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# Direct search applied to beam angle optimization in radiotherapy design

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**Abstract**

The intensity modulated radiation therapy (IMRT) treatment planning problem is usually divided in three smaller problems that are solved sequentially: geometry problem, intensity problem, and realization problem. The optimization community has made significant contributions to the improvement of IMRT treatment planning by addressing mainly the last two problems. However, the geometry problem or beam angle optimization (BAO) problem is still an open problem and, most of the times, beam directions continue to be manually selected in clinical practice, with only the fluences and the delivery being part of the optimization process. We propose a new approach for the BAO problem, by addressing it as a non-convex nonlinear (noisy) problem instead of a combinatorial problem, and by using direct search methods which are suited to tackle stochastic and non-stochastic noisy optimization problems. A clinical example of a head and neck case is used to discuss the benefits of using direct search methods in the optimization of the geometry problem, emphasizing the improvements achieved by using the optimized beam directions compared to the traditional equidistant set of incidence directions.

**Key words.** Radiotherapy, IMRT, Beam angle optimization, Direct Search.

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# 1 Introduction

The number of cancer patients continues to grow worldwide. There are several different treatments commonly used, depending on the type and stage of the cancer and include surgery, radiation therapy, chemotherapy, immunotherapy, etc. Here, one will focus on radiation therapy, in particular on intensity modulated radiation therapy (IMRT), where optimization can have an important role in the improvement of the treatment's quality.

The goal of radiation therapy is to deliver a dose of radiation to the cancerous region to sterilize the tumor minimizing the damages on the surrounding healthy organs and tissues. Radiation therapy is delivered with the patient immobilized on a coach that can rotate. Typically, radiation is generated by a linear accelerator mounted on a gantry that can rotate along a central axis (see Fig. 1). The rotation of the couch combined with the rotation of the gantry allows a radiation from almost any angle around the tumor. Despite the fact that almost every angle is possible for radiation delivery, except for rare cases (e.g. [30]), coplanar angles are considered. This is a way to simplify an already complex problem, and the angles considered lay in the plane of the rotation of the gantry around the patient. Despite evidence in the literature that appropriate radiation beam incidence directions can lead to plan's quality improvement (see e.g. [13, 28, 41]), in clinical practice, most of the times, the number of beams is assumed to be defined a priori by the treatment planner and the beam directions are still manually selected by the treatment planner that relies mostly on his experience.

An important type of radiation therapy is IMRT, where the radiation beam is modulated by a multileaf collimator. Multileaf collimators enable the transformation of the beam into a grid of smaller beamlets of independent intensities. Multileaf collimators can operate in two distinct ways: dynamic collimation or multiple static collimation. In the first case, the leaves move continuously during irradiation. In the second case, the "step and shoot mode", the leaves are set to open a desired aperture during each segment of the delivery and radiation is on for a specific fluence time or intensity. This procedure generates a discrete set (the set of chosen beam angles) of intensity maps. Here, one will consider IMRT optimization problems with multiple static collimation for coplanar angles and will assume that the number of beams is defined a priori by the treatment planner.

A common way to solve the inverse planning in IMRT optimization problems is to use a

Figure 1: Linear accelerator rotating through different angles [37].

beamlet-based approach. This approach leads to a large-scale programming problem with up to hundreds of thousands of variables and up to millions of constraints, depending on the resolution and/or sampling rate used. Due to the complexity of the whole optimization problem, many times the treatment planning is divided into three smaller problems which can be solved sequentially: geometry problem, intensity problem, and realization problem. Most of the effort in the IMRT optimization community has been devoted at optimizing beamlet intensities - intensity or fluence map optimization (FMO) problem, once the beam angles have been selected by the treatment planner. Comparatively fewer research effort has been directed to the optimization of beam angles - geometry or beam angle optimization (BAO) problem.

Except for rare exceptions, where the BAO problem is addressed as a non-convex nonlinear problem (e.g. [8]), for the vast majority of previous work on beam angle optimization, the continuous $[0°, 360°[$ gantry angles are discretized into equally spaced beam directions with a given angle increment, such as 5 or 10 degrees, where exhaustive searches are performed directly or guided by a variety of different heuristics including simulated annealing ([17, 18, 19]), genetic algorithms ([18, 19]), particle swarm ([25]) or other heuristics incorporating a priori knowledge of the problem. Another common alternative is scoring methods, where scores are assigned to beam angles based on geometric and dosimetric information (see e.g. [18, 27, 36]). Despite the fact that these methods reduce the computational time, they have the drawback of ignoring the inter-relationship between beam angles by calculating dosimetric parameters from a single incident beam angle plan. Set covering and vector quantization are two other single-step techniques used. A comparison of all those methodologies is presented in Ref. [20] leading to the conclusion that these techniques are very similar and intertwined even knowing that their clinical perspectives may differ.

The concept of beam's eye view has been a popular approach to address the geometry problem as well. The concept is similar to a bird's eye view, where the object being viewed is the tumor as seen from a beam. The bigger the area of the tumor is seen by the beam, the better candidate the beam is to be used in the treatment plan. Other approaches include the projection of the surrounding organs into the tumor. Pugachev and Xing (see Ref. [36]) present a computer assisted selection of coplanar angles based on scores assigned to each beam of every gantry position. The scores assigned to each beam are based on a variation of the beam's eye view concept. Many others attempts to address the geometry problem can be found in literature. Ehrgott et al. [19] propose a mathematical framework that unifies the approaches found in literature. Acosta et al. [1] focused on how different approximations of the organ dose affects the beam selection. Lee et al. [23] suggests a mixed integer programming (MIP) approach for simultaneously determining an optimal intensity map and optimal beam angles for IMRT delivery. This is an interesting large-scale approach but hard to solve even with the increasing computational capabilities of the modern days. It is a mixed integer programming model, with a continuous and a discrete variable associated to each voxel, easily leading to exhaustion of computer memory. D'Souza et al. [18] proposed a beam ranking procedure (MOD - median organ at risk dose) that is suited for organs sparing. Other approaches include maximal geometric separation of treatment beams ([13]) or gradient searches ([8]).

In order to drive the BAO problem, we will use the optimal solution of the FMO problem, an exact measure of the treatment plan quality attainable using a given beam angle set. Regardless the optimal solution of the FMO problem being the natural measure for the quality of a beam angle set, except for rare exceptions, the previous BAO studies are based on a variety of scoring methods or approximations to the FMO to gauge the quality of the beam angle set. When the BAO problem is not based on the optimal FMO solutions, the resulting beam angle set has no guarantee of optimality and has questionable reliability since it has been extensively reported that optimal beam angles for IMRT are often non-intuitive. The main reason to avoid using the optimal FMO solutions to drive the BAO problem is time related. Obtaining the optimal solution for a beam angle set is time costly and even if only a beam angle is changed in that set, a complete dose computation is required in order to compute and obtain the corresponding optimal FMO solution. To minimize this time issue, methods that require few function value evaluations should be used to tackle the BAO problem. Additionally, the BAO problem is quite difficult since it is a highly non-convex optimization problem with many local minima ([42, 8]). From 100 different starting beam angle sets, Craft's gradient searches ([8]) found 100 different local minima. Therefore, methods that avoid being easily trapped in local minima should be used as well.

