone marrow and OARs.

In addition to the probabilistic A/D, there are other variants of the A/D algorithm that we have implemented and are currently studying but cannot describe in detail here. One variant we are studying is a "dynamic δ" A/D, where the neighborhood size is modified after each iteration in response to how much the iterate shifted in that iteration. We are also studying the A/D algorithm in a multiple execution context where points sampled in one execution of the A/D are used to generate the starting point for the next execution of the A/D.

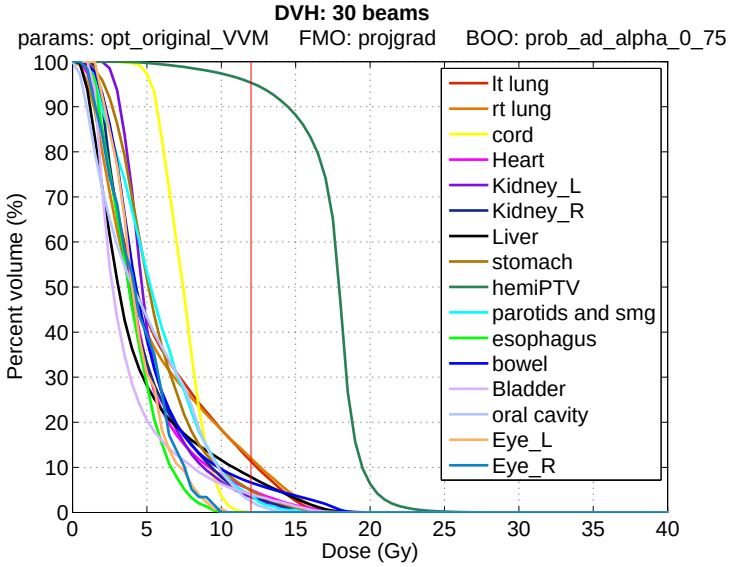

Figure 1: 30 beam probabilistic A/D DVHs, $\alpha = 0.75$.

Regardless of the speed of the algorithms and the quality of the resulting DVHs, the solutions which our algorithms return cannot currently be implemented in a clinical setting. Because of the large number of beams, the treatments will necessarily take longer to perform than normal treatments; with longer treatments, there is a greater risk of the patient's bone marrow and organs shifting during treatment, causing hot beamlets to miss the bone marrow and harm healthy tissue, reducing treatment effectiveness.

There are several possible directions in which this research can be taken. To bring this work closer to a clinically implementable plan, future research could explore the design of optimal intensity modulated arc therapy (IMAT) treatment plans. This would most likely involve designing an algorithm to "connect" the beams identified by our algorithms, and to fill in the individual bixel time profiles along the connecting arcs in some optimal way. In contrast, a different but also valid direction could be to factor patient motion into the FMO formulation and to use a robust optimization approach in order to make the treatment plans more suitable for implementation with conventional IMRT.

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