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Noncoplanar beam angle optimization in IMRT treatment planning using pattern search methods

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Abstract. Radiation therapy is used to treat localized cancers, aiming to deliver a dose of radiation to the tumor volume to sterilize all cancer cells while minimizing the collateral effects on the surrounding healthy organs and tissues. The planning of radiation therapy treatments requires decisions regarding the angles used for radiation incidence, the fluence intensities and, if multileaf collimators are used, the definition of the leaf sequencing. The beam angle optimization problem consists in finding the optimal number and incidence directions of the irradiation beams. The selection of appropriate radiation incidence directions is important for the quality of the treatment. However, the possibility of improving the quality of treatment plans by an optimized selection of the beam incidences is seldom done in the clinical practice. Adding the possibility for noncoplanar incidences is even more rarely used. Nevertheless, the advantage of noncoplanar beams is well known. The optimization of noncoplanar beam incidences may further allow the reduction of the number of beams needed to reach a clinically acceptable plan. In this paper we present the benefits of using pattern search methods for the optimization of the highly non-convex noncoplanar beam angle optimization problem.

1. Introduction

Cancer is one of the most significant health problems worldwide with respect to its incidence and mortality alike. One of the main treatment forms besides surgery and chemotherapy is radiation therapy. Approximately 60% of all patients diagnosed with cancer, which corresponds to nearly 7.6 million patients worldwide, benefit from radiation therapy, either to cure the disease or to palliate symptoms. With this therapy, several beams of ionizing radiation, sent at different incidence directions, pass through the patient. The intersection of these beams is centered at the tumor attempting to sterilize all cancer cells while the surrounding healthy organs and tissues receive radiation from some but not all radiation beams and may thus be spared. An important type of radiation therapy is intensity-modulated radiation therapy (IMRT), a modern technique where the radiation beam is modulated by a multileaf collimator allowing the irradiation of the patient using non-uniform radiation fields from selected angles. Multileaf collimators enable the transformation of the beam into a grid of smaller beamlets of independent intensities. A common way to solve the IMRT optimization problems is to use a beamlet-based approach leading to a large-scale programming problem. Due to the complexity of the whole optimization problem, computation of mathematical algorithms is mandatory to achieve valuable solutions.



Typically, radiation is generated by a linear accelerator mounted on a gantry that can rotate along a central axis and is delivered with the patient immobilized on a movable couch. The movement of the couch combined with the rotation of the gantry allows radiation from almost any angle around the tumor. Despite the fact that almost every angle is possible for radiation delivery, the use of coplanar angles, i.e., angles that lay in the plane of rotation of the gantry, is predominant. Furthermore, regardless of the evidence presented in the literature that selecting appropriate radiation beam incidence directions – beam angle optimization (BAO) problem – can lead to a plan’s quality improvement [4, 5, 37], in clinical practice, most of the time, beam directions continue to be either manually selected by the treatment planner in a time-consuming trial and error iterative process or patients are irradiated using evenly spaced coplanar beams. The difficulty of solving the BAO problem, a highly non-convex problem with many local minima on a large search space [14], is one possible justification for the manual selection or the use of coplanar incidence directions. However, evidence shows that noncoplanar incidence directions can lead to better treatment plans compared to plans obtained with coplanar incidence directions [5, 33, 38]. Moreover, the use of noncoplanar incidence directions is decisive for some types of cancers cases, e.g., brain tumors. More recently, some studies have been published where the advantages of noncoplanar incidences have also been shown for extra-cranial treatments like pancreatic cancer [11], prostate cancer [33], mediastinal lymphomas [13], or lung [36]. All of them report a significant increase of organs sparing without losing target coverage or homogeneity.

In this paper we present the benefits of using pattern search methods for the optimization of the highly non-convex noncoplanar BAO problem. A set of clinical cases of head-and-neck tumors treated at the Portuguese Institute of Oncology of Coimbra is used to discuss the potential of this approach in the optimization of the noncoplanar BAO problem. The paper is organized as follows. In the next Section we describe the noncoplanar BAO problem. Pattern search methods framework is presented in Section 3. Computational tests using clinical examples of head-and-neck cases are presented in Section 4. In the last Section we have the conclusions.