The objective of this research report is to introduce a new approach for the resolution of the BAO problem, using direct search methods to tackle this highly non-convex optimization problem. Direct search methods gather the two characteristics enumerated in the previous paragraph, making them suited to address the BAO problem. The research report is organized as follows. In the next section one describe the BAO problem formulation and the coupled FMO problem formulation. Section 3 briefly presents the direct search methods used. A clinical example of a head and neck case is presented in section 4 to illustrate the use of direct search methods in the optimization of the BAO problem. In section 5 the obtained results are presented and discussed. In the last section we have the concluding remarks.

## 2 Geometry Problem

Theoretically, the objective of the geometry problem, or beam angle optimization (BAO) problem, is to find the minimum number of beams and corresponding incidence directions that satisfy the treatment goals. Since only coplanar beams are considered here and the number of beams is assumed to be defined a priori by the treatment planner, the BAO problem consists in the determination of the linear accelerator gantry positions for which radiation is delivered.

In order to model the BAO problem as a mathematical programming problem, a quantitative measure to compare the quality of different sets of beam angles is required. For the reasons presented before, our approach for modelling the BAO problem, uses the optimal solution value of the FMO problem as measure for the quality of a given beam angle set. Thus, one will present the formulation of the geometry or BAO problem followed by the formulation of the FMO problem we used.

## 2.1 BAO model

Let us consider $k$ to be the fixed number of (coplanar) beams, i.e., $k$ beams are chosen on a circle around the CT-slice of the body that contains the isocenter (typically the center of mass of the tumor). A basic formulation for the BAO problem is obtained by selecting an objective function such that the best set of beams is obtained for the function's minimum:

$$\begin{aligned} \min \quad & f(\theta_1, \ldots, \theta_k) \\ s.t. \quad & \theta_1, \ldots, \theta_k \in \Theta, \quad \text{where } \Theta \text{ is the set of all possible angles.} \end{aligned} \tag{1}$$

Typically, the BAO problem is formulated as a combinatorial optimization problem, in which a specified number of beams is to be selected among a beam candidate pool. The continuous $[0°, 360°[$ gantry angles are generally discretized into equally spaced directions with a given angle increment, such as 5 or 10 degrees originating $\Theta = \Theta_1^k$, $\Theta_1 = \{0, 5, \ldots, 355\}$ or $\Theta = \Theta_2^k$, $\Theta_2 = \{0, 10, \ldots, 350\}$, respectively. One could think in all possible combinations of $k$ beam angles as an exhaustive global search method. However, this requires an enormous amount of time to calculate and compare all dose distributions for all possible angle combinations. Therefore, an exhaustive search of a large-scale combinatorial problem is considered to be too slow and inappropriate for a clinical setting. For example if we choose $k = 5$ angles out of 72 candidate beam angles ($\Theta_1$), there are $C_5^{72} = 13991544$ combinations. By decreasing the number of candidate beam angles to 36 ($\Theta_2$), the number of different combinations is still $C_5^{36} = 376992$, requiring an enormous amount of time to compare all the resulting plans regardless the measure considered in (1).

One will consider a different approach for the formulation of the BAO problem. All continuous $[0°, 360°[$ gantry angles will be considered instead of a discretized sample. Since the angle $-5°$ is equivalent to the angle $355°$ and the angle $365°$ is the same as the angle $5°$, we can avoid a bounded formulation and consider the following unconstrained BAO model:

$$\begin{aligned} \min \quad & f(\theta_1, \ldots, \theta_k) \\ s.t. \quad & \theta_1, \ldots, \theta_k \in \mathbb{R}^k \ (= \Theta). \end{aligned} \tag{2}$$

The objective $f(\theta_1, \ldots, \theta_k)$ that measures the quality of the set of beam directions $\theta_1, \ldots, \theta_k$ is chosen, in practice, in many different ways, expressing different criteria. Such functions may have numerous local optima, which increase the difficulty of obtaining a good global solution. Thus, the choice of the solution method becomes a critical aspect for obtaining a good solution. Our formulation was mainly motivated to enable the use of a class of solution methods that we consider to be suited to successfully address the BAO problem: direct search methods. Here, $f$ is defined to be the optimal solution of the beamlets intensities given by $\theta_1, \ldots, \theta_k$. This choice of $f$ is straightforward and is based on the fact that for a set of beam directions, a patient will be treated using an optimal fluence map. The FMO model used is presented next.

## 2.2 FMO model

For a given beam angle set, an optimal IMRT plan is obtained by solving the intensity or FMO problem - the problem of determining the optimal beamlet weights for the fixed beam angles. Many mathematical optimization models and algorithms have been proposed for the FMO problem, including linear models (e.g. [38, 39]), mixed integer linear models (e.g. [24, 35]), nonlinear models (e.g. [5, 43]), and multiobjective models (e.g. [9, 40]).

Radiation dose distribution deposited in the patient, measured in Gray (Gy), needs to be assessed accurately in order to solve the intensity problem, i.e., to determine optimal fluence maps. Typically, a dose matrix $D$ is constructed from the collection of beamlet weights, by indexing the rows of $D$ to each voxel and the columns to each beamlet, i.e., the number of rows of matrix $D$ equals the number of voxels and the number of columns equals the number of beamlets from all angles considered. Usually the total number of voxels considered reaches the millions and sometimes tens of millions, thus the row dimension of the dose matrix is of that magnitude. The size of $D$ originates large-scale problems being one of the main reasons for the difficulty of solving the FMO problem.

The first attempts to tackle the FMO problem used linear models. Some of the reasons for the use of linear models include the fact that dose deposition is linear, linear models are easy to implement and are broadly used. Given a prescription with a target goal ($TG_{PTV}$), lower ($LB_{PTV}$) and upper ($UB_{PTV}$) bounds for the planning target volume (PTV) dose ($D_{PTV}$), upper bound ($UB_{OAR}$) for the organs at risk (OAR) dose(s) ($D_{OAR}$), upper bound ($UB_{NT}$) for the normal tissue (NT) dose ($D_{NT}$) and given an upper bound ($M$) for the beamlet weight ($w$), most of the formulations of the linear models belong to a class of constrained optimization models such that an objective function is optimized while meeting these dose requirements. A simple formulation of a linear model is [27]:

$$\begin{array}{lllll} \min_w & f(D) & & & \\ s.t. & LB_{PTV} & \leq & D_{PTV} & \leq & UB_{PTV}, \\ & & & D_{OAR} & \leq & UB_{OAR}, \\ & & & D_{NT} & \leq & UB_{NT}, \\ & 0 & \leq & w & \leq & M. \end{array}$$

A variety of criteria may be represented by $f(D)$, leading to many different objective functions. One can consider, e.g., an average dose deviation in each structure for the objective function [26]:

$$f(D) = \alpha_{ptv} \frac{\|D_{PTV} - TG_{PTV}\|_p}{card(PTV)} + \alpha_{OAR} \frac{\|(D_{OAR} - UB_{OAR})_+\|_p}{card(OAR)} +$$

$$\alpha_{NT} \frac{\|(D_{NT} - UB_{NT})_+\|_p}{card(NT)}, \quad p = 1, 2, \infty,$$

where $(\cdot)_+ = max\{0, \cdot\}$, $\alpha_{(\cdot)}$ are weight factors that can be tuned by the treatment planner, and $card(\cdot)$ denotes the total number of voxels in the considered structure.

