INTERNATIONAL TRANSACTIONS IN OPERATIONAL RESEARCH

WILEY

INTERNATIONAL TRANSACTIONS IN OPERATIONAL RESEARCH

Intl. Trans. in Op. Res. 0 (2021) 1–15
DOI: 10.1111/itor.13068

An automated bi-level optimization approach for IMRT

P. Carrasqueira[a], M. J. Alves[a,b], J. M. Dias[a,b], H. Rocha[a,b,*], T. Ventura[a,c], B. C. Ferreira[a,d] and M. C. Lopes[a,c]

[a] *University of Coimbra, INESCC, Rua Silvio Lima, Coimbra 3030-290, Portugal*
[b] *University of Coimbra, FEUC, CeBER, Av. Dias da Silva 165, Coimbra 3004-512, Portugal*
[c] *IPOC-FG, EPE, Av. Bissaya Barreto 98, Coimbra 3000-075, Portugal*
[d] *Faculty of Sciences, IBEB, University of Lisbon, Campo Grande, Lisboa 1749-016, Portugal*
E-mail: pedro.carrasqueira@deec.uc.pt [Carrasqueira]; mjalves@fe.uc.pt [Alves]; joana@fe.uc.pt [Dias]; hrocha@fe.uc.pt [Rocha]; tiagoventura@ipocoimbra.min-saude.pt [Ventura]; bcferreira@fc.ul.pt [Ferreira]; mclopes@ipocoimbra.min-saude.pt [Lopes]

Received 11 May 2021; received in revised form 28 July 2021; accepted 28 September 2021

Abstract

Intensity-modulated radiation therapy is used worldwide to treat cancer patients. The objective of this treatment is to deliver a prescribed radiation dose to the tumor while sparing, as much as possible, all the healthy tissues, especially organs at risk (OAR). This means that the planning of a radiotherapy treatment should take into consideration conflicting objectives: to be able to spare as much as possible the OAR guaranteeing, at the same time, that the desired radiation is delivered to the volumes to treat. While the volumes to treat can be adequately irradiated from almost any set of directions, the radiation directions that are chosen have a determinant impact on the OAR. This means that those directions that provide an improved OAR sparing should be selected. The choice of radiation directions (beam angles) can thus be interpreted as being fundamentally determined by the OAR, with the radiation intensities associated with each of these directions being determined by the needed radiation to be delivered to the volumes to treat. In this work, we interpret the radiotherapy treatment planning problem as a bi-level optimization problem. At the upper level, OAR control the choice of the beam angles, which are selected aiming at OAR sparing. At the lower level, the optimal radiation intensities are decided by the volumes to treat, considering the beam angle ensemble obtained at the upper level. The proposed bi-level approach was tested using 10 clinical head-and-neck cancer cases already treated at the Portuguese Institute of Oncology in Coimbra.

Keywords: bi-level optimization; derivative-free optimization; noncoplanar IMRT; automated treatment planning

1. Introduction

Radiation therapy is widely used to treat cancer patients with localized tumors. Radiation is delivered to the patient by a linear accelerator (linac) mounted on a gantry, which rotates around a

*Corresponding author.

central axis parallel to the couch where the patient lies. The couch may also rotate, increasing the degrees of freedom of the possible directions from which the tumor can be irradiated, which enables better quality treatment plans to be achieved. A treatment plan is coplanar if the couch is fixed in a 0° angle during the whole treatment, being noncoplanar otherwise.

In intensity-modulated radiation therapy (IMRT), the head of the linear accelerator has a multileaf collimator that discretizes a beam into a set of beamlets. The multileaf collimator has a set of right and left moving leaves that can block the radiation during determined periods of time. These movements create beamlets with different intensities that allow the shaping of nonuniform radiation intensity maps. This intensity modulation allows to improve the treatment precision, conforming the radiation to the volumes to treat, while sparing surrounding healthy tissues and organs at risk (OAR) as much as possible. IMRT planning has two main goals: to assure that the prescribed dose is provided uniformly to the planning target volume (PTV) while simultaneously minimizing the radiation that reaches the OAR. These objectives are conflicting because radiation needs to go through healthy tissues to reach the PTV. Furthermore, while the PTV may be effectively irradiated from almost any direction, properly sparing the OAR can only be achieved if beam irradiation directions are adequately chosen. This means that beam angle optimization (BAO) is typically required to obtain a beam angle arrangement that leads to treatment plans with enhanced OAR sparing. For a given beam ensemble, the radiation to be delivered from each beam is then optimized (the fluence map optimization—FMO) aiming to fulfill the prescribed and the tolerance doses.

