A Response Surface Approach to Beam Orientation Optimization in Intensity Modulated Radiation Therapy Treatment Planning

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We view the beam orientation optimization (BOO) problem in intensity modulated radiation therapy (IMRT) treatment planning as a global optimization problem with expensive objective function evaluations. We propose a response surface method that, in contrast with other approaches, allows for the generation of problem data only for promising beam orientations as the algorithm progresses. This enables the consideration of additional degrees of freedom in the treatment delivery, i.e., many more candidate beam orientations than is possible with existing approaches to BOO. This ability allows us to include noncoplanar beams and consider the question of whether or not noncoplanar beams can provide significant improvement in treatment plan quality. We also show empirically that using our approach, we can generate clinically acceptable treatment plans that require fewer beams than are used in current practice.

Key words: IMRT optimization; radiation therapy treatment planning; beam orientation optimization; fluence map optimization; response surface method

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1. Introduction

Every year, hundreds of thousands of patients receive cancer treatment by radiation therapy. During this therapy, beams of radiation pass through a patient, thereby killing both cancerous and normal cells. Thus, the radiation treatment must be carefully planned so that a clinically prescribed dose is delivered to targets containing cancerous cells while nearby organs and tissues (called critical structures) are spared. This is achieved by irradiating the patient using several beams sent at different orientations spaced around the patient so that the intersection of these beams includes the targets, which thus receive the highest radiation dose, whereas the critical structures receive radiation from some but not all beams and may thus be spared. Currently, a technique called intensity modulated radiation therapy (IMRT) is considered to be the most effective radiation therapy for several forms of cancer, including head-and-neck and prostate cancer treatment.

The problem of designing an IMRT treatment plan for an individual patient is a large-scale mathematical programming problem that is not yet solved satisfactorily. Current treatment planning systems decompose the planning problem into several stages, and the corresponding subproblems are solved sequentially. This paper addresses the integration of the beam orientation optimization (BOO) and fluence map optimization (FMO) subproblems based on a convex formulation of the latter and an associated efficient algorithm for solving it, an approach that has not received much attention in previous studies.

In IMRT, each beam is modeled as a collection of hundreds of small beamlets, the fluences of which can be controlled individually. These fluence values are known as a fluence map, and optimization of these fluences given a fixed set of beams is known as fluence map optimization. The optimal solution value of the FMO problem quantifies the quality of the treatment plan, where quality means the ability of the plan to deliver the prescribed radiation dose to the specified target structures while sparing critical structures by ensuring that they receive an acceptably low amount of radiation. Thus, the quality of a set of beams can be measured by the optimal solution value of the FMO problem performed with those beams.

For head-and-neck cancers, typical IMRT treatment plans use five to nine equispaced coplanar beams.
Coplanar beams are those beams obtained from the rotation of only the gantry of the linear accelerator, the machine that delivers radiation beams to the patient. If all other components of the linear accelerator are fixed, the rotation of the gantry sweeps out a set of coplanar beams. The couch upon which the patient lies can rotate and translate in three dimensions and the head of the gantry can rotate independently, creating an even larger set of beams. Beams obtained from the movement of more than one component from the linear accelerator are known as noncoplanar beams. Whether or not noncoplanar orientations can increase the quality of a treatment plan is unknown, although most previous studies imply that coplanar beams alone are sufficient.

Many approaches have been taken to solve the BOO problem. Evolutionary algorithms (Schreibmann et al. 2004) and variants of evolutionary algorithms, particularly genetic algorithms (Ezzell 1996, Haas et al. 1998, Li et al. 2004), have been used. Li et al. (2005) use a particle swarm optimization method that is conceptually based on evolutionary algorithms. Bortfeld and Schlegel (1993), Djajaputra et al. (2003), Lu et al. (1997), Pugachev and Xing (2002), Rowbottom et al. (1999a), and Stein et al. (1997) have all used variations of simulated annealing to determine a beam solution. Söderstrom and Brahme (1992) selected coplanar beam orientations using two measures, entropy and the integral of the low-frequency part of the Fourier transform of the optimal beam profiles, both of which are based on the size and shape of the target structure. Söderstrom and Brahme (1995) also use an iterative technique to determine the optimal number of coplanar beams required using BOO. Das and Marks (1997) use a quasi-Newton method. Rowbottom et al. (1999b) use artificial neural network algorithms to select beam orientations. Gokhale et al. (1994) use a measure of each beam’s “path of least resistance” from the patient surface to the target location to determine the best beam directions. Meedt et al. (2003) use a fast exhaustive search to obtain a noncoplanar solution. The concept of beam’s-eye view (BEV) has also been commonly used to approach the BOO problem (Chen et al. 1992; Cho et al. 1999; Goitein et al. 1983; Lu et al. 1997; Pugachev and Xing 2001a, b, 2002).

Although techniques to quantify the quality of a beam solution vary, it is widely accepted that the optimal solution to the FMO problem presents the most relevant measure (Bortfeld and Schlegel 1993; Djajaputra et al. 2003; Holder and Salter 2004; Lee et al. 2003, 2006; Li et al. 2004, 2005; Meedt et al. 2003; Morrill et al. 1991; Oldham et al. 1998; Rowbottom et al. 1999a, b, 1998; Schreibmann et al. 2004; Söderstrom and Brahme 1992; Stein et al. 1997; Wang et al. 2004, 2005; Woudstra and Heijman 2004). However, the FMO problem can be time-consuming to solve depending on its formulation, making it prohibitive to use in conjunction with the BOO problem. Only Das and Marks (1997), Haas et al. (1998), and Schreibmann et al. (2004) of the previously cited works use the optimal FMO solution value as the quantitative measure of the quality of a beam solution.

The previous works predominantly only consider a subset of coplanar angles, and so the impact of noncoplanar beams is unknown. Das and Marks (1997), Gokhale et al. (1994), Meedt et al. (2003), Lu et al. (1997), Rowbottom et al. (1999a), and Wang et al. (2005) consider noncoplanar orientations, but only a small subset of possible noncoplanar beams. This is likely due to the computational difficulties associated with the inclusion of noncoplanar orientations as well as the widespread belief that noncoplanar orientations do not improve the quality of a treatment plan. Acceptable treatment plans can be obtained using only coplanar beams, but it is possible that noncoplanar could provide improved treatments.

Although multicriteria optimization is popular in recent FMO literature (Breedveld et al. 2007, Craft et al. 2007, Thieke et al. 2007), Romeijn et al. (2004) showed that most of the treatment plan evaluation criteria proposed in the medical physics literature are equivalent to convex penalty function criteria when viewed as a multicriteria optimization problem. For each set of treatment plan evaluation criteria from a very large class, there exists a class of convex penalty functions that produces an identical Pareto-efficient frontier. Therefore, we will use a convex penalty function-based approach to evaluating treatment plans to investigate the BOO problem.

We view the BOO problem in IMRT treatment planning as a global optimization problem with expensive objective function evaluations, each of which involves solving a FMO problem. We propose a response surface method that, unlike other approaches, allows for the generation of problem data only for promising beam orientations on-the-fly as the algorithm progresses, enabling the consideration of far more candidate orientations than is currently feasible. This method will allow us to assess the potential of noncoplanar beams in developing quality treatment plans. Additionally, the response surface method used provides convergence to a globally optimal solution if run for enough iterations. Although in our implementation the algorithm is not run long enough to ensure convergence, the algorithm does return good solutions and can easily be run long enough for convergence if that is desired. We will also demonstrate that it is possible to obtain quality treatment plans with fewer beams than are currently used in practice.