The optimal set of beam angles depends on weights of the objective function and constraints selected. For example, for a head and neck cancer case, a higher weight on the parotid objective results in a set of beams which will enhance better parotid sparing. For multi-objective IMRT optimization (e.g. [22]), each Pareto optimal treatment plan will have a distinct set of optimal beam angles. For traditional trial-and-error parameter tuning for IMRT planning, it is not clear how BAO should be incorporated into the planning process [8]. In order to reduce the dependence of the plan on these parameters, we choose to minimize the mean dose of the OARs and NT while imposing hard constraints to the targets to ensure that enough radiation is delivered to fulfill the dose prescription. The linear model used for this study was

$$
\begin{array}{lrcccl}
\min_w & \multicolumn{5}{l}{\frac{1}{card(OAR)} \sum_{OARs} D(OARs) + \frac{1}{card(NT)} \sum_{NT} D(NT)} \\
s.t. & LB_{PTV} & \leq & D_{PTV} & \leq & UB_{PTV}, \\
 & & & D_{OAR} & \leq & UB_{OAR}, \\
 & & & D_{NT} & \leq & UB_{NT}, \\
 & 0 & \leq & w & \leq & M.
\end{array}
$$

It is beyond the scope of this study to discuss if this formulation of the FMO problem is preferable to others. The choice of this linear model was motivated by the fact that linear models are widely used, easy to model and fast to solve. Nevertheless, the conclusions drawn regarding BAO coupled with this linear models are valid if different FMO formulations are considered.

# 3 Direct Search Methods

Direct search methods are iterative methods, that belong to a broader class of derivative-free optimization methods, such that iterates progression is solely based on a finite number of function values evaluation in each iteration, without explicit or implicit use of derivatives. In each iteration, the goal of direct search methods is to determine a new iterate such that a function decrease is achieved. We present direct search methods for unconstrained optimization problems of the form

$$
\begin{array}{ll}
\min & f(x) \\
s.t. & x \in \mathbb{R}^n,
\end{array}
$$

where the decision vector $x$ is used as input into the black-box function $f$. This type of resolution methods is suited for the beam angle problem formulation presented in (2) since similarly to other derivative-free optimization methods, when minimizing non-convex functions with a large number of local minima, due to their blindness caused by the non-use of derivatives, direct search methods have the ability to avoid being trapped by the closest local minima of the starting iterate, and find a local minimum in a lowest region.

There are two main types of direct search methods: simplicial direct search methods and directional direct search methods (see Ref. [6] for a detailed overview). The Nelder-Mead method [33] is probably the most popular example of simplicial direct search methods. The name simplicial is due to the fact that each iteration of this method is based on the evaluation of the objective function at the vertices of a simplex. The progression of the method is based on reflection, expansion or contraction of the simplex (for more details see [33]). It is a very simple method that managed to survive since 1965 and continues to be amongst the top performing derivative-free optimization methods (see [12, 31] or the Benchmarking Derivative-Free Optimization Algorithms web page [32]). There are many different implementations of the Nelder-Mead method, including the MATLAB function $fminsearch$. Although the referred qualities of the Nelder-Mead algorithm, directional direct search methods are better suited to address the BAO problem since they have the flexibility of incorporating previous optimization methods or heuristics tailored to address the BAO problem. The pattern search methods framework [4], where each iteration is composed by a search step and a poll step, originate the class of the most used and implemented directional direct search methods. We briefly describe next the pattern search methods framework as described in [4] or later in [2].

## 3.1 Pattern Search Methods

Pattern search methods are iterative methods generating a sequence of iterates $\{x_k\}$ using *positive bases* or *positive spanning sets* and moving in the direction that would produce a function decrease. Therefore, in order to describe pattern search methods one needs to describe the notions and motivations of the use of *positive bases*.

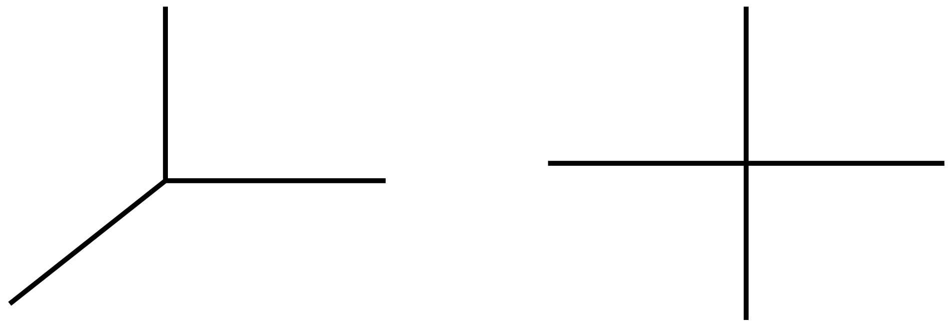
The *positive span*[1] of a set of vectors $v_1 \cdots v_m \in \mathbb{R}^n$ is the convex cone

$$L_0^+(v_1, \ldots, v_m) \;=\; \{v \in \mathbb{R}^n : \; v = \alpha_1 v_1 + \cdots + \alpha_m v_m, \quad \alpha_i \geq 0, \; i = 1, \ldots, m\}\,.$$

The set $\{v_1, \ldots, v_m\}$ is said to be *positively dependent* if one of the vectors is in the convex cone positively spanned by the remaining vectors, i.e., if one of the vectors is a positive combination of the others. Otherwise the set is *positively independent*.

A *positive basis* for $\mathbb{R}^n$ is a positively independent set of $\mathbb{R}^n$, whose positive span is $\mathbb{R}^n$. A positive basis for $\mathbb{R}^n$ can also be defined as a set of nonzero vectors of $\mathbb{R}^n$ whose positive combinations span $\mathbb{R}^n$, but no proper set does.

[1] Strictly speaking we should say *nonnegative* instead of positive.



(a) (b)

Figure 2: Examples of minimal – 2(a) and maximal – 2(b) positive bases in $\mathbb{R}^2$.

It can be shown that a positive basis for $\mathbb{R}^n$ contains at least $n+1$ vectors and cannot contain more than $2n$ [14]. Positive basis with $n+1$ and $2n$ elements are referred to as *minimal* and *maximal* positive basis, respectively. In Figure 2 we have an illustration of a minimal positive basis ($[I \ \ -e]$, with $I$ being the identity matrix and $e = [1 \ \ 1]^T$) and a maximal positive basis ($[I \ \ -I]$).

The following theorem [14] present three necessary and sufficient characterizations for positive bases and are the motivation for directional direct search methods:

**Theorem 3.1** *Let $\{v_1, \ldots, v_m\}$, with $v_i \neq 0$ for all $i \in \{1, \ldots, m\}$, span $\mathbb{R}^n$. Then the following are equivalent:*

**(i)** *$\{v_1, \ldots, v_m\}$ is a positive basis for $\mathbb{R}^n$.*

**(ii)** *For every $i = 1, \ldots, m$, $-v_i$ is in the convex cone positively spanned by the remaining $v_j$, $j \neq i$.*

**(iii)** *There exist real scalars $\alpha_1, \ldots, \alpha_m$ with $\alpha_i > 0$, $i \in \{1, \ldots, m\}$, such that $\sum_{i=1}^{m} \alpha_i v_i = 0$.*

**(iv)** *For every nonzero vector $b \in \mathbb{R}^n$, there exists an index $i$ in $\{1, \ldots, m\}$ for which $b^\top v_i > 0$.*

The characterization given by Theorem 3.1.iv (considering $b = -\nabla f(x_k)$) imply that, unless the current iterate is at a stationary point, there is always a vector $v_i$ in a positive basis (or positive spanning set) that is a descent direction, i.e.,

$$-\nabla f(x_k)v_i > 0.$$

In other words, the previous inequality means that there is always a vector $v_i$ in a positive basis that forms an acute angle with $-\nabla f(x_k)$. Therefore $v_i$ is a descent direction in the sense that there is an $\alpha > 0$ such that $f(x_k + \alpha v_i) < f(x_k)$. This is the core of directional direct search methods and in particular of pattern search methods.