A treatment plan is often selected by the medical physicist after some trial and error experiences. First, the medical physicist, based on her/his own experience, manually selects a beam ensemble. Then, the FMO takes place, considering these angles fixed. The resulting solution is then analyzed by the medical physicist who may change some of the beam angles, or other input parameters considered in the FMO, aiming at increasing the quality of the treatment plan. The FMO problem is solved again, and this laborious and time-consuming process is repeated until a satisfactory treatment plan is obtained. It is not possible to assure that the treatment plans obtained by this process are the best possible ones for each patient (Pugachev et al., 2001; Cabrera et al., 2018). Automated treatment planning is nowadays considered essential to guarantee that treatment plans with improved quality are consistently obtained with less intervention of the planner. Within an automated framework, different formulations have been proposed for the BAO and the FMO problems that are typically solved in a sequential manner. In this study, we propose an automated bi-level optimization approach for IMRT treatment planning, where BAO and FMO problems are, respectively, the upper and lower level problems. Therefore, the beam search is guided by the quality of the solutions from the OAR's point of view. The PTV will guide the definition of the fluence map.

Bi-level optimization models (Bard, 1998; Dempe, 2002) enable to formulate optimization problems with a hierarchical structure between two decision levels. The *leader* (at the upper level) and the *follower* (at the lower level) control different sets of variables and pursue different objectives in a non-cooperative manner. The leader makes her/his decisions first. The follower reacts by choosing an optimal solution according to her/his objective function on the feasible region restricted by the leader. Thus, the lower level optimization problem is embedded in the upper level feasible region. Although the decisions are made sequentially, the leader must incorporate the follower's response into his optimization process because it affects the value of the upper level objective function. This is a suitable formulation for representing conflicting and hierarchically related optimization problems. However, bi-level optimization problems are very difficult to solve, and even the linear bi-level problem is NP-hard (Jeroslow, 1985; Dempe, 2002). Only optimal solutions for the lower level problem are feasible to the bi-level problem. The optimal solution of the bi-level problem is the one that optimizes the upper level objective function among the solutions that satisfy all the upper level constraints and are optimal for the lower level problem.

As far as we know, only one attempt has been made to apply bi-level programming to radiotherapy treatment planning. Recently, Sayed et al. (2020) proposed a bi-level formulation to address the BAO problem in intensity-modulated proton therapy (IMPT). The upper level decision variables are the couch and gantry angles, which are discretized in 5° spacing angles to reduce the computational effort. An IMPT multiobjective problem is considered at the lower level. A differential evolution algorithm is applied to solve each of the upper and lower level problems. The FMO problem is run several times for each beam configuration considering different weights for the objective functions, aiming at producing a set of Pareto-optimal solutions. This approach is different from the one presented in this paper. Not only the algorithmic choices are different, but the way in which the problem is modeled is also distinct (we make a clear distinction between dose-based target and OAR objectives).

In the bi-level optimization approach for IMRT treatment planning optimization we propose in this work, the OAR control the beam angles, and the PTV controls the radiation delivered. This option is justified by the fact that the beam choice is mostly determined by the OAR. In addition, the fulfillment of the prescribed and the tolerance doses and their optimization for the PTV is assured at the lower level for each beam angle ensemble. Therefore, the final solution will be the one that spares OAR as much as possible without jeopardizing the PTV coverage.

The proposed bi-level optimization approach was tested using 10 anonymized clinical head-and-neck cancer cases already treated at IPO Coimbra. The resulting treatment plans were compared with treatment plans considering equispaced beams, the option that is often used in the clinical setting, since BAO is seldom performed. The paper is organized as follows. In the next section, the clinical cases used to test the proposed bi-level approach are described. In Section 3, the bi-level optimization approach is detailed. The computational experiment and the results obtained are discussed in Section 4. The last section presents the conclusions.