2. Noncoplanar beam angle optimization in IMRT treatment planning

The BAO problem is a quite difficult problem to solve since it is a highly non-convex optimization problem with many local minima. In most of the previous works on BAO, the entire range, $[0^\circ, 360^\circ]$ in the coplanar case, of gantry angles is 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 [7], genetic algorithms [19], particle swarm optimization [24] or other heuristics incorporating a priori knowledge of the problem [20]. Although those global heuristics can theoretically avoid local optima, globally optimal or even clinically better solutions cannot be obtained without a large number of objective function evaluations. The concept of beam’s-eye-view (BEV) has been a popular approach to address the BAO problem as well [28]. This approach uses topographic criteria to rank the candidate beam directions. Despite the computational time efficiency of these approaches, the quality of the solutions proposed cannot be guaranteed since the interplay between the selected beam directions is ignored. Other approaches include set cover [22], neighborhood search approaches [3], hybrid approaches [6] or gradient searches [14]. Aleman et al. [4] propose a response surface approach and include noncoplanar angles in beam orientation optimization. Lim and Cao [25] propose an approach that consists of two sequential phases: branch-and-prune and local neighborhood search. Schreibmann et al. [34] propose a hybrid multiobjective evolutionary optimization algorithm for IMRT treatment planning and apply it to the optimization of the number of incident beams, their orientations and intensity profiles. Ehr Gott et al. [21] discuss a mathematical framework that unifies the approaches found in literature.

Many of the previous BAO studies are based on a variety of scoring methods or

approximations of the fluence map optimization (FMO) problem to gauge the quality of the beam angle set leading to beam angle sets with no guarantee of optimality and questionable reliability since it has been extensively reported that optimal beam angles for IMRT are often non-intuitive [35]. The optimal solution of the FMO problem has been used to drive the coplanar BAO problem [3, 14, 26, 34] including in our works [19, 29, 30, 31]. Many mathematical optimization models and algorithms have been proposed for the FMO problem, including linear models [32], mixed integer linear models [23], nonlinear models [12], and multicriteria models [8]. Our approach for modeling the noncoplanar BAO problem uses the optimal solution value of the FMO problem as the measure of the quality for a given beam angle set. Thus, we will present the formulation of the noncoplanar BAO problem followed by the formulation of the FMO problem we used. We will assume that the number of beam angles is defined a priori by the treatment planner.

2.1. Noncoplanar BAO Model

Let us consider n to be the fixed number of (noncoplanar) beam directions. Let θ denote the gantry angle and ϕ denote the couch angle. Note that, the usual coplanar angles are obtained for a fixed couch position at $\phi = 0$. In our formulation, instead of a discretized sample, all continuous gantry angles and couch angles will be considered. Since the angle -1° is equivalent to the angle 359° and the angle 361° is the same as the angle 1° , we can avoid a bounded formulation. For the coplanar optimization, there are no limitations on the choice of candidate directions in the optimization problem. However, for noncoplanar setups, collisions between the patient/couch and the gantry may occur for some candidate directions. In order to keep an unbounded formulation, that information will be embedded in the objective function. A simple formulation for the BAO problem is obtained by selecting an objective function such that the best set of beam angles is obtained for the function's minimum:

$$\begin{aligned} \min \quad & f\left((\theta_1, \phi_1), \dots, (\theta_n, \phi_n)\right) \\ \text{s.t.} \quad & \left((\theta_1, \phi_1), \dots, (\theta_n, \phi_n)\right) \in \mathbb{R}^n \times \mathbb{R}^n. \end{aligned} \tag{1}$$

In this work, the objective function $f\left((\theta_1, \phi_1), \dots, (\theta_n, \phi_n)\right)$ that measures the quality of the set of beam directions $(\theta_1, \phi_1), \dots, (\theta_n, \phi_n)$ corresponds to the optimal value of the FMO problem for each fixed set of beam directions and incorporates the collisions that may occur between the patient/couch and the gantry for some candidate directions:

$$f\left((\theta_1, \phi_1), \dots, (\theta_n, \phi_n)\right) = \begin{cases} +\infty & \text{if collisions occur} \\ \text{optimal value of the FMO} & \text{otherwise.} \end{cases}$$

The used formulation and resolution of the FMO problem are presented next.