Pattern search methods are iterative methods generating a sequence of non-increasing iterates $\{x_k\}$. Given the current iterate $x_k$, at each iteration $k$, the next point $x_{k+1}$ is chosen from a finite number of candidates on a given *mesh* $M_k$ aiming to provide a decrease on the objective function: $f(x_{k+1}) < f(x_k)$.

In order to define the mesh $M_k$, let us consider the positive spanning set $\mathcal{V}$ and denoted by $|\mathcal{V}|$ its cardinality. For convenience, let us abuse notation and also denote by $\mathcal{V}$ the matrix whose columns correspond to the $|\mathcal{V}|$ vectors in the positive spanning set $\mathcal{V}$. The mesh at iteration $k$ is then defined as

$$M_k = \{x_k + \Delta_k \mathcal{V} z : \; z \in \mathbb{Z}_+^{|\mathcal{V}|}\}, \tag{3}$$

where $\mathbb{Z}_+$ is the set of nonnegative integers.

Pattern search methods consider two phases at every iteration. The first phase, or step, consists of a finite search on the mesh, with the goal of finding a new iterate that decreases the value of the objective function at the current iterate. This step, called the *search step*, has the flexibility to use any strategy, method or heuristic, or take advantage of a priori knowledge of the problem at hand, as long as it searches only a finite number of points in the mesh. If the search step is unsuccessful, a second phase or step, called the *poll step*, is performed around the current iterate with the goal of decreasing the objective function.

The poll step follows stricter rules and appeals to the concepts of positive bases. In this step the candidate for a new iterate $x_{k+1}$ is chosen in the *mesh neighborhood* around $x_k$

$$\mathcal{N}(x_k) = \{x_k + \Delta_k v : \text{ for all } v \in V\} \subset M_k,$$

where $V$ is a positive basis (or positive spanning set) chosen from the finite set $\mathcal{V}$.

We have now all the ingredients to describe pattern search methods.

**Algorithm 3.1 (Pattern search methods)**

**0. Initialization** Choose $x_0 \in \mathbb{R}^n$, $\Delta_0 \in \mathbb{R}_+$, and a positive spanning set $V \subset \mathcal{V}$. Choose a rational number $\tau > 1$ and an integer number $m_{max} \geq 1$. Set $k = 0$.

**1. Search step (in current mesh)** Try to obtain a decrease of the objective function value at $x_k$ by evaluating $f$ at a finite number of points in $M_k$. If $x_{k+1} \in M_k$ is found satisfying $f(x_{k+1}) < f(x_k)$, go to step 3, expanding $M_k$ (search step and iteration are declared successful).

**2. Poll step (in mesh neighborhood given by the positive spanning set)** This step is only performed if the search step is unsuccessful. If $f(x_k) \leq f(x)$ for every $x$ in the mesh neighborhood $\mathcal{N}(x_k)$, go to step 4, shrinking $M_k$ (poll step and iteration are declared unsuccessful). Otherwise, choose a point $x_{k+1} \in \mathcal{N}(x_k)$ such that $f(x_{k+1}) < f(x_k)$ and go to step 3, expanding $M_k$ (poll step and iteration are declared successful).

**3. Mesh expansion (at successful iterations)** Let $\Delta_{k+1} = \tau^{m_k^+} \Delta_k$ (with $0 \leq m_k^+ \leq m_{max}$). Increase $k$ by one, and return to step 1 for a new iteration.

**4. Mesh reduction (at unsuccessful iterations)** Let $\Delta_{k+1} = \tau^{m_k^-} \Delta_k$ (with $-m_{max} \leq m_k^- \leq -1$). Increase $k$ by one, and return to step 1 for a new iteration.

The search step provides the flexibility for a global search since it allows searches away from the neighborhood of the current iterate, and influences the quality of the local minimizer or stationary point found by the method. The poll step is applied when the search step fails to produce a better point. The poll step attempts to perform a local search in a mesh neighborhood that, for a sufficient small mesh parameter $\Delta_k$, is guaranteed to provide a function reduction, unless the current iterate is at a stationary point (a fact that can be inferred by Theorem 3.1.iv with $b = -\nabla f(x_k)$). So, if the poll step also fails, the mesh parameter $\Delta_k$ must be decreased. The most common choice for mesh parameter update is to half the mesh parameter at unsuccessful iterations and to keep it or double it at successful ones. Note that if the initial mesh parameter is a power of 2, ($\Delta_0 = 2^k, k \in \mathbb{N}$), the positive spanning set $V$ is the minimal or the maximal positive basis described above, and the initial point is a vector of integers, using this common mesh update, all iterates will be a vector of integers until the mesh parameter size becomes inferior to 1. This possibility is rather interesting for our BAO problem at hands.

Typically, the stopping criteria of the pattern search methods is based either on the maximum number of function value evaluations allowed or in convergence criteria related with the mesh size. Provided the following assumption is made on the mesh: each column $i$ of $\mathcal{V}$ is given by $G\bar{z}_i$, where $G \in \mathcal{R}^{n\times n}$ is a nonsingular generating matrix and $\bar{z}_i$ is an integer vector in $\mathbb{Z}^n$, pattern search methods share the following convergence result [2]:

**Theorem 3.2** *Suppose that the level set* $L(x_0) = \{x \in \mathbb{R}^n : \; f(x) \le f(x_0)\}$ *is compact and that* $f$ *is continuously differentiable in an open set containing* $L(x_0)$. *Then*

$$\liminf_{k \longrightarrow +\infty} \|\nabla f(x_k)\| \; = \; 0,$$

*and there exists at least one limit point* $x_*$ *such that* $\nabla f(x_*) = 0$.

*Furthermore, if* $\lim_{k\longrightarrow+\infty} \Delta_k = 0$, $\|x_{k+1} - x_k\| \le C\Delta_k$ *for some constant* $C > 0$ *independent of the iteration counter* $k$, *and* $x_{k+1} = argmin_{x\in\mathcal{N}(x_k)} f(x)$ *in the poll step, then*

$$\lim_{k \longrightarrow +\infty} \|\nabla f(x_k)\| \; = \; 0,$$

*and every limit point* $x_*$ *satisfies* $\nabla f(x_*) = 0$.

The results of Theorem 3.2 concern the ability of pattern search methods to converge globally (i.e. from arbitrary points) to local minimizers candidates. We recall, despite the inexistence of any supporting theory, that due to their blindness caused by the nonuse of derivatives, and also by the flexibility of the search step to incorporate global search procedures while the poll step continues to assure convergence to local minima, numerical evidence about the capability of pattern search methods to compute global minimizers has been reported (see the papers [12, 2, 3, 44]).