Shi et al. (2006) use a nested partition approach to coplanar BOO that identifies promising regions of
the solution space to explore. The response surface method that we propose is an extension of the work presented in Aleman et al. (2006) and differs from the nested partition approach in that the response surface method identifies a single most promising point to sample, rather than an entire region to investigate. In addition, we will consider the noncoplanar solution space.

The paper is organized as follows. Section 2 describes the BOO and FMO models, §3 describes the response surface method, §4 provides the results, and §5 details conclusions and future research directions.

2. Beam Orientation Optimization

In a typical head-and-neck treatment plan, radiation beams are delivered from five to nine nominally spaced coplanar orientations around the patient. Intuitively, better treatment plans could be obtained using “optimal” beam orientations, in that better target coverage or organ sparing could be realized.

2.1. BOO Model

For $k$ beams orientations to be optimized in the treatment plan, the vector of decision variables representing the beam orientations is defined as $\Theta = (\theta_1, \ldots, \theta_k)^T$. The decision vector $\Theta$ is used as input into the black-box function $F(\Theta)$ to determine the ability of the beam solution to deliver the prescribed treatment without unduly damaging normal tissue and critical structures. The BOO problem is then formulated as

$$\min F(\Theta)$$
subject to $\Theta \in \mathcal{B}^k$,

where $\mathcal{B}$ is the set of candidate beams and $\mathcal{B}^k$ is the collection of all subsets of $\mathcal{B}$ with cardinality $k$. The number of beams to be used, $k$, is treated as input into the model. The candidate set of beams can be selected according to any user-specified criteria; for example, the beams can be coplanar or noncoplanar, continuous or discrete, or only represent a subset of the available beams. It is also possible to fix some beams and only optimize a subset of the total number of beams to be used. Theoretically, the linear accelerator is able to capture a continuous set of orientations, but due to machine tolerances, the actual beams delivered may not be exactly the desired beams. Therefore, it is common to only consider a discretized set of beam orientations.

In our BOO model, the black-box function $F(\Theta)$ is the convex FMO problem described in §2.2, thus ensuring a measure of the quality of each beam solution based on the beam solution’s treatment plan. However, even though $F(\Theta)$ is convex for a fixed $\Theta$, this formulation of the BOO problem is fundamentally nonlinear because the physics of dose deposition change with each beam orientation; that is, the effect of a beam on each patient can be drastically different than the effect of a neighboring beam. To illustrate the nonlinearity of the problem, Figure 1 shows the FMO problem as a function of just two coplanar beam angles. From this illustration, it is evident that the FMO function, particularly in higher, more realistic dimensions, is likely to also be multimodal.

Although the FMO problem itself can be solved quickly using the convex model presented in §2.2, to perform the FMO, lengthy calculations must be made to determine each candidate beam’s effect on each voxel of the patient (see §2.2 for a definition of voxel). The data necessary to measure the dose delivered from each beam are very computationally expensive to calculate and very expensive to store in terms of hard drive space. Using the methods proposed by Fox et al. (2006), these calculations require $\approx 13$ minutes per beam to calculate and thus make each evaluation of the FMO problem expensive. Despite the time required for each function evaluation, the limiting factor in beam orientation optimization is the hard drive space required to store the beam data for each candidate beam. If the candidate set of beams is small, these data can be precomputed and stored, allowing the FMO problem to be solved quickly in the BOO problem. But if the candidate set of beams is large—for example, consisting of noncoplanar orientations—then the data cannot be precomputed due to storage requirements.

Because of these difficulties with the BOO problem, previous studies have been largely unable to consider the entire solution space of available beams. This issue has been typically addressed by restricting the size of $\mathcal{B}$, most commonly by considering only coplanar beams. By using the response surface method, which is specifically designed to model
expensive nonlinear black-box functions, we can iteratively identify promising beam solutions and generate beam data for these solutions on-the-fly, thus circumventing the issue of storage space and allowing for the consideration of all deliverable beam orientations. A significantly larger solution space than previously thought possible could be key to finding improved solutions.

2.2. FMO Model

A convex penalty function-based approach to the FMO model as described in Romeijn et al. (2003) is used to quantify the quality of the treatment plan by appropriately making the trade-off between delivering the prescribed radiation dose to the target structures while sparing critical structures. Lim et al. (2008) also use penalty functions; however, those penalties functions are structure based, whereas the ones used in this work are voxel based. Using this approach, the FMO problem can be formulated as a quadratic programming problem with linear constraints as follows:

Denote the set of all potential beam orientations as $\mathcal{B}$. The structures (both targets and critical structures) are irradiated using a predetermined set of beam angles $\Theta$, consisting of $k$ beams. Each beam is decomposed into a rectangular grid of beamlets, yielding typically 100–400 beamlets per beam. The position and intensity of all beamlets in a beam can be represented by a vector of values representing the beamlet intensities, called *bixels*. The set of all bixels in beam $\theta$ is denoted by $B_\theta$. The core task in IMRT treatment planning is finding radiation intensities for all beamlets.

Denote the total number of structures by $S$ and the number of targets by $T$. Each structure $s$ is discretized into a finite number $v_s$ of volume cubes, known as voxels. On average, around 80,000 voxels are required to accurately represent the targets and surrounding structures of a head-and-neck cancer site in the cases tested.

Denote $D_{ij}$ as the dose received by voxel $j$ in structure $s$ from beamlet $i$ at unit intensity. Let $x_i$ denote the intensity of bixel $i$. The total dose received by voxel $j$ in structure $s$ is approximated by

$$z_{js} = \sum_{h=1}^{k} \sum_{i \in B_{\theta_h}} D_{ij} x_i,$$

although the goal of IMRT treatment planning is to control the dose received by each structure, imposing hard constraints on the amount of dose received by each structure may result in no feasible solutions. In some cases, it may be necessary to sacrifice organs to treat targets, and if that possibility is not allowed in the model, then a feasible or a satisfactory solution may not exist. Thus, in our model, a penalty is assigned to each voxel based on the dose it receives for a given set of beamlet intensities. Let $F_{js}$ denote a convex penalty function for voxel $j$ in structure $s$ of the following form:

$$F_{js}(z_{js}) = \frac{1}{v_s} (w_s |(T_s - z_{js})| + \bar{w}_s |(z_{js} - T_s)|)^p,$$

where $T_s$ is the dose threshold value for structure $s$, $w_s$ and $p_s$ are weighting factors for underdosing, and $\bar{w}_s$ and $\bar{p}_s$ are weighting factors for overdosing. Additionally, $(\cdot)^+$ denotes $\max(0, \cdot)$. The function is normalized over the number of voxels by the coefficient $1/v_s$. By setting $w_s$, $\bar{w}_s \geq 0$, and $p_s$, $\bar{p}_s \geq 1$, convexity is ensured.

A basic formulation of the FMO problem is then

$$\begin{align*}
\text{minimize} & \sum_{s=1}^{S} \sum_{j=1}^{v_s} F_{js}(z_{js}) \\
\text{subject to} & \quad z_{js} = \sum_{h=1}^{k} \sum_{i \in B_{\theta_h}} D_{ij} x_i, \quad j = 1, \ldots, v_s, s = 1, \ldots, S \\
& \quad x_i \geq 0 \quad i \in B_{\theta_h}, \quad h = 1, \ldots, k.
\end{align*}$$

The FMO problem is the black-box function $F(\Theta)$ in the BOO model to quantify the quality of beam vector $\Theta$. In contrast with the methods presented by all of the previously cited FMO studies except for Das and Marks (1997), Haas et al. (1998), and Schreibmann et al. (2004), this measure of beam vector quality is based on the actual solution value of the FMO problem rather than on heuristic methods or scoring approaches, which are unlikely to accurately optimize the beam orientations due to their approximate nature.