2. Head-and-neck clinical cases

In this work, a pool of 10 anonymized head-and-neck cancer cases already treated at IPO Coimbra were used to assess the interest of the bi-level approach proposed. The treatment for these selected cases is particularly difficult to plan due to the proximity of very important organs and the tumor area. The OAR considered in this study are the spinal cord, brainstem, oral cavity, left and right parotids, and the remaining normal tissue, named as Body. The OAR can be classified as being serial organs (if their functionality becomes compromised even if a small part of the organ is damaged) or parallel organs (when the functionality is kept provided that only a small part of the organ has been damaged). In head-and-neck cancer cases, two of the most important OAR are the spinal cord and brainstem, which are serial organs. The other OAR are parallel. For the serial OAR, a maximum dose has to be respected, whereas a mean dose is considered for the parallel OAR. The PTV is

Table 1
Prescribed/tolerance doses

		Tolerance dose	
Structure	Prescribed dose	Mean	Max
PTV_{70}	70.0 Gy	–	–
$PTV_{59.4}$	59.4 Gy	–	–
Left parotid	–	26 Gy	–
Right parotid	–	26 Gy	–
Oral cavity	–	45 Gy	–
Spinal cord	–	–	45 Gy
Brainstem	–	–	54 Gy
Body	–	–	80 Gy

composed of two regions where different radiation levels should be delivered, the tumor (PTV_{70}) and the lymph nodes ($PTV_{59.4}$), with the subscripts referring to the dose to be delivered. The patient structures are discretized into voxels (small volume elements) and the dose is computed for each voxel being measured in Gray (Gy). The treatments were planned considering the prescribed and tolerance doses presented in Table 1.

3. Bi-level optimization for IMRT

IMRT treatment planning optimization requires the computation of optimal fluence maps for each of the beam angle directions that need to be optimally selected as well. A bi-level optimization approach is proposed to address simultaneously the noncoplanar BAO problem and the FMO problem.

3.1. Beam angle optimization approaches

Different formulation and optimization methods have been proposed to address the BAO problem. Some approaches are based on geometry data of the patient while others use the optimal value of the FMO problem to guide the BAO search. Llacer et al. (2009) and Bangert and Oelfke (2010) propose geometry-based approaches where the proportion of the OAR that overlaps the tumor seen from each beam will determine the optimal beam ensemble. In these approaches, the beam ensemble is selected before the FMO problem is tackled. Freitas et al. (2019) propose a mixed-integer nonlinear optimization model addressing both dose intensity and beam selection. In Cabrera et al. (2018), an algorithm is proposed to solve the BAO problem in two phases. In the first phase, a set of beam ensembles is considered and, for each one, a local search is performed to find a predefined number of BAO local optimal solutions. The solutions obtained in the first phase are analyzed in a multiobjective perspective in the second phase, considering tumor irradiation and OAR sparing objectives. Fiege et al. (2011) join the BAO and FMO problems into a single multiobjective optimization problem, which is solved by a multiobjective genetic algorithm embedded in a toolbox, where PTV irradiation and OAR sparing objectives are considered. Schreibmann et al. (2004) propose an interactive method that uses the genetic algorithm NSGA-II to solve the BAO problem, considering the minimization of the square deviation of the prescribed dose for the PTV, the square overdose (calculated only for the cases where dose value exceeds the tolerance dose) for OAR and normal tissue, as well as the number of beams of the beam ensemble, while a deterministic solver is used to solve the FMO problem. Nazareth et al. (2015) use a genetic algorithm to obtain a five-beam IMRT treatment plan to treat a prostate patient. In Li et al. (2005), a particle swarm algorithm is proposed to select a beam ensemble with five beams, obtained from a 10° gantry angle spacing set. Other approaches include matheuristics based on tabu search (Obal et al., 2018), hybrid approaches (Bertsimas et al., 2013), branch and prune (Lim and Cao, 2012), neighborhood search (Aleman et al., 2008), and gradient search (Craft, 2007). In our previous works, the optimal value of the FMO function has been used to guide the highly non-convex BAO problem, which is addressed using derivative-free algorithms (Rocha et al., 2013a, 2013b, 2013c; Dias et al., 2014, 2015; Rocha et al., 2016, 2019; Carrasqueira et al., 2021). Pattern search methods (PSM), in particular, proved to be well suited to address this multimodel problem (Rocha et al., 2013a, 2013b, 2013c, 2016, 2019; Carrasqueira et al., 2021). On one hand, by not making explicit or implicit use of derivatives, PSM have the ability to avoid local entrapment and evolve into more promising regions of the BAO search space. On the other hand, as they require few function evaluations to obtain good solutions, they are computationally time-competitive, which is very important in the presence of an expensive function in terms of computational time (each function evaluation takes approximately three to five minutes).