To address the BAO problem, efficiency on the number of function value computation is of the utmost importance. Therefore, the number of trial points in the search step should be minimalist, and guided by some physic/biological meaning. On the other hand, when search step fail to obtain a decrease on the function value, polling should also be oriented in order to further reduce the number of function value evaluations (at least for successful iterations). Recently, the efficiency of direct search methods improved significantly by reordering the poll directions according to descent indicators built from simplex gradients [10]. Adding to that, the search step was provided with the use of minimum Frobenius norm quadratic models to be minimized within a trust region, which can lead to a significant improvement of direct search for smooth, piecewise smooth, and noisy problems [11]. For driving the resolution of the BAO problem, we will use the last version of SID-PSM [10, 11] which is a MATLAB implementation that incorporate the referred improvements for the search and the poll steps.

Although the mentioned capability of pattern search methods to compute global minimizers, the choice of good initial points is decisive for an effective global search with the goal of obtaining the best possible local minimum. Initial points whose vectors span the entire search space are desirable. In many cases that is impossible to achieve due to the dimension of the search space and random points is many times the best solution found. For the BAO problem, random points are also typically used, and a large number (e.g. 100 initial points in [8]) of initial iterates is considered. In order to span the entire search space, with an efficient number of initial points, and correspondingly efficiency on the number of function value evaluations, we suggest next a strategy for the choice of the initial points.

## 3.2 Choice of the initial points

This study focuses on obtaining high-quality coplanar beam directions for a head and neck clinical example. A typical head and neck treatment plan consists of radiation delivered from 5 to 9 equally spaced coplanar orientations around the patient. Here we will consider 7 coplanar orientations. Since equally spaced orientations are commonly used in clinical practice, the BAO solutions avoid resulting incidence beams too close, and some approaches include maximal geometric separation of treatment beams ([13]), 7 equally spaced coplanar orientations were considered as initial points. Our choice of the initial points, aim to span the entire search in the best possible way in order to perform a global search space. Considering the 7 equally spaced coplanar orientations starting in 0 degrees, other initial points can be obtained by rotation of all beam angles. The following rotation procedure can produce a small set of initial points that spans fairly well the search space.

Let us consider the 7 equally spaced coplanar angles $(0°, 51°, 103°, 154°, 206°, 257°, 309°)$

and the corresponding matrix of unit vectors in $\mathbb{R}^2$:

$$B = [v_1 \cdots v_7] = \begin{bmatrix} 0 & 0.7771 & 0.9744 & 0.4384 & -0.4384 & -0.9744 & -0.7771 \\ 1.0000 & 0.6293 & -0.2250 & -0.8988 & -0.8988 & -0.2250 & 0.6293 \end{bmatrix}.$$

The correspondence between an angle $\theta$ and the coordinates $(x, y)$ of a unit vector is given using the conversion between cartesian and polar coordinates:

$$\begin{cases} x = cos(\theta) \\ y = sin(\theta) \end{cases}.$$

For convenience and abuse of notation, initial points will be referred to as the set of beam angles or as the corresponding set of unit vectors, indistinctly.

Our goal is to generate a set of initial points to span (in amplitude) $\mathbb{R}^2$ in the best possible way. In order to do that we will "rotate" $v_1$ into $\pm e_i$, with $e_i$ being the $i$th column of the identity matrix of $\mathbb{R}^2$. In other words, we aim to "rotate" $v_1$ into (the positive and negative parts of) the coordinate axes. In order to "rotate" $v_1$ into $\pm e_i$, we need to find rotation matrices, $R_i^{\pm}$, such that $R_i^{\pm} v_1 = \pm e_i$, $i = 1, 2$. That rotation matrices can be obtained using the Householder transformation:

$$R_i^{\pm} = I - \pi^{-1} u u^{\top}, \quad u = v_1 \mp e_i, \quad \pi = \frac{1}{2}\|u\|^2.$$

Using these rotation matrices we can obtain 4 different starting points corresponding to the matrices of unit vectors obtained by multiplying $R_i^{\pm}$ by $B$ . Note that $R_2^{+} \times B = B$ since $v_1$ coincide with $e_2$.

In Figure 3(b) we depict the unit vectors of all 4 initial points and can verify that they are reasonably well distributed by amplitude in $\mathbb{R}^2$. The 7 unit vectors corresponding to the 7 equally spaced coplanar angles $(0°, 51°, 103°, 154°, 206°, 257°, 309°)$ are presented in Figure 3(a) and correspond to the black vectors in Figure 3(b). Green, blue and red vectors in Figure 3(b) correspond to the rotation of $v_1$ of $B$ into $e_1$, $-e_1$, $-e_2$, respectively. Most of the starting points in previous studies are random and in larger number. A rationalized number of well distributed initial points is desirable to diminish the overall computing time of the BAO problem.

The four initial points presented in Figure 3(b) could be obtained in a simpler way by adding the same value (the rotation angle value) to each angle value. In order to obtain an

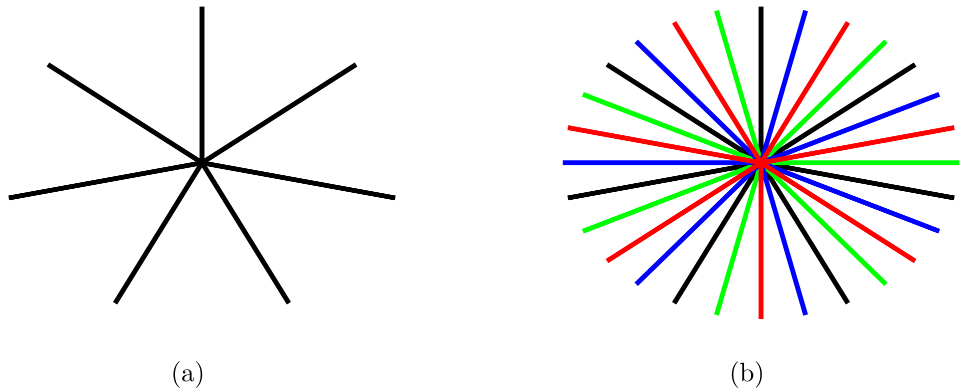



Figure 3: Seven equally spaced coplanar orientations – 3(a) and set of four initial points with seven equally spaced coplanar orientations – 3(b).

uniform distribution of all vectors as the previous procedure, one just need to divide the amplitude of the equally spaced angles by the number of initial points we want to consider. However, this simple procedure in $\mathbb{R}^2$ (coplanar angles) cannot be applied in $\mathbb{R}^3$ (non-coplanar angles). On the other hand, the previously described procedure of generating a set of initial points can be easily extended for $\mathbb{R}^3$, i.e., for non-coplanar beam orientations.