To solve such a problem, all beam data must be precomputed for every beam orientation. This poses a significant restriction on the size of the solution space that can be considered in a mixed-integer program (MIP) formulation.

3. Response Surface Method

Because beam data generation is costly, a method that iteratively identifies only promising beam orientations is required. The response surface (RS) method is such an algorithm. The RS method is designed to efficiently model expensive black-box functions. In mathematics, a function may be called a dependent variable, which in turn may also be called a response variable, hence the name of the response surface method. In this application, the FMO solver is our black box and the set of beams to be used is the input. We use the response surface method, the details of which can be found in Jones (2001) and Jones et al. (1998). We do not repeat the details; however, we provide a high-level overview of the algorithm and discuss the modifications required in the application of the algorithm to the BOO problem.
3.1. Overview

The response surface method identifies promising solutions based on the performance of previous solutions. The function value and expected improvement over the current best solution of a certain point is estimated based on the function behavior learned from previously sampled points and their calculated objective function values. The function values of points are related by correlation functions that depend on each point’s distance from the previously sampled points. From the correlation functions, the algorithm predicts the probability that the best solution will improve at unexplored points in the solution space. Using this probability, a promising solution is identified. For the BOO problem, beam data only need to be generated for these promising solutions, thus saving both computation time and storage space.

The response surface method models the objective function as a stochastic process of the form

$$F(\Theta) = \mu + \epsilon(\Theta),$$

where $\mu$ is a constant representing an average of the function $F$ over all feasible points and $\epsilon(\Theta)$ is a random error term associated with the point $\Theta$. In the general case, the error terms between two points, say $\Theta^{(1)}$ and $\Theta^{(2)}$, are correlated by

$$\text{Corr}(\epsilon(\Theta^{(1)}), \epsilon(\Theta^{(2)})) = \exp[-d(\Theta^{(1)}, \Theta^{(2)})],$$

where $d(\Theta^{(1)}, \Theta^{(2)})$ is a weighted distance measure between $\Theta^{(1)}$ and $\Theta^{(2)}$. Intuitively, if two points are very close together, the correlation between them will be close to one; similarly, if two points are very far apart, the correlation between them will approach zero. In contrast to the distance measure proposed by Jones et al. (1998), we use the following weighted distance measure for BOO:

$$d(\Theta^{(1)}, \Theta^{(2)}) = c \|(\Theta^{(1)} - \Theta^{(2)})\|_p,$$

where $\|\cdot\|_p$ denotes the $\ell_p$-norm. This differs from the measure suggested in the original description of the response surface algorithm in that the weighting parameters $c$ and $p$ do not vary with each $\theta_h \in \Theta$, $h = 1, \ldots, k$. This is an intuitive modification because no beam is more important than another beam, and thus all should be weighted equally. To ensure tractability of the subproblems described in §3.2, the value $p = 2$ is used, whereas $c$ may assume any value. In the case of coplanar beams, $\theta_h \in [0, 360)$ for $h = 1, \ldots, k$, and so the distance between coplanar beams is simply the absolute value of the difference in beam angles squared and multiplied by $c$. Due to the cyclic nature of angles, that is, $0^\circ = 360^\circ$, the difference between, for example, $5^\circ$ and $355^\circ$ is $10^\circ$, yielding the weighted distance $c(10^2)$.

In addition, the distance value used is the smallest value obtained from all permutations of the order of the elements in the vectors $\Theta^{(1)}$ and $\Theta^{(2)}$. For example, if $\Theta^{(1)} = [1, 121, 241]$ and $\Theta^{(2)} = [119, 239, 359]$, then the two points are quite close. However, inputting these two points into Equation (3) would result in a large value. Thus, the distance value used is obtained by inputting into Equation (3) the permutations of the two vectors that yield the smallest distance: $\Theta^{(1)} = [1, 121, 241]$ and $\Theta^{(2)} = [359, 119, 239]$.

The idea of the RS method is to iteratively evaluate the true function $F$ at certain beam vectors $\Theta$, and then construct the conditional stochastic process given these function values. This conditional stochastic process is then used to decide where to evaluate the function $F$ next. Due to the time and space required to generate the beam data necessary to evaluate the function $F$, it is desirable to only evaluate points that will either improve the best solution with a significant probability or significantly increase our knowledge of the function. The optimization models to determine the next observation are described in §3.2.

Let $\Theta^{(1)}, \ldots, \Theta^{(n)}$ be $n$ previously sampled points, where the superscript $(i)$ represents the $i$th point. $\mathbf{R}_n$ is the matrix of correlations between the previously sampled points, $\mathbf{y}_n$ is the vector of function values $F(\Theta^{(i)})$ of the previously sampled points, and $\bar{\mu}_n$, $\bar{\sigma}_n$ are estimators of the average and variance of the function $F$, respectively. The response surface algorithm is given by

1. Initialization:
   (a) Choose values for the parameters $c$ and $p$.
   (b) Choose an initial sample size $n$ and a set of angles $\Theta^{(i)}$, $i = 1, \ldots, n$. Evaluate the function $F$ at each of these points, yielding the values $y_i$, $i = 1, \ldots, n$.

2. Iteration:
   (a) Compute or update the values of $\mathbf{R}_n$, $\mathbf{R}_n^{-1}$, $\bar{\mu}_n$, $\bar{\sigma}_n$, and $E_n$, the minimum observed objective function value.
   (b) Determine the next point to observe using one of the methods described in §3.2 and call this point $\Theta^{(n+1)}$.
   (c) Find the value $y_{n+1} = F(\Theta^{(n+1)})$, set $n \leftarrow n + 1$, and go to iteration 2(a).

3.2. Determining the Next Observation

Because the function $F$ is expensive to evaluate, we want to sample as few points as possible. Thus, in each iteration, an optimization problem is solved that determines the “best” next point at which to observe the true function $F$. Some of the optimization problems that have been proposed in the literature depend on the uncertainty of the predictor as a function of $\Theta$, as well as the expected improvement over the current best solution (Jones 2001, Jones et al. 1998). The reader
is referred to Jones (2001) and Jones et al. (1998) for
detailed explanations and derivations of the following
expressions.