2.2. FMO formulation and resolution

Treatment plan optimization is inherently a multicriteria process. However, typically, the FMO problem is modeled as a weighted sum function where constraints are often implemented as objectives. This formulation of the FMO problem makes it harder to capture an accurate trade-off between objectives without violating constraints and may lead to inferior treatment plans. Multicriteria approaches for the FMO problem have been proposed in recent works [15, 27]. The advantage of these approaches is the possibility of selecting, *a posteriori*, a desired solution from a set of Pareto-optimal treatment plans. This option is not suitable to include in a fully automated BAO process. Recently, a multicriteria optimization approach has been developed, where a set of *a priori* defined criteria have to be met (objectives and constraints)

Table 1. Wish-list for head and neck cases.

	Structure	Type	Limit			
Constraints	PTV1	Maximum	74.9 Gy (=107% of prescribed dose PTV1)			
	PTV2	Maximum	63.6 Gy (=107% of prescribed dose PTV2)			
	PTV1 shell	Maximum	59.5 Gy (=85% of prescribed dose PTV1)			
	PTV2 shell	Maximum	50.5 Gy (=85% of prescribed dose PTV2)			
	Spinal cord	Maximum	45.0 Gy			
	Brainstem	Maximum	54.0 Gy			
	Body	Maximum	70.0 Gy			
	Structure	Type	Priority	Goal	Sufficient	Parameters
Objectives	PTV1	Minimize LTCP	1	1	0.5	$T_i = 70$ Gy; $\alpha = 0.75$
	PTV2	Minimize LTCP	2	1	0.5	$T_i = 59.4$ Gy; $\alpha = 0.75$
	Parotid (R)	Minimize mean	3	26 Gy	–	–
	Parotid (L)	Minimize mean	4	26 Gy	–	–
	Body	Minimize mean	5	–	–	–

[8, 9, 10]. This approach is suited for an automated BAO process. In this work, a multicriterial optimization based on a prescription called wish-list [8, 9, 10] is our choice to address the FMO problem. The wish-list contains hard constraints and prioritized objectives. Constraints have to be strictly met while objectives are optimized taking into account priorities defined in the wish-list. The higher an objective priority is, the higher the probability that the corresponding objective will be met. The wish-list used for the clinical examples of retrospective treated cases of head and neck tumors at the Portuguese Institute of Oncology of Coimbra is given in Table 1. 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 organs at risk (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 cases in study, two PTVs (PTV1 and PTV2) were defined, to be treated with a simultaneous integrated boost technique. The wish-list contains seven constraints and five objectives based on the prescribed doses for all the structures considered in the optimization. All constraints are maximum-dose constraints. To support the dose optimization in the tumor volumes, PTV1 shell and PTV2 shell are surfaces constructed by computerized volume expansions (ring with no width) positioned at 10 mm distance from PTV1 and PTV2, respectively. The imposed maximum-dose constraints avoid high doses far from the PTVs. Objectives with priorities 1 and 2 aim at dose coverage of PTV1 and PTV2, respectively. Priorities 3–5 aim at sparing the parotids and unspecified tissue (Body).

For the target dose optimization, Breedveld et. al [8, 9, 10] choose the logarithmic tumor control probability (LTCP) [1],

$$LTCP = \frac{1}{N_T} \sum_{i=1}^{N_T} e^{-\alpha(D_i - T_i)},$$

where N_T is the number of voxels in the target structure, D_i is the dose in voxel i , T_i is the prescribed dose, and α is the cell sensitivity parameter. For doses D_i lower than T_i , the LTCP has an exponential penalty while for doses higher than the prescribed dose, the value slowly approaches 0. LTCP equals 1 for a homogeneous dose equal to T_i . A higher α results in less voxels with a low dose, and thus a higher percentage of the PTV receiving 95% of the prescribed dose (PTV coverage).

The algorithm used for multicriterial optimization of beam intensity profiles using the wish-list is the *2pec* [9]. The algorithm is organized in two phases. In the first phase, following the prioritization of the wish-list, the objectives are minimized within constraints. After each objective minimization, a constraint based on the minimized objective results is added to be used in the minimization of the next priority objectives. This action guarantees that higher order priority objective results are not deteriorated by lower priority objective optimization. In the end of the first phase, the plan obtained fulfills all the constraints of the wish-list and each objective has an attained value that is equal to its goal (even if better results could have been achieved), or higher than its goal if the constraints (including higher priority objective constraints) did not allow better results. In the second phase, following the prioritization, all objectives apart from LTCP objectives are sequentially fully minimized. The minimization for the LTCP objectives stops at the defined sufficient value to leave space for lower prioritized objectives improvement, and not to escalate the dose. For a detailed description of the algorithm see Breedveld et al.[9].