3.2. Bi-level optimization—definitions

A general bi-level optimization problem can be formulated as follows:

$$\begin{array}{ll} \min_{x,w} & F(x, w) \\ \text{s.t.} & G(x, w) \leq 0, \\ & w \in \operatorname{argmin}_{\hat{w}}\{f(x, \hat{w}) : g(x, \hat{w}) \leq 0\}, \end{array} \tag{1}$$

where $x \in \mathbb{R}^{n_1}$ is the vector of variables controlled by the leader at the upper level and $w \in \mathbb{R}^{n_2}$ is the vector of variables controlled by the follower at the lower level. $F(x, w)$ and $f(x, w)$ are the leader's and the follower's objective functions, respectively, and $G(x, w) \leq 0,\ g(x, w) \leq 0$ represent general constraints placed at each level.

The follower optimizes its objective function $f(x, w)$ after variables x have been instantiated by the leader. However, the leader's decision is implicitly affected by the follower's reaction. The follower's *feasible* region for a given x' is $W(x') = \{w \in \mathbb{R}^{n_2} : g(x', w) \leq 0\}$ and the corresponding follower's *rational reaction* set is $\Psi(x') = \{w' \in \mathbb{R}^{n_2} : w' \in \arg\min_{w \in W(x')} f(x', w)\}$. The feasible set of the bi-level optimization problem, which is generally called *inducible region*, is $IR = \{(x, w) \in \mathbb{R}^{n_1} \times \mathbb{R}^{n_2} : G(x, w) \leq 0, w \in \Psi(x)\}$. The bi-level optimization problem is equivalent to optimizing the leader's objective $F(x, w)$ over IR. Finding a global optimal solution to a bi-level optimization problem remains a great challenge due to its inherent nonconvexity.

In (1), the optimistic formulation of the bi-level optimization problem is considered, which means that, if multiple optimal solutions to the follower exist, then the one benefiting the leader the most is selected. This is why the minimization at the upper level is formulated with respect to x and w. Considering the context of radiotherapy treatment planning optimization, the optimistic formulation is the only one that is adequate: if it is possible to spare more the OAR (upper level), while not diminishing the irradiation of the targets (lower level), then this is the solution that should be chosen. Although the existence of optimal alternative solutions in the lower level is not likely (sparing more the OAR is usually only achieved at the expense of PTV coverage), in formal terms this is the correct way of formulating the problem.

3.3. The proposed model

In the bi-level model for IMRT proposed in this work, the selection of beam irradiation directions is made at the upper level with the main goal of finding a beam angular arrangement that improves OAR sparing. The aim is to select a predefined number n of beams to irradiate the patient, trying to choose beam directions that achieve the best OAR sparing in a feasible noncoplanar setting of n ordered pairs $x_k = (\theta_k, \phi_k)$ of gantry angle θ_k and couch angle $\phi_k,\ k = 1, \dots, n$. Thus, the pairs $x = (\theta, \phi)$ represent the upper level variables denoted above by x in the general bi-level model. The lower level variables are the fluence intensities, which are represented by variables w_j defining the weight (the intensity) of each beamlet j. For each OAR structure r, the measure of its damage is given by function F_r that calculates the square deviation of the delivered dose from the defined tolerance dose, if the first exceeds the latter

$$F_r(x, w) = \lambda_r \sum_{i\in V(r)} \left[\left(\sum_{j\in N_b(x)} D_{ij} w_j - T_r \right)_+ \right]^2 . \tag{2}$$

Each pair $x = (\theta, \phi)$ is discretized into a set of beamlets j. $N_b(x)$ represent the set of beamlets that are defined by x. For each of these beamlets, it is possible to calculate D_{ij}: the radiation that is delivered to voxel i by beamlet j if it had unitary intensity. T_r is the tolerance dose for OAR r, $V(r)$ is the set of voxels of the structure r, λ_r is the penalty for the structure r and $(\cdot)_+ = \max\{0, \cdot\}$. This means that if a voxel of a given OAR is given a radiation dose above the tolerated dose prescribed then this deviation will contribute to F_r. This function is thus dependent on both the beam arrangement $x = (\theta, \phi)$ and the intensities w that are determined in the lower level problem.