Let \( r_i(\Theta) \) be the vector of correlations between \( \Theta \)
and the \( n \) previously sampled points. The uncertainty
after \( n \) sampled points is then given by

\[
\hat{\sigma}_n^2(\Theta) = \hat{\sigma}_n^2 \left[ 1 - r_n(\Theta)^\top R_n^{-1} r_n(\Theta) + \frac{1 - 1^\top R_n^{-1} r_n(\Theta)}{1^\top R_n^{-1} 1} \right],
\]

where

\[
\hat{\sigma}_n^2 = \frac{1}{n} (y_n - \hat{\mu}_n)^\top R_n^{-1} (y_n - \hat{\mu}_n)
\]
is the estimator of the variance \( \sigma_n^2 \) based on the
\( n \) observations. The value \( y_n \) is the vector of the \( n \)
previously observed function values. The estimator of the
function average after \( n \) sampled points, \( \hat{\mu}_n \), is defined as

\[
\hat{\mu}_n = \frac{1^\top R_n^{-1} y_n}{1^\top R_n^{-1} 1}.
\]

The expected improvement of a point \( \Theta \) over the
current best solution, denoted by \( I_n(\Theta) \), is given by

\[
I_n(\Theta) = \hat{\sigma}_n(\Theta) [z \Phi(z) + \phi(z)],
\]

where

\[
z = \left( \frac{E_n - \hat{F}_n(\Theta)}{\hat{\sigma}_n(\Theta)} \right),
\]

and \( E_n = \min\{y_1, \ldots, y_n\} \) is the current best solution.
\( \Phi \) and \( \phi \) are the cumulative distribution function and
probability density function of a standard normal random
variable, respectively. The estimated function value \( \hat{F}_n(\Theta) \)
is expressed by

\[
\hat{F}_n(\Theta) = \hat{\mu}_n + r_n(\Theta)^\top R_n^{-1} (y_n - \hat{\mu}_n).
\]

The selection of the next point will be based on
selecting the point that maximizes either the uncertainty
or the expected improvement, or a combination of both.
The motivation for selecting the point that maximizes the uncertainty is that we wish to know
as much about the function’s behavior as possible.
By sampling the point with the most uncertainty, the
uncertainty at that point becomes zero, thus decreasing
the total uncertainty about the function by as
much as possible.

3.2.1. Maximizing the Expected Improvement.
Jones (2001) and Jones et al. (1998) recommend selecting
the next point to sample as the point \( \Theta \) for which
the expected improvement over the current best solution
value, \( I_n(\Theta) \), is largest. This corresponds to solving
the following optimization problem:

\[
\begin{align*}
\max & \quad I_n(\Theta) \\
\text{subject to} & \quad \theta_h \in \mathbb{R} \quad h = 1, \ldots, k.
\end{align*}
\]

Although this is a difficult optimization problem, it
can be solved using a branch-and-bound technique,
but in order to do so, an upper bound on \( I_n(\Theta) \) must
be obtained. This can be done by solving for the
expected improvement in Equation (4) while substitu-
ting an upper bound on the uncertainty and a lower
bound on \( \hat{F}_n(\Theta) \), used in Equation (5) to determine
the value \( z \). The method of bounding \( \hat{F}_n(\Theta) \) is taken
directly from Jones (2001) and Jones et al. (1998) and
is not discussed further here. The method of bound-
ing \( \hat{\sigma}_n(\Theta) \) is improved from the original formulation
in Jones et al. (1998) to overcome numerical insta-
bilities, and is presented in §3.2.2. The branch-and-
bound algorithm used to maximize \( I_n(\Theta) \) is described
in §3.2.3.

3.2.2. Obtaining an Upper Bound on the Uncer-
tainty. Due to the complexity of the \( \hat{\sigma}_n(\Theta) \) function,
maximizing the uncertainty is a difficult problem
to solve. However, it can be relaxed into a linearly
constrained quadratic programming problem as fol-
lows (Jones et al. 1998). The resulting solution to
the relaxed uncertainty maximization problem is an
upper bound on the uncertainty that can be used in
determining an upper bound on \( I_n(\Theta) \) as described
in §3.2.1. This relaxation does not affect the conver-
gence of the algorithm.

The relaxation of the maximum uncertainty prob-
lem primarily consists of treating each correlation
\( r_i(\Theta, \Theta^{(0)}) \) as an independent variable \( r_i \) rather than
as a function of \( \Theta \). Then, a set of constraints are
required to ensure that each variable \( r_i \) assumes the
actual correlation value of \( r_i(\Theta, \Theta^{(0)}) \). As these con-
straints are nonlinear, they are relaxed using linear
underestimators.

Let \( r = [r_1, \ldots, r_n] \), where \( r \) is a vector of decision
variables independent of \( \Theta \). By treating both \( r \) and \( \Theta \) as
decision variables, a quadratic objective function is
obtained. Because \( r \) is now a decision variable inde-
pendent of \( \Theta \), an equality constraint must be added
to the problem to ensure that \( r \) assumes the correct
correlation values according to the correlation defini-
tion in Equation (2). This constraint is nonlinear, but
it can be relaxed by expressing the single equality
as two inequalities (\( \leq \) and \( \geq \)) and then replacing
the nonlinear terms generated by \( \ln(r_i) \) and \( c[\Theta - \Theta^{(0)}]_+^2 \)
with linear underestimators \( a_i + b_i r_i \) and \( p_{i,j} + q_{i,j} |\theta_i - \theta_j| \),
respectively. The different types of linear estimators
require different values for \( a_i, b_i, p_{i,j} \) and \( q_{i,j} \) and are
differentiated by a superscript \( c \) for the chord under-
estimators and a superscript \( t \) for the tangent line
underestimators in the model formulation, denoted as
Problem \( s^c-UB \).

Unfortunately, this relaxation provided by Jones
et al. (1998) can become numerically unstable if two
sampled points are very close together. If such a
s\textsuperscript{2}-UB: Choose r and \Theta to

\[
\min -\sigma^2 \left[ 1 - r R_n^{-1} r + \frac{1 - T R_n^{-1} t}{T R_n^{-1}} \right] + \sum_{i=1}^{n} (w_i^L)^2 + \sum_{i=1}^{n} (w_i^U)^2
\]

subject to

\[
(a_i^L + b_i r) + c \sum_{h=1}^{k} (p_i^L, h + q_i^L, h \theta_h) \leq 0 \quad i = 1, \ldots, n
\]

\[
(a_i^L + b_i r) + c \sum_{h=1}^{k} (p_i^L, h + q_i^L, h \theta_h) \leq 0 \quad i = 1, \ldots, n
\]

\[
w_i^L \leq 0 \quad i = 1, \ldots, n
\]

\[
w_i^L \leq r_i - r_i^L \quad i = 1, \ldots, n
\]

\[
w_i^U \leq 0 \quad i = 1, \ldots, n
\]

\[
w_i^U \leq r_i^U - r_i \quad i = 1, \ldots, n
\]

\[l_h \leq \theta_h \leq u_h \quad h = 1, \ldots, k.
\]

Using the upper bound on the uncertainty provided by Problem s\textsuperscript{2}-UB, the point yielding the maximum uncertainty is obtained by using the same branch-and-bound method described in §3.2.3, except that \(s_h^2(\Theta)\) is maximized rather than \(l_h(\Theta)\).

Alternatively, another approach would be to choose the next point based on maximizing the uncertainty rather than the expected improvement. The branch-and-bound approach described in §3.2.3 can be adapted to solve the problem of maximizing uncertainty rather than maximizing the expected improvement.

3.2.3. Branch and Bound. A branch-and-bound method is used to determine the maximum expected improvement in each iteration. At some stage in the algorithm, \(n\) points, \(\Theta(1), \ldots, \Theta(n)\), have already been observed. The solution space is divided into regions based on these previously sampled points, and each region is considered a separate subproblem.

Each of these subproblems is solved using branch and bound. First, the upper bound on the uncertainty is determined as described in §3.2.2 using the subregion’s lower and upper bounds on \(\Theta\). Next, the lower bound \(\hat{F}\) on \(\hat{F}_h(\Theta)\) is determined using the method in Jones (2001) and Jones et al. (1998).