The reasons for the choice of initial points equally distant remain valid for non-coplanar BAO. Given $k$, the number of incidence directions desired, it is not trivial to determine $k$ unit equidistant vectors in $\mathbb{R}^3$. That problem is equivalent to the problem of place $k$ points on a sphere (in $\mathbb{R}^3$) so as to minimize the maximum distance of any point on the sphere from the closest one of the $k$ points. This maximum distance is called the covering radius. This is a well studied problem known as spherical covering problem and the general problem has not been solved yet. Hardin et al. [21] give tables of optimal solutions for this problem in 3, 4 and 5 dimensions with k = 4, ..., 130 points. The solution for $k = 7$ in $\mathbb{R}^3$, with the first vector rotated into $e_1$ correspond to the matrix of unit vectors in $\mathbb{R}^3$

$$B = [v_1 \cdots v_7] = \begin{bmatrix} 1.0000 & -0.8090 & -0.8090 & -0.0000 & 0.3090 & -0.0000 & 0.3090 \\ 0.0000 & -0.2102 & 0.2102 & -0.9339 & 0.3401 & 0.9339 & -0.3401 \\ 0.0000 & -0.5489 & 0.5489 & 0.3576 & 0.8882 & -0.3576 & -0.8882 \end{bmatrix}$$

or equivalently to the matrix of gantry angles ($\theta$) and couch angles ($\phi$)

$$\begin{bmatrix} \theta_1 & \cdots & \theta_7 \\ \phi_1 & \cdots & \phi_7 \end{bmatrix} = \begin{bmatrix} 0 & 277 & 83 & 315 & 24 & 45 & 336 \\ 0 & 343 & 17 & 10 & 31 & 350 & 329 \end{bmatrix}.$$

(a) (b)

Figure 4: Seven equally spaced non-coplanar orientations – 4(a) and set of six initial points with seven equally spaced non-coplanar orientations – 4(b).

This solution is illustrated in Figure 4(a).

The correspondence between angles $\theta$ (gantry angle) and $\phi$ (couch angle) and the coordinates $(x, y, z)$ of a unit vector in $\mathbb{R}^3$ is given using the conversion between spherical and cartesian coordinates:

$$\begin{cases} x = sin(\theta)cos(\phi) \\ y = sin(\theta)sin(\phi) \\ z = cos(\theta) \end{cases} .$$

Black, Green, blue, red, yellow and cyan vectors in Figure 4(b) correspond to the rotation of the first vector of the solution illustrated in Figure 4(a) into $e_1$, $e_2$, $e_3$, $-e_1$, $-e_2$, and $-e_3$, respectively. We can verify that the vectors of all 6 initial points are reasonably well distributed by amplitude in $\mathbb{R}^3$. Again, for non-coplanar BAO, most of the starting points in previous studies are random and in larger number. A rationalized number of well distributed initial points is desirable to diminish the overall computing time of the BAO problem.

This study focuses on obtaining high-quality coplanar beam vectors for a head and neck clinical case using a pattern search methods framework approach. The head and neck clinical example used for our tests is presented next.

# 4 Head & Neck clinical example

Since the head and neck region is a complex area where, e.g., the parotid glands or the spinal cord are usually in close proximity to or even overlapping with the target volume, careful selection of the radiation incidence directions can be determinant to obtain a satisfying treatment plan.

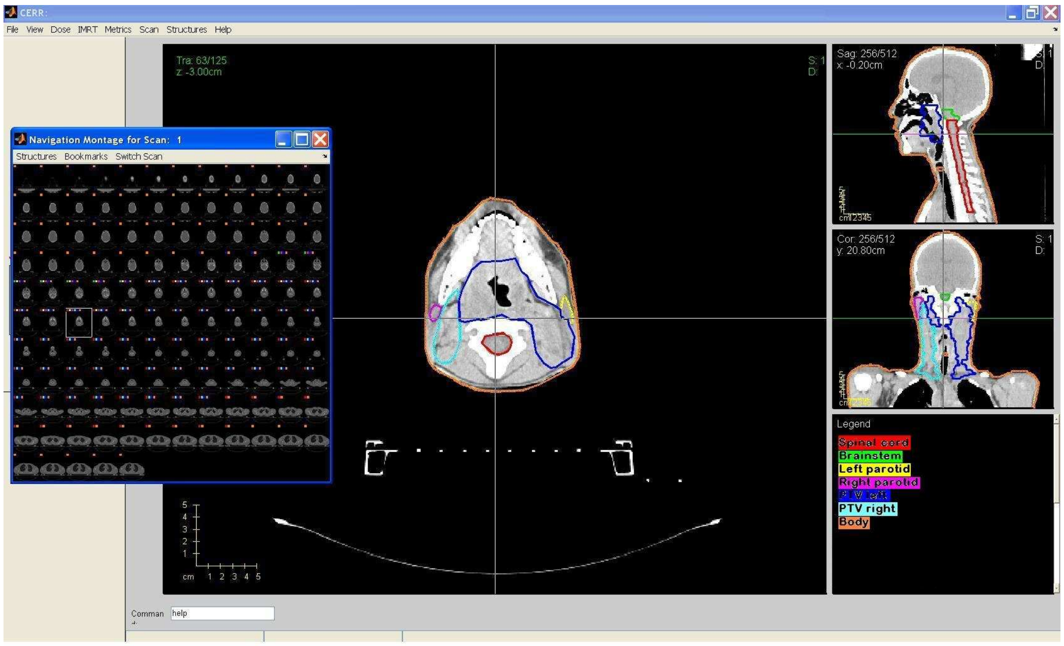



Figure 5: Structures considered in the IMRT optimization visualized in CERR.

The spinal cord and the brainstem are some of the most critical organs at risk (OARs) in the head and neck tumor cases. These are serial organs, i.e., organs such that if only one functional subpart is damaged, the whole organ functionality is compromised. Therefore, if the tolerance dose is exceeded, it may result in functional damage to the whole organ. Thus, it is extremely important not to exceed the tolerance dose prescribed for these type of organs. Other than the spinal cord and the brainstem, the parotid glands are also important OARs. The parotid gland is the largest of the three salivary glands. A common complication due to parotid glands irradiation is xerostomia (the medical term for dry mouth due to lack of saliva). This decreases the quality of life of patients undergoing radiation therapy of head and neck, causing difficulties to swallow. The parotid are parallel organs, i.e., the organ functionality depends on the amount of volume affected by

| Structure | Mean Dose | Max Dose | Prescribed Dose | Priority |
|---|---|---|---|---|
| **Spinal cord** | – | 45 Gy | – | 1 |
| **Brainstem** | – | 54 Gy | – | 1 |
| **Left parotid** | 26 Gy | – | – | 3 |
| **Right parotid** | 26 Gy | – | – | 3 |
| **PTV left** | – | – | 59.4 Gy | 2 |
| **PTV right** | – | – | 50.4 Gy | 2 |
| **Body** | – | 70 Gy | – | – |

Table 1: Prescribed doses for all the structures considered for IMRT optimization.

radiation. Their tolerance dose depends strongly on the fraction of the volume irradiated. Hence, if only a small fraction of the organ is irradiated the tolerance dose is much higher than if a larger fraction is irradiated. Thus, for these parallel structures, the organ mean dose is generally used instead of the maximum dose as an objective for inverse planning optimization.

In general, the head and neck region is a complex area to treat with radiotherapy due to the large number of sensitive organs in this region (e.g. eyes, mandible, larynx, oral cavity, etc.). For simplicity, in this study, the OARs used for treatment optimization were limited to the spinal cord, the brainstem and the parotid glands. The tumor to be treated plus some safety margins is called planning target volume (PTV). For the head and neck case in study it was separated in two parts: PTV left and PTV right (see Figure 5). The prescribed doses for all the structures considered in the optimization are presented in Table 1. In the last column of Table 1 we have the priority of the structures. For this case, the most important objectives to achieve are those for the serial critical organs, spinal cord and brainstem. Then follows the target volumes and last in the prioritization list are the parotid glands.