The objective function that guides the beam selection, F_{oar}, is given by the sum of the individual F_r functions for all the OAR, $r = 1, \dots, S_{OAR}$, as follows:

$$F_{oar} = \sum_{r=1}^{S_{oar}} F_r(x, w). \tag{3}$$

In the lower level, the beam arrangement is considered fixed. The intensity fluence maps are optimized aiming at providing the prescribed dose to the target, constrained by the tolerance dose levels established for the OAR. In this work, f_s is considered for each target structure s of the PTV, $s = 1, \dots, S_{ptv}$:

$$f_s(x, w) = \underline{\lambda}_s \sum_{i \in V(s)} \left[\left(T_s - \sum_{j \in N_b(x)} D_{ij} w_j \right)_+ \right]^2 + \overline{\lambda}_s \sum_{i \in V(s)} \left[\left(\sum_{j \in N_b(x)} D_{ij} w_j - T_s \right)_+ \right]^2, \tag{4}$$

where T_s is the prescribed dose for target s, $V(s)$ is the set of voxels of the structure s, $\underline{\lambda}_s$ and $\overline{\lambda}_s$ are the underdose and overdose penalties for structure s. Each target function assesses the deviation between dose delivered and dose prescribed for each voxel of that target structure. In (4), the underdosage and overdosage are evaluated separately enabling different weights to be set for each case. Note that overdosage of the target is harmful because it could promote the existence of biological cell behaviors that would impact the treatment outcome. Thus, an uniform irradiation of the tumor is the goal to be pursued.

The objective function of the FMO problem, f_{ptv}, is obtained by summing up the quadratic functions f_s relative to each target structure s, the tumor and the lymph nodes. The FMO problem is modeled as a convex quadratic constrained optimization problem. The tolerance dose levels prescribed to the OAR are included as constraints in order to assure that every feasible solution of the bi-level problem fulfills these requirements. The FMO optimization problem is formulated as follows:

$$\begin{aligned} \min \quad & f_{ptv} = \sum_{s=1}^{S_{ptv}} f_s(x, w) \\ \text{s.t.} \quad & \\ & D^r_{max}(x, w) \le T_r, \quad \forall r : r \text{ is a serial OAR} \\ & D^r_{mean}(x, w) \le T_r, \quad \forall r : r \text{ is a parallel OAR} \\ & w_j \ge 0, \ j \in N_b(x), \end{aligned} \tag{5}$$

where $D^r_{max}(x, w)$ is the maximum dose deposited in any voxel of a serial OAR r and $D^r_{mean}(x, w)$ stands for the mean dose considering all the voxels of a parallel OAR r.

Let $W(x) = \{D^r_{max}(x, w) \le T_r, \forall r \text{ serial OAR}, D^r_{mean}(x, w) \le T_r, \forall r \text{ parallel OAR}, w_j \ge 0, j \in N_b(x)\}$, that is, the feasible region of (5) for a given x. The complete bi-level formulation is presented next, where the upper level represents the noncoplanar BAO problem and the FMO problem is at the lower level:

$$\begin{aligned} \min_{x,w} \quad & F_{oar} = \sum_{r=1}^{S_{oar}} F_r(x, w) \\ \text{s.t.} \quad & \\ & w \in \operatorname{argmin}_{\hat{w}} \left\{ \sum_{s=1}^{S_{ptv}} f_s(x, \hat{w}) : \hat{w} \in W(x) \right\}. \end{aligned} \tag{6}$$

3.4. Bi-level IMRT optimization algorithm

In this study, a bi-level algorithm has been designed to address the above bi-level formulation. This algorithm combines a tailored PSM to tackle the upper level problem with an interior-point method to solve the lower level problem for each instantiation of the upper level variables.