The FMO model is used as a black-box function and the conclusions drawn regarding BAO coupled with this formulation/resolution are valid also if different FMO formulations/resolutions are considered.

3. Pattern Search Methods

Pattern search methods are derivative-free optimization methods that require few function value evaluations to converge and have the ability to avoid local entrapment. These two characteristics gathered together make pattern search methods suited to address the BAO problem.

Pattern search methods use the concept of positive bases (or positive spanning sets) to move towards a direction that would produce a function decrease. A positive basis for \mathbb{R}^n can be defined as a set of nonzero vectors of \mathbb{R}^n whose positive combinations span \mathbb{R}^n (positive spanning set), but no proper set does. A positive spanning set contains at least one positive basis. It can be shown that a positive basis for \mathbb{R}^n contains at least $n + 1$ vectors and cannot contain more than $2n$ [18]. Positive bases with $n + 1$ and $2n$ elements are referred to as minimal and maximal positive basis, respectively. Commonly used minimal and maximal positive bases are $[I - e]$, with I being the identity matrix of dimension n and $e = [1 \dots 1]^\top$, and $[I - I]$, respectively. The motivation for directional direct search methods such as pattern search methods is given by one of the main features of positive basis (or positive spanning sets) [18]: there is always a vector \mathbf{v}^i in a positive basis (or positive spanning set) that is a descent direction unless the current iterate is at a stationary point, i.e., there is an $\alpha > 0$ such that $f(x^k + \alpha \mathbf{v}^i) < f(x^k)$. This is the core of directional direct search methods and in particular of pattern search methods. The notions and motivations for the use of positive bases, its properties and examples can be found in [2, 18].

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} , aiming to provide a decrease of the objective function, is chosen from a finite number of candidates on a given mesh M_k defined as

$$M_k = \{x^k + \alpha_k \mathbf{V} \mathbf{z} : \mathbf{z} \in \mathbb{Z}_+^p\},$$

where α_k is the mesh-size (or step-size) parameter, \mathbb{Z}_+ is the set of nonnegative integers and \mathbf{V} denote the $n \times p$ matrix whose columns correspond to the p ($\geq n + 1$) vectors forming a positive spanning set.

Pattern search methods are organized around two steps at every iteration. The first step consists of a finite search on the mesh, free of rules, 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. 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.

If the search step fails to produce a decrease in the objective function, a second step, called the poll step, is performed around the current iterate. The poll step follows stricter rules and, using the concepts of positive bases, attempts to perform a local search in a mesh neighborhood around \mathbf{x}^k , $\mathcal{N}(\mathbf{x}^k) = \{\mathbf{x}^k + \alpha_k \mathbf{v} : \text{for all } \mathbf{v} \in P_k\} \subset M_k$, where P_k is a positive basis chosen from the finite positive spanning set \mathbf{V} . For a sufficiently small mesh-size parameter α_k , the poll step is guaranteed to provide a function reduction, unless the current iterate is at a stationary point [2]. So, if the poll step also fails to produce a function reduction, the mesh-size parameter α_k must be decreased. On the other hand, if both the search and poll steps fail to obtain an improved value for the objective function, the mesh-size parameter is increased or held constant. The most common choice for the mesh-size parameter update is to halve the mesh-size parameter at unsuccessful iterations and to keep it or double it at successful ones.

4. Computational results

The pattern search methods framework was tested for the optimization of the noncoplanar BAO problem using a set of two clinical examples of retrospective treated cases of head-and-neck tumors at the Portuguese Institute of Oncology of Coimbra (IPOC). Treatment plans with five to nine equispaced coplanar beams are used at IPOC and are commonly used in practice to treat head-and-neck cases [3]. We considered plans with five beams because the importance of BAO increases when a lower number of beam directions is considered. Therefore, treatment plans of five coplanar and noncoplanar orientations were obtained using pattern search methods and denoted *coplanar* and *noncoplanar*, respectively. These plans were compared with the typical 5-beam equispaced coplanar treatment plans denoted *equi*. The objective of these comparisons is twofold. First, to demonstrate that pattern search methods are suited to address the highly non-convex BAO problem producing good results both in 2D (coplanar) and 3D (noncoplanar) search spaces. Second, to show that using this approach, higher quality treatment plans using a noncoplanar beam angle set can be obtained.