The upper bound on \(s_h^2(\Theta)\) and lower bound on \(\hat{F}\) are now used to determine an upper bound on \(I_h(\Theta)\) over the current subregion by solving for \(I_h(\Theta)\) substituting \(\hat{F}_h(\Theta) = \hat{F}\) and \(s_h(\Theta) = s_h^2\) as described in Jones (2001) and Jones et al. (1998). In addition, the \(\Theta\) that yielded the maximum uncertainty can be used to evaluate the function \(I_h(\Theta)\), yielding a lower bound on \(I_h(\Theta)\) over the interval \(l_h \leq \theta_h \leq u_h\), \(h = 1, \ldots, k\).

This value is used to update the current best lower bound found (i.e., if the current best lower bound is less than the new lower bound found, the current best lower bound is replaced by the new one; otherwise, the current best lower bound is unchanged).

If the upper bound is less than the current best lower bound, the subregion is discarded as it is not interesting. If the lower and upper bounds are very close, we say that we have found the optimum over the current subregion. Otherwise, the upper bound is significantly larger than the current lower bound, so the subregion is further divided into subregions as described below and the procedure is repeated for each of the new regions. This is the branching step.

The algorithm terminates when there are no more subregions to consider, as we have either decided they are not interesting or have found the optimal solution for that subregion. Then, the algorithm terminates, and the current best lower bound is the optimal solution for \(I_h(\Theta)\) over the current region.

This branch-and-bound procedure is applied to each of the regions, and the overall largest \(I_h(\Theta)\) value is then the maximum \(I_h(\Theta)\). The corresponding \(\Theta\) is the next point at which to evaluate the FMO function.

Selecting the Subregions. An important component of the branch-and-bound algorithm is the method of selecting the subregions. The definition of these subregions, as well as the order in which they are explored, can have significant impact on both the amount of time and memory required to perform the algorithm. As our implementation of the branch-and-bound method requires that the entire solution space be divided into subregions before the branch-and-bound algorithm begins, the selection of these initial regions may also affect the speed of the algorithm.

Initial Regions. Before beginning the branch-and-bound process, the solution space of the decision variables, \(\theta_h \in [0, 360]\) for all \(h = 1, \ldots, k\), is divided into a set of initial regions. If \(\Theta\) represents noncoplanar orientations, we consider two ways of selecting the regions defined by the noncoplanar orientations. First, we consider the entire solution space as the
only region; that is, instead of dividing the solution space into several subregions, we only consider one subregion that encompasses the entire solution space. Denote this scheme as B0.

Next, we consider dividing the solution space according to some index \( \bar{h} \in \{1, \ldots, k\} \). The previously sampled points are sorted according to the value of \( \theta^{(i)}_h \), and the subregions impose upper and lower bounds on \( \theta_h \) according to the boundaries of each \( \theta^{(i)}_h \).

The other indices are unrestricted. If the gantry and the couch are allowed to move to create noncoplanar beams, then \( \theta_1 \) refers to the gantry position and \( \theta_2 \) refers to the couch position. Denote the initial region scheme of branching on the gantry position as B1 and the scheme of branching on the couch angle as B2.

Last, we consider dividing the solution space into subregions along every index. If both the gantry and the couch are allowed to rotate, such a scheme is denoted as B3.

**Bounds for Discrete and Continuous Variables.** If \( \Theta \) is discrete, the points on the boundary between the two subregions will be contained in both subregions, thus creating an inefficiency. This overlap can be avoided when \( \Theta \) is integral by adjusting the bounds between subregions in such a way as to prevent overlapping between any subregions. If the lower bound \( l_h \) on \( \theta_h \) in a subregion is fractional, then we discard the nonintegral solutions by setting \( l_h = \lfloor l_h \rfloor \). Similarly, if the upper bound \( u_h \) on \( \theta_h \) in a subregion is fractional, then \( u_h = \lceil u_h \rceil \). If the \( l_h \) and \( u_h \) bounds are integral and \( l_h = u_h \), overlapping is avoided by setting \( l_h = l_h - 1 \). If \( \Theta \) is continuous, the bounds cannot be adjusted.

**Branching Scheme.** The basic principle of the branch-and-bound method is to decompose regions into smaller subregions in such a way that as many subregions as possible can be discarded as uninteresting, leaving a reduced number of subregions that must actually be searched. There are numerous methods of selecting the subregions in a branch-and-bound scheme. Regions may be divided into two equal subregions (bisection) or, more generally, into multiple subregions that may or may not be equal in size (multisection) (Csalnok et al. 2000, Lagouanelle and Soubry 2004). Some other common methods include selecting only a subset of variables on which to branch (Epperly and Pistikopoulos 1997), using Langrangian duality to obtain lower bounds (Barrientos and Correa 2000, Thoai 2002, Tuy 2005) and applying decomposition algorithms (Phong et al. 1995, Bomze 2002, Cambini and Sodini 2005).

In our implementation, we divide the region into two subregions along the point yielding the upper bound on the uncertainty. In each branching step, we select the index to branch on by cycling through each of the indices \( h = 1, \ldots, k \) sequentially.

In our branching step, we form the subregions based on some point in the region. The region is divided at this point along one of the indices. We branch by dividing the region horizontally into two subregions at \( \Theta^{(i)}_h \), taking into account the adjustments to the bounds described above so as to avoid overlapping regions.

In the general case, we divide the region into two subregions along the branching index while cycling through each of the indices \( h = 1, \ldots, k \) sequentially. For the branching index \( \bar{h} \), the bounds for one new subregion are \( l_{\bar{h}} = l_{\bar{h}} \) and \( u_{\bar{h}} = \theta_{\bar{h}, \bar{h}} - 1 \), and the bounds for the other new subregion are \( l_{\bar{h}} = \theta_{\bar{h}, \bar{h}} \) and \( u_{\bar{h}} = u_{\bar{h}} \). The lower and upper bounds on the region for the remaining indices are unchanged for both new subregions; i.e., \( l_{\bar{h}} = l_{\bar{h}} \) and \( u_{\bar{h}} = u_{\bar{h}} \) for \( h \neq \bar{h} \).

In the noncoplanar case, a beam in \( \Theta \) may be represented by more than one index. For example, if a single noncoplanar beam consisting of couch and gantry rotation is optimized, the vector \( \Theta \) consists of \( \theta_1 \) representing the gantry angle and \( \theta_2 \) representing the couch angle. The branching index \( \bar{h} \in \{1, 2\} \) represents branching on either the gantry angle or on the couch angle. If two such noncoplanar beams are optimized, then \( \Theta \) consists of \( \theta_1, \theta_2, \theta_3 \) and \( \theta_4 \) representing the gantry and couch angles of the first beam, respectively, and \( \theta_3 \) and \( \theta_4 \) representing the gantry and couch angles of the second beam, respectively. The branching index \( \bar{h} \in \{1, 2, 3, 4\} \) then represents branching on a single component of a single beam.

**Accounting for Symmetry.** In the case where \( \Theta \) represents a set of coplanar beam angles, the ordering of the variables in \( \Theta \) is irrelevant to the FMO value obtained at \( \Theta \). For example, if \( \Theta^{(1)} = (10, 20, 30, 40) \) and \( \Theta^{(2)} = (20, 30, 40, 10) \), then \( F(\Theta^{(1)}) = F(\Theta^{(2)}) \). Thus, it is redundant to consider both \( \Theta^{(1)} \) and \( \Theta^{(2)} \), and elimination of these redundant regions can greatly decrease the size of the solution space. In the case of coplanar beams, we can simply require that \( \theta_1 < \cdots < \theta_k \) in the optimization problem of maximizing the uncertainty and in selecting subregions to explore in the branch-and-bound algorithm.