The parotid glands are in close proximity to or even overlapping with the PTV. Since the PTV has higher priority than parotid glands, this can be one of the reasons that helps explaining the difficulty of parotid sparing. Adequate beam directions can help on the overall optimization process and in particular in parotid sparing. Results of direct search methods applied to BAO for this head and neck case are presented in the next section.

# 5 Results

In order to facilitate convenient access, visualization and analysis of patient treatment planning data, as well as dosimetric data input for treatment plan optimization research, the computational tools developed within Matlab [29] and CERR [15] (computational environment for radiotherapy research) are used widely for IMRT treatment planning research. The ORART (operations research applications in radiation therapy) collaborative working group [16] developed a series of software routines that allow access to influence matrices. CERR enables easiest collaboration between optimization researchers already working in this challenging application field and radiation oncology specialists – physicians and physicists. CERR also furnishes the tools for many researchers to start working on IMRT optimization. There are other available softwares that incorporate dose calculation models (e.g. RAD (Radiotherapy optimAl Design software) [1] or PLanUNC [34]) and provide the necessary dosimetry data to perform optimization in IMRT. CERR was elected as the main software platform to embody our optimization research.

Our tests were performed on a 2.66Ghz Intel Core Duo PC with 3 GB RAM. We used CERR 3.2.2 version and Matlab 7.4.0 (R2007a). The dose was computed using CERR's pencil beam algorithm (QIB). An automatized procedure for dose computation for each given beam angle set was developed, instead of the traditional dose computation available from IMRTP module accessible from CERR's menubar. This automatization of the dose computation was essential for integration in our BAO algorithm. To address the linear problem of the FMO problem we used one of the most effective commercial tools to solve large scale linear programs (and MIP as well) – Cplex[7]. We used a barrier algorithm (*baropt* solver of Cplex 10.0) to tackle our linear problem. Solving the linear problem using Cplex, or using other computational tool, may easily lead to memory issues and sampling is required. Since CERR allows non-uniform sampling, the sample rate considered for all the structures was 4, while the sample rate considered for the largest but simultaneously the least important structure (Body) was 32. In Table 2 we present the volume, the original number of voxels and the number of voxels of each structure for each sample rate (S.R.) considered.

One of the main advantages of this pattern search methods framework is the flexibility provided by the search step, where any strategy can be applied as long as only a finite

| Structure | Volume $cm^3$ | nr. voxels | S.R. | nr. voxels (sample) |
|---|---|---|---|---|
| **Spinal cord** | 53.456 | 22464 | 4 | 1380 |
| **Brainstem** | 12.079 | 5076 | 4 | 322 |
| **Left parotid** | 10.818 | 4546 | 4 | 277 |
| **Right parotid** | 12.638 | 5311 | 4 | 347 |
| **PTV left** | 392.160 | 164798 | 4 | 10299 |
| **PTV right** | 146.355 | 61503 | 4 | 3844 |
| **Body** | 9060.310 | 3807431 | 32 | 3682 |

Table 2: Size of structures ($cm^3$) and number of voxels of each structure for the original size and for the corresponding sample rates (S.R.).

number of points is tested. This allows the insertion of previously used and tested strategies/heuristics that successfully address the BAO problem and enhance for a global search by influencing the quality of the local minimizer or stationary point found by the method. Adding to the search step flexibility and blindness of the method that prevent from getting stuck on the closest valley to the initial point, the choice of the initial point is also important for obtaining good local minima as a result of a global search attempt. The set of four initial points with seven equally spaced coplanar orientations presented in Figure 3(b) was used.

The last version of SID-PSM was used as our pattern search methods framework. We ran SID-PSM for the BAO problem considering each initial point at a time. The spanning set used was the positive spanning set ($[e \;\; -e \;\; I \;\; -I]$, with $I$ being the identity matrix and $e = [1 \;\; 1]^T$). Each of this directions correspond to, respectively, the rotation of all incidence directions clockwise, to the rotation of all incidence directions counter-clockwise, the rotation of each individual incidence direction clockwise, and the rotation of each individual incidence direction counter-clockwise. Other spanning sets were tested, namely the minimal and the maximal positive bases, but the results did not improve. The initial size of the mesh parameter was set to 2. Other powers of 2 were tested as initial size for mesh parameter, namely 4 and 8, leading to the exact same local minima, but at the cost of more functions evaluations. Since the initial points were integer vectors, all iterates will have integer values while the mesh parameter don't become inferior to 1. Therefore, the

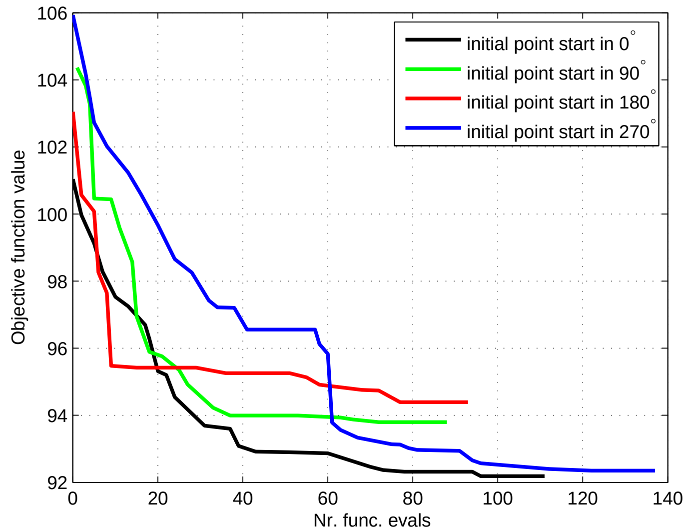
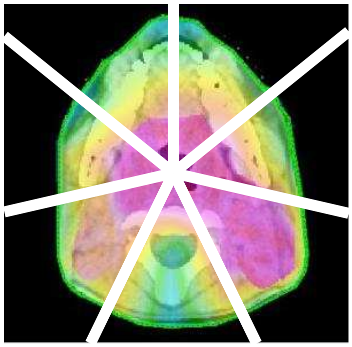


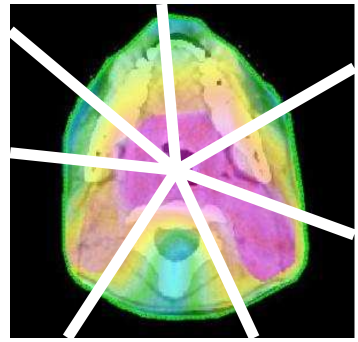

Figure 6: History of the BAO process for each initial point.

stopping criteria adopted was the mesh parameter become smaller than 1.