We choose to implement the pattern search methods algorithm taking advantage of the availability of an existing pattern search methods framework implementation used successfully by us to tackle the BAO problem [29, 30, 31] – the last version of SID-PSM [16, 17]. The spanning set used was the positive spanning set $([e \ -e \ I \ -I])$. Each of these directions corresponds to, respectively, the rotation of all incidence directions clockwise, 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. Since we want to improve the quality of the typical equispaced treatment plans, the starting point considered is the equispaced coplanar 5-beam angle set. 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. In the last version of SID-PSM, 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 [16]. However, these models cannot be computed until a minimum number of points is evaluated. Moreover, the points already tested should span the search space as best as possible to increase the radius of the search. Therefore, both for the coplanar and noncoplanar cases, in the first iterations, the trial points computed in the search step correspond to the points presented in the previous section, that span the 2D and the 3D search spaces, respectively.

Our tests were performed on a Dell Precision T5600 with 8-core Intel Xeon processor E5-2687W, 64GB 1600MHz DDR3 ECC RDIMM. For importing DICOM images, compute and

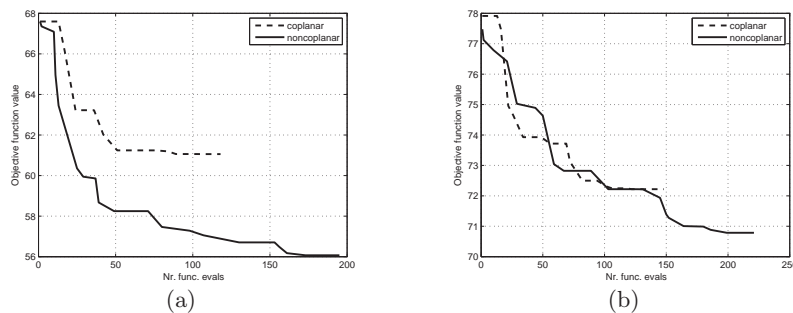


Figure 1. History of the 5-beam angle optimization process for coplanar and noncoplanar angles, considering the equispaced configuration (*equi*) as starting point, for cases 1 and 2, 1(a) to 1(b) respectively.

Table 2. Target coverage, conformity and homogeneity obtained by treatment plans.

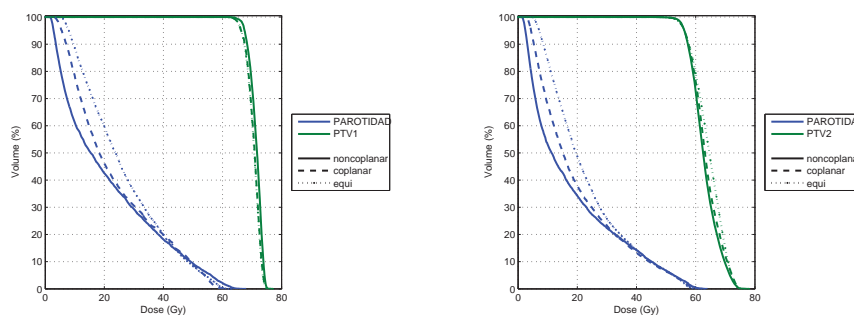
Case	Target parameters	<i>noncoplanar</i>	<i>coplanar</i>	<i>equi</i>
1	PTV1 Coverage	0.983	0.944	0.943
	PTV1 Conformity	0.140	0.114	0.087
	PTV1 Homogeneity	0.909	0.899	0.901
	PTV2 Coverage	0.940	0.940	0.940
	PTV2 Conformity	0.733	0.710	0.726
	PTV2 Homogeneity	0.793	0.779	0.779
2	PTV1 Coverage	0.994	0.984	0.985
	PTV1 Conformity	0.176	0.202	0.158
	PTV1 Homogeneity	0.921	0.913	0.919
	PTV2 Coverage	0.957	0.952	0.942
	PTV2 Conformity	0.570	0.582	0.598
	PTV2 Homogeneity	0.801	0.795	0.776

visualize dose, and optimize dose distributions, we used YARTOS, an in-house optimization suite developed at Erasmus MC Cancer Institute in Rotterdam. YARTOS is written in MATLAB and contains an optimizer based on a primal-dual interior-point algorithm, capable of solving general nonlinear non-convex optimization problems, and tailored for IMRT treatment planning making full use of multi-threaded computing. The optimal value of the FMO problem used to drive our BAO algorithm was obtained using the YARTOS optimizer.