An additional symmetry that could be considered is the similarity of parallel-opposed beams. Parallel-opposed beams are beams that are 180° apart. However, the purpose of this work is to consider as many beams as possible without the a priori exclusion of any beams. Thus, parallel-opposed beams are allowed, although such an extension could be considered in the future.

For the case of noncoplanar orientations, a similar symmetry to the coplanar orientation symmetry exists. Consider an implementation where two noncoplanar beam orientations are optimized and are obtained from rotating both the gantry and the couch. Each beam is represented by two variables in the
solution vector, one variable indicating the degree of gantry rotation and one variable indicating the degree of couch rotation. Let $\theta_1$ and $\theta_2$ be the gantry rotation and couch rotation of the first beam, respectively, and $\theta_3$ and $\theta_4$ be the gantry rotation and couch rotation of the second beam, respectively. Then, the solution vector $\{\theta_1, \theta_2, \theta_3, \theta_4\}$ is identical to the solution vector $\{\theta_1, \theta_4, \theta_1, \theta_2\}$. Because the couch angle selected is dependent on the gantry angle (and vice versa), this symmetry can be exploited by only removing redundant solutions from one of the beam variables, that is, by requiring that $\theta_1 \leq \theta_2$ (removing redundancy from the gantry angles) or $\theta_2 \leq \theta_4$ (removing redundancy from the couch angles). In general, if $d$ degrees of motion are used to obtain $m$ beam orientations and the linear accelerator motion variables are in the same order for each beam, then $\theta_j \leq \theta_{j+d} \leq \theta_{j+2d} \leq \cdots \leq \theta_{j+(m-1)d}$ for some $j \in \{1, \ldots, d\}$.

### 3.3. Method of Obtaining the Next Observation

The RS algorithm allows for two methods of selecting the next point to observe: by maximizing the expected improvement or by maximizing the uncertainty. In this implementation, the point to observe is obtained by first selecting the point that maximizes the expected improvement until the maximum expected improvement falls below a certain threshold and then switching to the point that maximizes the uncertainty. Once the maximum uncertainty also falls below a certain threshold, the algorithm terminates. By first selecting according to the expected improvement, the method quickly obtains a good solution. By then selecting according to uncertainty, theoretical convergence to the global minimum is ensured.

### 4. Results

The response surface method was tested on six head-and-neck cases using a Windows XP computer with a 3.2 GHz Pentium IV processor and 2 GB of RAM. Each algorithm was allowed to run for 12 hours, which is not an unreasonable run length because BOO will not be performed on a day-to-day basis. It is anticipated that BOO will be performed once overnight between the time the patient is imaged and the time the patient begins radiation therapy. A good beam vector chosen before treatment begins should continue to provide quality treatment plans throughout the patient’s treatment, which is typically 35 days.

The beam orientations from which linear accelerators are capable of delivering radiation are not restricted to integer value degrees. However, in this study, integral beam orientations are desired to account for setup tolerances. If beams are allowed to assume fractional values, it can be difficult to position the patient to exactly achieve the treatment plan, especially when there are several treatment fractions during which the patient must be set up and treated. For example, it would be nearly impossible to position the patient to consistently reproduce the effect of a beam angle of 9.19°, especially considering tolerances in gantry and couch positioning. For the same reasons, beam orientations are considered on a 1° grid. To obtain integral solutions, in the subproblem of maximizing $I(\theta)$, the integer constraint is relaxed in the problem of determining an upper bound on $\hat{s}(\theta)$, and the resulting solution is rounded to integer values.

The branching scheme used treats the rounded solution as integral and branches so as to avoid overlapping subregions as described in §3.2.3. Results are provided for each possible initial region scheme. The point at which branching is performed in each region, $\theta_b$ in §3.2.3, is chosen as the midpoint of the region. Also, $\vec{r}$ and $\theta_b$ in the underestimating terms in Problem $s^2$-UB in §3.2.2 are taken to be the midpoints of their respective intervals.

It is anticipated that the weighted distance measure in Equation (3) will have a significant impact on the algorithm’s performance. Intuitively, a small weighted distance corresponds to a small correlation between points, which will cause the algorithm to behave locally. To induce the algorithm to behave globally, the algorithm must assume less correlation between two points. If the points are less correlated, the algorithm will be less likely to stay in the neighborhood of previously sampled points. The correlation between two points can be decreased by increasing the weighted distance between the points, which can be done by increasing $c$ or $p$. Because $p = 2$ provides desirable problem structure, we will only consider manipulating the values of $c$. If $c$ becomes sufficiently large, the correlation between points will be effectively zero, thus yielding an effectively random search algorithm. To test these expectations, $c$ was tested with values of 10.0, 100.0, and 500.0. In each test, five randomly selected starting points were used to initialize the RS algorithm. The results indicate that the starting points chosen do not significantly affect the outcome of the algorithm.

Treatment plans consisting of four beams are obtained and compared with 7-beam equispaced coplanar treatment plans. This comparison demonstrates that with some BOO, it is possible to use only four beams and still deliver a high-quality treatment plan.

#### 4.1. Proof of Concept

To test the accuracy of the RS method, a single case was tested wherein the problem of adding a single coplanar beam to an equispaced, coplanar 3-beam solution over a 1° grid was considered. The algorithm was initialized with two randomly selected starting
points. By considering such a small-scale problem, the solution space in each iteration can be explicitly enumerated in order to exactly obtain the next best point to sample. The ability to enumerate the solution space will also allow us to determine how accurately the RS method models the FMO objective function.

At each point that has been sampled, both the uncertainty and the expected improvement will be zero. This result is not only theoretically true but also intuitive because once the FMO value at a certain point is known, there will be no improvement over the current best FMO value by sampling that point again. It is also expected that as the algorithm progresses, the approximation of the FMO function will become increasingly accurate, with the approximation obtaining the exact FMO values at sampled points.

Figure 2 demonstrates how the RS method behaved as predicted at different points in the RS algorithm. The expected value is zero at sampled points, and the approximation of the FMO function almost perfectly fits the true FMO function by the time the algorithm terminates.

The importance of the starting points, the points sampled before the algorithm begins to give the method some baseline information about the FMO function, was also tested. To test the dependence on starting points, the RS method was run 100 times using two uniformly randomly generated starting points each time. The RS method obtained the global optimum in 90.6% of trials, indicating that the performance of the algorithm is not significantly dependent on the starting points. The RS method will only be run once for each of the tests on clinical data.

4.2. Adding a Noncoplanar Beam to a Coplanar Solution

Next, the problem of adding a noncoplanar beam to a 3-beam locally optimal coplanar solution was considered for six head-and-neck cases. Only one noncoplanar beam is allowed due to the very large
solution space that even one noncoplanar beam creates. The algorithm is easily extendable to consider more noncoplanar beams or degrees of freedom. A final treatment plan consisting of four beams is sought to demonstrate that whereas current practice uses five to seven beams for head-and-neck treatments, four beams are suitable if BOO is applied.

The locally optimal solution is obtained using the add/drop algorithm (Aleman et al. 2007). The add/drop algorithm takes an initial starting beam solution and iteratively changes one beam to an improving neighboring beam until there are no improving moves to be made. The neighborhood size used for each beam is 40°. The objective function value used for each beam solution is the optimal FMO solution value.