The results are presented in terms of number of function evaluations instead of overall computational time since for different dose engines, beamlet optimization methods or even other objective function strategies, the overall computational time may have a totally different magnitude. The time needed for each function evaluation was about 5 minutes. Each function evaluation (for every different set of seven coplanar beam angles) require a dose computation using QIB (where most of the 5 minutes was spent) and the beamlet optimization using Cplex to solve the corresponding linear problem. By stating the time cost of each function evaluation and the number of function evaluations we can have an idea of the total amount of time spent. Moreover, our objective is to emphasize the few number of function evaluations required by pattern search methods. In Figure 6, the objective function value decrease versus number of function evaluations required is presented. Note that objective function values correspond to the optimal values of the FMO problem for each set of beam angles. It is worth to highlight two things: the rapid initial decrease of the function value and the small number of function evaluations of the overall optimization process. If optimality is not the goal but rather obtaining a significant decrease of the function value, one may consider as stopping criteria the maximum number of function evaluations. By setting that number at 50, e.g., lot of time would be spared, at few cost of



(a)



(b)

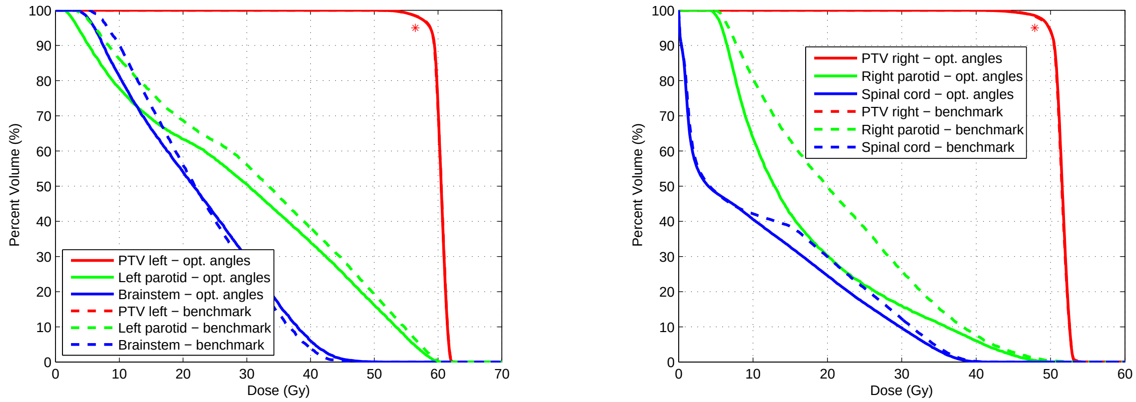
Figure 7: Benchmark angle set – 7(a) an optimal angle set – 7(b).

function decrease.

In order to verify if there is an effective improvement on the quality of the treatment plan for the set of the optimal beam angles found, one needs to compare this set of beam angles with a benchmark case. The benchmark case considered was the set of 7 equally spaced coplanar angles $(0°, 51°, 103°, 154°, 206°, 257°, 309°)$. This set of beam angles is typically used in clinical practice for head and neck cancer cases. Figure 7 present the benchmark angle set – Figure 7(a) and the set of optimal beam angles $(355°, 60°, 110°, 155°, 213°, 276°, 310°)$ – Figure 7(b). This optimal beam angle set was obtained using the benchmark set as initial point. In Figure 6 one can verify that the best optimal set is obtained using the benchmark case as initial point.

The quality of the results can be perceived considering a variety of metrics and can change from patient to patient. Typically, results are judged by their cumulative dose-volume histogram (DVH) and by analyzing isodose curves, i.e., the level curves for equal dose per slice. An ideal DVH for the tumor would present 100% volume for all dose values ranging from zero to the prescribed dose value and then drop immediately to zero, indicating that the whole target volume is treated exactly as prescribed. Ideally, the curves for the organs at risk would instead drop immediately to zero, meaning that no volume receives radiation.

Results for the benchmark angle set and for the optimal angle set of beam angles are presented in Figure 8. By a simple inspection of Figure 8 one can see that OARs sparing




(a) (b)

Figure 8: Cumulative dose volume histogram comparing the results obtained by using the benchmark angle set and the plan obtained by using the optimal beam angle set for PTV left – 8(a) and PTV right – 8(b).

in general and parotid sparing in particular is achieved when using the optimal angle set. Adding to that, a mean dose value decrease is obtained for parotid glands. By using the optimal angle set instead of the benchmark set, the mean dose for right parotid decrease from 21.586 Gy to 16.971 Gy and the mean dose for left parotid decrease from 32.015 Gy to 29.199 Gy.

Another metric usually used for plan evaluation is the volume of PTV that receives 95% of the prescribed dose ($D_{95}$). Typically, 95% of the PTV volume is required. $D_{95}$ is represented in Figures 8(a) and 8(b) with an asterisk. By observing Figure 8 we realize that both angle sets fulfill the goal of having 95% of the prescribed dose for 95% of the volume for both PTV right and PTV left.

One of the main difficulties when solving the BAO problem is the high number of local minima ([42, 8]). From 100 different starting beam angle sets, Craft's gradient searches ([8]) found 100 different local minima. Additionally to the 4 initial points considered, other initial points in the neighborhood of those points were considered. Initial points obtained from the 4 considered ones by changing one, several, or all directions up to 5°, lead to the same exact local minima the majority of times. This is another indication of the ability of pattern search methods to avoid being easily trapped in local minima and move lo lower regions.

# 6 Concluding Remarks

The beam selection problem is important since the choice of adequate directions is decisive for the quality of the treatment, both for maximizing tumor doses and for OARs sparing. Selecting beam directions is still done manually in most health care centers. Typically it requires many trial and error iterations between selecting beam angles and computing fluence patterns until a suitable treatment is achieved. This process is tedious, time consuming (usually taking several hours), has no guarantees of producing good treatments and relies solely on the experience of the treatment planner. The goal of beam selection optimization is to improve the quality of the directions used and, at the same time, release the treatment planner for other tasks.

The objective of this research report is to introduce a new approach for the resolution of the BAO problem, using direct search methods and formulating the BAO problem as a non-convex optimization problem instead of the traditional combinatorial optimization problem. The formulation of the BAO problem is a natural formulation since BAO problem is in fact a continuous optimization problem. The common choice on formulating the BAO problem as a combinatorial optimization problem was mainly caused by the absence of appropriate methods to address the non-convex nonlinear formulation, namely methods that require few functions evaluations, and that are suited to address noisy problems in the sense of the existence of many local minima.

Pattern search methods framework is a suitable approach for the resolution of the non-convex BAO problem due to their structure, organized around two phases at every iteration, one where convergence to a local minima is assured (poll), and other (search), where flexibility is conferred to the method since any strategy can be applied as long as only a finite number of points is tested. This allows the insertion of previously used and tested strategies/heuristics that successfully address the BAO problem and enhance for a global search by influencing the quality of the local minimizer or stationary point found by the method. Adding to the search step flexibility, and similarly to other derivative-free optimization methods, when minimizing non-convex functions with a large number of local minima, due to their myopia caused by the non-use of derivatives, pattern search methods have the ability to avoid being trapped by the closest local minima of the starting iterate, and find a local minima in a lowest region.

Although the mentioned capability of pattern search methods to compute global minimizers, the choice of good initial points may be decisive for an effective global search with the goal of obtaining the best possible local minimum. Initial points whose vectors span the entire search space are desirable. For the BAO problem, random initial points are also typically used, and a large number of initial iterates is considered. Since pattern search methods have the ability to escape to the closest valleys, a set of only few initial points whose vectors span well (in amplitude) the entire search space are an efficient choice.

A head and neck clinical example was used to test the ability of pattern search methods on obtaining high-quality coplanar beam directions. The results obtained were compared with the usual equidistant set of beam incidence directions. The optimal beam set obtained using SID-PSM lead to optimal plans where OARs sparing is better, namely parotid sparing is enhanced by the use of the optimal beam set. Adding to that, one have to highlight the ability to avoid the local optima closest to the initial point as well as the low number of function evaluations required to obtain optimal solutions. The efficiency on the number of function value computation is of the utmost importance, particularly when the BAO problem is modeled using optimal values of the FMO problem.

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