The history of the 5-beam angle optimization process, presented in terms of the number of function evaluations, is shown in Figure 1 for the two clinical cases of head-and-neck tumors. Both *coplanar* and *noncoplanar* plans obtained considerable improvements in terms of FMO optimal value, with respect to the initial point (typical clinically used equispaced configuration *equi*), with the later obtaining better results at the cost of few more function value evaluations. Despite the improvement in the FMO value, the quality of the results can be perceived considering a variety of metrics. A metric usually used for plan evaluation is the volume of PTV that receives 95% of the prescribed dose (coverage). Typically, 95% of the PTV volume is required. The conformity and homogeneity are other metrics typically screened. These metrics are output values of the YARTOS optimizer and are reported in Table 2. We can

Table 3. OARs sparing obtained by treatment plans.

Case	OAR	Mean Dose (Gy)			Max Dose (Gy)		
		<i>noncoplanar</i>	<i>coplanar</i>	<i>equi</i>	<i>noncoplanar</i>	<i>coplanar</i>	<i>equi</i>
1	Spinal cord	–	–	–	48.311	48.429	49.715
	Brainstem	–	–	–	51.760	54.484	54.694
	Left parotid	17.980	20.082	23.142	–	–	–
	Right parotid	21.253	23.510	26.396	–	–	–
2	Spinal cord	–	–	–	45.233	45.174	45.100
	Brainstem	–	–	–	54.179	54.240	54.629
	Left parotid	25.126	25.367	28.303	–	–	–
	Right parotid	34.844	35.950	38.069	–	–	–

**Figure 2.** Cumulative dose volume histogram comparing the results obtained by *noncoplanar*, *coplanar* and *equi* for the first case.

verify that *noncoplanar* treatment plans consistently obtained slightly better target coverage, conformity and homogeneity numbers compared to *coplanar* treatment plans. Both optimized plans outperform the *equi* treatment plans. Mean and/or maximum doses of OARs are usually displayed to verify organ sparing. Organ sparing results are shown in Table 3. The maximum dose values for the spinal cord and the brainstem are similar for the different treatment plans, with a slightest advantage for the *noncoplanar* treatment plans. However, as expected, the main differences reside in parotid sparing. The optimized treatment plans enhance better parotid sparing compared to the *equi* treatment plans. The *noncoplanar* treatment plans manage to obtain an average reduction of the parotid's mean dose irradiation in 4.2 Gy compared to the *equi* treatment plans while the *coplanar* treatment plans only obtained a 2.7 Gy average decrease.

Typically, results are judged also by their cumulative dose-volume histogram (DVH). For illustration, DVH results for the first patient are displayed. For clarity, only parotids and tumor volumes are displayed and the DVHs were split as an attempt to better visualize the results. The results displayed in Figure 2 confirm the benefits of using the optimized beam directions obtained and in particular noncoplanar treatment plans.

5. Discussion and conclusions

The BAO problem is a continuous global highly non-convex optimization problem known to be extremely challenging and yet to be solved satisfactorily. An approach for the resolution of the noncoplanar BAO problem, using a pattern search methods framework, was proposed and tested using two clinical head-and-neck cases. 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. The poll step, where convergence to a local minima is assured, and the search step, where flexibility is conferred to the method since any strategy can be applied. The use of minimum Frobenius norm quadratic models to be minimized within a trust region are used in the search step and can lead to a significant improvement of direct search for the type of problems at hand, particularly if a prior proper exploration of the search space is guaranteed. 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, 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 lowest regions.

For the clinical cases retrospectively tested, the use of noncoplanar directions in our approach showed a positive influence on the quality of the minimizer found. The improvement of the local solutions in terms of objective function value corresponded, for the head-and-neck cases tested, to high quality treatment plans with better target coverage and with improved organ sparing, in particular better parotid sparing. Moreover, we have to highlight the low number of function evaluations required to obtain locally optimal solutions, even using noncoplanar directions and consequently exploring a much larger search space, which is a major advantage compared to other global heuristics where the continuous solution space is confined to a discrete subset, often only considering coplanar irradiation angles to achieve clinically acceptable computation times. The efficiency on the number of function value computations is of the utmost importance, particularly when the BAO problem is modeled using the optimal values of the FMO problem.

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