The beam data for the noncoplanar beam being optimized are generated on-the-fly and consist of gantry and couch rotations, where the both gantry and couch are allowed to rotate a full 360° on a 10° grid. These two degrees of freedom result in a two-dimensional BOO problem. Despite only having two dimensions, there are 362 = 1,296 possible solutions, too many to precompute or store the necessary beam data. Five uniformly randomly selected starting points will be used to initialize the response surface algorithm, and each point sampled by the algorithm is judged on its optimal FMO solution value. Initial region schemes B0, B1, and B4 are tested, along with c = {10.0, 100.0, 500.0}. The varying values of c will provide insight into the RS method’s ability to locate a good solution with respect to how local/global its search is.

As the final solution of the noncoplanar RS plan will be a 4-beam plan, the results from the response surface solution are compared to the locally optimal coplanar 4-beam add/drop plan, denoted 4 A/D. The plans will also be compared to an equispaced, coplanar 7-beam plan, denoted 7 equi, which is commonly used in practice to treat head-and-neck cancers. These comparisons will be made on both the FMO values of each plan and on the clinical quality of each plan as described in §4.3.

As shown by Table 1, there is relatively little deviation in the final solutions between the different parameter choices and initial regions schemes. The results also indicate that the starting points chosen do not significantly affect the outcome of the algorithm. This implies that the response surface algorithm is robust with respect to varying implementations.

Although the 4-beam RS (4 RS) solutions obtained an average of 5.44% decrease in FMO value from the 7 equi plans, the 4 RS solutions did in fact obtain an average of 16.12% improvement in FMO value over the 4 A/D solutions. Despite the differences in FMO value, all treatment plans examined were similar in clinical quality, as discussed in §4.3.

Although the algorithm was allowed to run for 12 hours in each scenario, the minimum FMO value obtained by the RS method was found early on. On average, the best FMO value found was obtained in 6.15 hours after sampling 27–40 points.

For each of the RS method variations tested, both the number of points sampled and the relative improvements in FMO value are nearly identical. This indicates that the algorithm is robust with respect to parameter and implementation changes. The time spent generating beam data comprises approximately 84% of the algorithm’s run time, whereas the response surface portion on average accounts for only 13%. Thus, it is expected that changes to the RS method, including improvements to the branch-and-bound routine, will not have a very strong impact on the number of points the algorithm will sample in its allotted run time.

### 4.3. Clinical Results

Rather than relying strictly on FMO value, a tool commonly used by physicians to judge the quality of a treatment plan is the dose-volume histogram (DVH). This histogram is a measure of the cumulative dose received by a given structure. It specifies the fraction of each structure’s volume that receives at least a certain amount of dose. Although there are several critical structures to be considered in head-and-neck cases, the saliva glands are notoriously the most difficult to spare due to their proximity to common tumor locations. Thus, for clarity, the DVH results provided include only target structures and saliva glands. Each of the treatment plans spares any organs not shown in the DVHs.

#### 4.3.1. Evaluating Plan Quality

To formulate an optimization problem, a quantitative measure of the treatment plan quality is needed. This measure, the FMO function value, needs to appropriately make the trade-off between the contradictory goals of covering targets and sparing critical structures.

Typically, a good plan ensures that at least a certain percent of each target receives the prescription dose.
A coldspot occurs when less than a certain percentage of the target receives the prescription dose. Similarly, a hotspot occurs if a significant percentage of the target receives more than the prescription dose.

**Target Coverage.** Each of the plans contains two target structures or planning tumor volumes (PTV). PTV2 consists of the gross tumor volume (GTV) expanded to account for both subclinical disease as well as daily setup errors and internal organ motion; PTV1 is a larger target that also contains high-risk nodal regions, again expanded to account for subclinical disease and setup errors and organ motion. The dose prescribed for PTV1 is less than the dose prescribed for PTV2.

For target structures, we require that at least 95% of the target receives the full prescription dose, so the dose that is received by at least 95% of each of the targets is measured. However, we want to restrict the amount of the target that receives more than the prescription dose. Because PTV2 is contained inside PTV1, PTV2 will necessarily have a sizable but less important area receiving an overdose. Thus, we are only concerned with PTV2 overdose. To evaluate the size of the hotspot, we check the percent volume of PTV2 that receives more than 110% of the prescription dose. To evaluate the coldspots, we check the percent volume of both PTV1 and PTV2 that receives at least 93% of the prescription dose. The prescription doses are set to 54 Gy for PTV1 and 73.8 Gy for PTV2, which are the dose values used at Shands Hospital at the University of Florida.

Table 2 displays the target coverage achieved by the different treatment plans. The values for the response surface plans are obtained by using $c = 10$ and from initial region scheme B3; however, the differences in target coverage between the RS implementations are small. On average, the 7 equi plan was able to deliver the most amount of dose to PTV2, but the 4 RS plan still usually delivers at least the prescribed dose. The 4 A/D plans underdosed PTV2 more frequently than either the 4 RS or 7 equi plans. Both of the 4-beam plans usually deliver PTV1 dose closer to the prescription dose than the 7 equi plan, although in one instance the 4 A/D plan underdosed the PTV1, whereas neither the 4 R/S nor the 7 equi plans did. Although neither of the 4-beam plans performed well in Case 6 in Table 2, it is worth noting that the 7 equi plan was also unable to achieve a satisfactory treatment plan.

Figures 3 and 4 illustrate two representative cases where the 4 RS, 4 A/D, and 7 equi plans each have

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**Table 2** Target Coverage Achieved by the Treatment Plans for Each Case

<table>
<thead>
<tr>
<th>Case</th>
<th>Target coverage</th>
<th>4 RS</th>
<th>4 A/D</th>
<th>7 equi</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PTV2 dose at 95% volume</td>
<td>73.04 Gy</td>
<td>72.14 Gy</td>
<td>74.42 Gy</td>
</tr>
<tr>
<td></td>
<td>PTV2 % receiving &gt; 110% of Rx (%)</td>
<td>10.26</td>
<td>13.71</td>
<td>17.37</td>
</tr>
<tr>
<td></td>
<td>PTV2 % receiving &gt; 95% of Rx (%)</td>
<td>99.65</td>
<td>99.47</td>
<td>99.81</td>
</tr>
<tr>
<td></td>
<td>PTV1 dose at 95% volume</td>
<td>54.47 Gy</td>
<td>54.80 Gy</td>
<td>55.65 Gy</td>
</tr>
<tr>
<td></td>
<td>PTV1 % receiving &gt; 95% of Rx (%)</td>
<td>98.12</td>
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<td>98.60</td>
</tr>
<tr>
<td>2</td>
<td>PTV2 dose at 95% volume</td>
<td>74.57 Gy</td>
<td>74.52 Gy</td>
<td>75.41 Gy</td>
</tr>
<tr>
<td></td>
<td>PTV2 % receiving &gt; 110% of Rx (%)</td>
<td>7.11</td>
<td>4.13</td>
<td>30.01</td>
</tr>
<tr>
<td></td>
<td>PTV2 % receiving &gt; 95% of Rx (%)</td>
<td>100.00</td>
<td>100.00</td>
<td>100.00</td>
</tr>
<tr>
<td></td>
<td>PTV1 dose at 95% volume</td>
<td>53.91 Gy</td>
<td>54.12 Gy</td>
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</tr>
<tr>
<td></td>
<td>PTV1 % receiving &gt; 95% of Rx (%)</td>
<td>97.66</td>
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<td>97.81</td>
</tr>
<tr>
<td>3</td>
<td>PTV2 dose at 95% volume</td>
<td>74.21 Gy</td>
<td>73.25 Gy</td>
<td>75.15 Gy</td>
</tr>
<tr>
<td></td>
<td>PTV2 % receiving &gt; 110% of Rx (%)</td>
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<td></td>
<td>PTV1 dose at 95% volume</td>
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<td>54.64 Gy</td>
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<tr>
<td></td>
<td>PTV1 % receiving &gt; 95% of Rx (%)</td>
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<td>98.51</td>
</tr>
<tr>
<td>4</td>
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<td>74.22 Gy</td>
<td>73.25 Gy</td>
<td>74.02 Gy</td>
</tr>
<tr>
<td></td>
<td>PTV2 % receiving &gt; 110% of Rx (%)</td>
<td>5.44</td>
<td>4.94</td>
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<tr>
<td></td>
<td>PTV2 % receiving &gt; 95% of Rx (%)</td>
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<td>99.29</td>
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<tr>
<td></td>
<td>PTV1 dose at 95% volume</td>
<td>52.16 Gy</td>
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<td></td>
<td>PTV1 % receiving &gt; 95% of Rx (%)</td>
<td>94.60</td>
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</tr>
<tr>
<td>5</td>
<td>PTV2 dose at 95% volume</td>
<td>74.36 Gy</td>
<td>74.00 Gy</td>
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</tr>
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<td>99.77</td>
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<tr>
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<td>PTV1 dose at 95% volume</td>
<td>54.23 Gy</td>
<td>53.15 Gy</td>
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<td>PTV1 % receiving &gt; 95% of Rx (%)</td>
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</tr>
<tr>
<td>6</td>
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<tr>
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</tr>
<tr>
<td></td>
<td>PTV1 dose at 95% volume</td>
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<td>57.01 Gy</td>
<td>68.11 Gy</td>
</tr>
<tr>
<td></td>
<td>PTV1 % receiving &gt; 95% of Rx (%)</td>
<td>99.16</td>
<td>99.00</td>
<td>95.19</td>
</tr>
</tbody>
</table>