The highly nonconvex nature of the noncoplanar BAO problem advises the use of derivative-free optimization methods. In this study, PSM are used to address the noncoplanar BAO problem. PSM are derivative-free optimization methods that are able to avoid local entrapment and proved, in previous works, that are suitable to address the BAO problem (Rocha et al., 2013a, 2013b, 2013c, 2016, 2019). PSM are directional direct search methods that use positive bases to move in a direction that produces a decrease in the objective function. A positive basis is composed of a minimum set of directions (nonzero vectors) that positively span the search space. In this work, the positive basis used is the set of $2n$ vectors $[I; -I]$ where $I = [e_1 \cdots e_n]$ corresponds to the identity matrix. Following each of these $2n$ directions corresponds to the rotation of each beam direction clockwise and counterclockwise for a certain amount (step size) at each iteration. The step size was selected as in Rocha et al. (2013a, 2013b, 2013c, 2016, 2019), being initialized as a power of 2 ($\alpha_0 = 2^i, i \in \mathbb{N}$). At each iteration k, the step size α_k remains constant if the iteration succeeds to improve the objective function value at current iterate, otherwise it is halved. As the initial beam variables x^0 are integers, the x^k variables obtained after each iteration k continue to be integers, until the step-size becomes smaller than $\alpha_{min} = 1$, that means the stop criterion was reached. The main feature of a positive basis is that for any given vector, in particular for the gradient vector, there is a vector of the positive basis that forms an acute angle with the (unknown) gradient vector that corresponds to a descent direction (Alberto et al., 2004). PSM are organized in two steps at every iteration. The first step, called search step, provides a global search by using any strategy including taking advantage of *a priori* knowledge of the problem at hand, as long as it searches only a finite number of points. If this optional step fails to improve the objective function value, the second step, called poll step, is applied. The poll step is performed around the current solution and follows stricter rules. It uses the concepts of positive bases and guarantees convergence to a stationary point. The interior-point method used to solve the lower level problem guarantees that optimal solutions to the lower level problem are obtained, which is a required condition for such solutions being feasible to the bi-level problem.

The proposed bi-level algorithm starts by solving the FMO problem for the initial beam ensemble x^0. At each iteration, the neighborhood of the current beam ensemble is searched aiming at improving the current solution. The algorithm evolves iteratively, searching the neighborhood of the current solution and, if it succeeds, the current beam ensemble is updated and the step size remains constant, otherwise, the step size is halved. This process is repeated until the stopping criterion ($\alpha_k < \alpha_{min}$) is reached. The pseudocode of the bi-level algorithm is presented in Algorithm 1.

The bi-level IMRT algorithm was implemented in Matlab, and integrates the matRad (Wieser et al., 2017) built-in functions and IPOPT (Wachter and Biegler, 2006) to perform dose calculations and fluence optimization with the pattern search algorithm to improve the beam ensemble. matRad is a research tool for radiation therapy treatment planning developed at German Cancer Research Center. This open source software, written in Matlab, has a set of functionalities, including data importing, dose calculation, and fluence dose optimization. This tool can be customized by

Algorithm 1. Bi-level IMRT

Initialization:

- Set $k \leftarrow 0$;
- Choose the initial beam ensemble x^0, $\alpha_0 > 0$ and α_{min};
- Solve the FMO problem for x^0, whose optimal objective value is $f_{ptv}(x^0, w^0)$. Compute $F_{oar}(x^0, w^0)$;

Iteration:

1. In the neighborhood of the current beam ensemble, i.e., $\forall x \in \mathcal{N}(x^k) = \{x^k \pm \alpha_k e_i, i = 1, \ldots, n\}$,
   (a) Solve the lower level FMO problem, obtaining $f_{ptv}(x, w)$;
   (b) Evaluate $F_{oar}(x, w)$;
   If $\min_{\mathcal{N}(x_k)} F_{oar}(x, w) < F_{oar}(x^k, w^k)$ then
   $(x^{k+1}, w^{k+1}) \longleftarrow (x^*, w^*) : F_{oar}(x^*, w^*) = \min_{\mathcal{N}(x_k)} F_{oar}(x, w)$;
   $\alpha_{k+1} \longleftarrow \alpha_k$;
   Else
   $(x^{k+1}, w^{k+1}) \longleftarrow (x^k, w^k)$;
   $\alpha_{k+1} \longleftarrow \frac{\alpha_k}{2}$;
2. If $\alpha_{k+1} \geq \alpha_{min}$ return to step 1 and set $k \longleftarrow k + 1$;

selecting, from a set of options available, objectives, constraints, weights assigned to each structure and solution methods. Thus, matRad provides flexibility to design a custom optimization procedure in a fully automated manner, in the sense that after loading a patient with the prescribed and tolerance doses as well as the number of beam angles, it can obtain a treatment plan with no further interactions from the human planner.