---

**Figure 3** 7 equi (Dotted), 4 A/D (Dashed), and 4 RS (Solid) Target and Saliva Gland DVHs
clinically acceptable target coverage. The vertical line at 73.8 Gy indicates the prescription dose for PTV2.

**Critical Structure Sparing.** The critical structures involved in each case vary depending on their proximity to the tumor. Parallel structures, e.g., saliva glands, will continue to function as long as a certain percentage of the organ receives less than a certain amount of dose. Series structures, on the other hand, will cease to function if any of the organ receives over a certain amount of dose. The spinal cord is one example of a serial structure. The sparing criteria for each of the common critical structures in head-and-neck cancer are listed in Table 3.

The loss of critical structures can greatly affect the patient’s quality of life. Table 3 shows the ability of each of the treatment plans to spare the organs in the cases tested. As there was no difference in organ sparing between the different RS implementations, the numbers shown are from a single arbitrarily chosen 4 RS implementation. Surprisingly, both the 4 RS and the 4 A/D plan are equivalent to or outperform the 7 equi plan in terms of organ sparing. In the 4-beam plans, the left submandibular gland (SMB) is spared in 83% of the treatment plans developed, whereas it is only spared in 67% of the 7 equi plans.

Head-and-neck tumors are usually situated in such a way that it can be particularly difficult to spare the saliva glands in the FMO optimization. Therefore, the DVH results shown only portray the saliva glands for organ sparing. It can be inferred from Table 3 that all other organs are spared in all treatment plans. One case illustrating equivalent organ sparing is shown in Figure 3, and one case demonstrating improved organ sparing over the 7 equi plan is shown in Figure 4. Isocontours for one case are shown in Figure 5 (a full-color version is available in the Online Supplement, available at http://joc.pubs.informs.org/ecompanion.html). However, just as PTV2 underdosage in the 4 A/D plans likely contributed to the smaller hotspots, it is possible that the improved organ sparing in the 4 A/D plans is also a result of the underdosage.

### Table 3 Percentage of Plans in Which an Organ Is Spared

<table>
<thead>
<tr>
<th>Structure</th>
<th>Sparing criteria</th>
<th>4 RS Sparing frequency (%)</th>
<th>4 A/D Sparing frequency (%)</th>
<th>7 equi Sparing frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain stem</td>
<td>100% volume &lt; 55 Gy</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Mandible</td>
<td>100% volume &lt; 70 Gy</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Left optic nerve</td>
<td>100% volume &lt; 50 Gy</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Right optic nerve</td>
<td>100% volume &lt; 50 Gy</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Left eye</td>
<td>50% volume &lt; 30 Gy</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Right eye</td>
<td>50% volume &lt; 30 Gy</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Optic chiasm</td>
<td>100% volume &lt; 55 Gy</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Left parotid gland</td>
<td>50% volume &lt; 30 Gy</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Right parotid gland</td>
<td>50% volume &lt; 30 Gy</td>
<td>67</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>Left SMB gland</td>
<td>50% volume &lt; 30 Gy</td>
<td>83</td>
<td>83</td>
<td>67</td>
</tr>
<tr>
<td>Right SMB gland</td>
<td>50% volume &lt; 30 Gy</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>100% volume &lt; 45 Gy</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Skin</td>
<td>100% volume &lt; 60 Gy</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

5. Conclusions and Future Work
We have shown that for head-and-neck cases, quality plans with fewer beams than a standard treatment plan can be obtained if either BOO method presented is applied. The response surface algorithm operates in a clinically reasonable timeframe, although it is not applicable to same-day treatment planning. The method is generally successful in selecting noncoplanar beam orientations to improve the FMO value over that of locally optimal coplanar add/drop solutions. The FMO values of the 4-beam response surface plans were also only slightly larger than that of the 7-beam equispaced coplanar treatment plans, indicating comparable treatment plans despite the decreased number of beams. Examination of DVHs for the tested cases confirms this implication.

In terms of clinical results, the most significant benefit of the noncoplanar solutions over the locally optimal coplanar solutions is the ability to deliver a higher amount of dose to the target structures. Both
the noncoplanar and locally optimal coplanar solutions were able to obtain treatment plans with organ sparing that were comparable to or improved upon the 7-beam equispaced coplanar treatment plans.

Whereas the inclusion of noncoplanar orientations in BOO is useful in terms of FMO value and target coverage, the resulting improvements in the treatment plan may not always be clinically significant. The advantage of the response surface method is its ability to consider noncoplanar beams, but with better parameter tuning or neighborhood structure it is possible that the add/drop algorithm could obtain coplanar treatment plans with improved target coverage. This could make the response surface plans and the add/drop plans clinically equivalent, although the add/drop method would be preferred in clinical practice due to a much shorter run time.

Although most BOO research is restricted to coplanar orientations, there has not yet been a study assessing the solution quality of coplanar versus noncoplanar solutions. The response surface method in our implementation has not run long enough to converge to the globally optimal solution, but the quality of the noncoplanar solutions obtained suggests that it is likely that noncoplanar beams do not significantly improve the quality of treatment plans in head-and-neck cases. This provides some basis for the common practice of restricting the solution space to the smaller, more tractable set of coplanar beams for head-and-neck beam optimization.

The patient cases in this work were all head-and-neck cases. Different tumor sites, e.g., breast, lung, and prostate, could possibly benefit from noncoplanar BOO and perhaps may experience greater improvements in treatment plan quality than that seen in head-and-neck cases. Total body irradiation may also benefit from the availability of noncoplanar beams. In future work, these sites will be tested to assess the general clinical usefulness of noncoplanar orientations and the response surface method.

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References