4. Computational results

The proposed bi-level algorithm was used to obtain coplanar and noncoplanar treatment plans, designated as *cBlvl* and *ncBlvl*, respectively, for 10 clinical head-and-neck tumor cases already treated at IPO Coimbra, considering the prescribed and tolerance doses detailed in Table 1. Matlab 9.5 version was used to perform these computational experiments. Typically, IMRT treatment plans are performed considering five to nine beams. In our work, beam ensembles with $n = 7$ beams were considered for all the IMRT treatment plans obtained by the bi-level algorithm. This beam ensemble cardinality was also adopted to obtain the IMRT equispaced coplanar solution, designated as *Equi*, for all cases, serving as benchmark for the proposed bi-level approach. *Equi* treatment plans are commonly used in clinical practice. Actually, most treatment planning softwares available do not offer BAO tools, so choosing an equidistant solution is the least expensive alternative in terms of time for the planner and, most of the times, it is possible to obtain a clinical acceptable plan having this beam configuration as fixed. The computational effort required to obtain a treatment plan using the bi-level approach, either coplanar or noncoplanar, was less than 12 hours, considering a full dose calculation for every beam ensemble tested.

Table 2
Objective function values for *Equi* and *Blvl* plans

Case	*Equi*		*cBlvl*		*ncBlvl*	
	F_{oar}	f_{ptv}	F_{oar}	f_{ptv}	F_{oar}	f_{ptv}
1	5.1616	143.4511	3.7259	138.5956	3.0651	140.4492
2	8.2010	45.9343	7.0140	43.1398	5.7179	42.3107
3	14.0997	235.7002	10.4087	229.2430	9.5265	221.6536
4	10.3782	179.9890	8.5636	176.3051	6.4122	171.8532
5	14.3172	112.5368	11.4268	107.4270	10.1116	106.2023
6	29.5929	63.8701	23.9377	55.8450	21.9146	53.7113
7	12.4572	41.6579	9.9805	35.6820	7.6438	30.4945
8	11.8694	37.1265	8.4285	29.6631	8.3476	31.0571
9	10.2023	32.6350	7.5694	30.8678	5.3077	23.7488
10	1.9270	20.1468	1.7309	21.5536	1.3083	19.8778

The objective function values (F_{oar} and f_{ptv}) of the solutions obtained by the bi-level approach, in the upper and lower levels, respectively, are presented in Table 2. This table also includes the objective function values corresponding to *Equi* treatment plans. Considering the 10 cases analyzed, the *ncBlvl* and *cBlvl* plans achieved an average reduction of, respectively, 34.53% and 21.01% for the objective function F_{oar} in relation to the *Equi* plans. Although both bi-level plans were able to reduce significantly the objective function relative to OAR in all the tested cases, achieving better OAR sparing, the largest reduction was obtained by the *ncBlvl* plans. Thus, OAR sparing is achieved without jeopardizing tumor coverage, since the f_{ptv} objective function values corresponding to *ncBlvl* plans are also lower in all cases.

Additional metrics are also used to assess the quality of treatment plans in terms of tumor coverage and OAR sparing. The dose received by 95% of the PTV (*D*95) is a performance measure commonly used to assess tumor coverage, which is herein considered. The results are depicted in Fig. 1a and b, for tumor and lymph nodes, respectively. The horizontal lines are drawn in both figures indicating the 95% threshold of the prescribed dose. In clinical practice an acceptable treatment plan should have PTV dose values above this threshold. As it can be observed, *ncBlvl* treatment plans obtained the best tumor coverage for most of the cases, whereas the *cBlvl* plans could improve the *Equi* treatment plan for many of the cases.

Aiming at further evaluating OAR sparing, the maximum and mean doses deposited in each OAR are also considered, for serial and parallel OAR, respectively. The results relative to these metrics are depicted in Fig. 2a–f, where the horizontal lines represent the tolerance dose levels for the corresponding structures. For the serial organs, spinal cord, and brainstem, all plans fulfilled the maximum tolerance doses with advantage for *ncBlvl* plans in terms of spinal cord sparing and advantage for *Equi* plans in terms of brainstem sparing, where *ncBlvl* delivers slightly more dosage but yet it lays significantly below the maximum tolerance dose. For the parallel organs, parotids, and oral cavity, *ncBlvl* plans clearly outperformed *cBlvl* and *Equi* plans. For the Body, all treatment plans' outcomes are below the tolerance dose established. The coplanar bi-level approach obtains intermediate results between equidistant and noncoplanar bi-level approaches for most of the cases on the brainstem, left and right parotids, oral cavity, and Body.

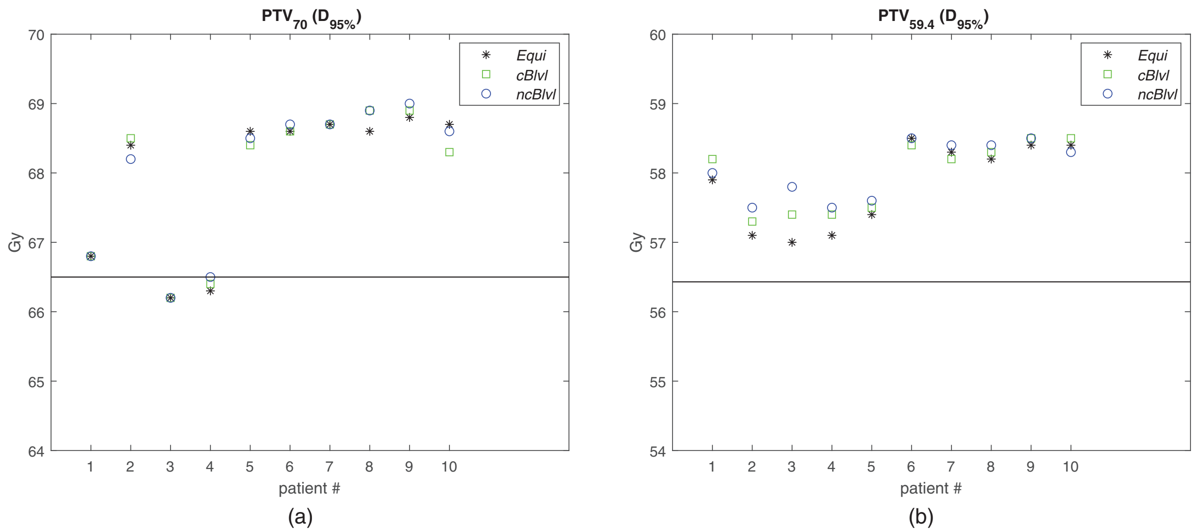

Fig. 1. Comparison of PTV coverage metrics (D95) obtained by *Blvl* and *Equi* treatment plans. The horizontal lines displayed represent D_{95}.

5. Conclusions

The two main problems of IMRT treatment planning are finding the optimal selection of beam directions and finding the optimal fluence intensities for the corresponding beams. Optimal beam directions can improve the quality of IMRT treatment plans, providing additional protection to the healthy tissues, namely critical organs surrounding the tumor area, while the tumor remains effectively irradiated. In this work, a new formulation has been adopted, modeling IMRT treatment planning as a bi-level optimization problem, aiming to capture its hierarchical nature, where the goal of delivering the prescribed dose to the target is embedded on the main goal, the OAR sparing. In the upper level problem, the beam angles are selected aiming at minimizing the radiation received by the OAR. In the lower level problem, the fluence intensity delivered through the selected beams is modulated to fulfill the treatment plan dosimetric prescription.

The solution of the bi-level IMRT problem was obtained using the bi-level algorithm herein designed. Both coplanar and noncoplanar instances of the problem were considered. In the upper level there is the nonconvex BAO problem, which is addressed by a pattern search derivative-free method. This method is based on a PSM, earlier tailored by the authors, which proved to be effective to solve the BAO problem, as it is able to escape local optima. In the lower level, an interior-point optimization method implemented in the solver IPOPT was used to solve the FMO problem.

A pool of 10 clinical nasopharyngeal tumor cases already treated at IPO Coimbra was considered to assess the quality of the treatment plans obtained by the bi-level optimization approach for coplanar and noncoplanar beam ensembles. The results were then compared to the coplanar equidistant seven-beam solution, considered as a benchmark, which was significantly outperformed in terms of both upper and lower level objective functions' values. Treatment plans obtained by the bi-level algorithm, either for coplanar or noncoplanar cases, could improve significantly OAR

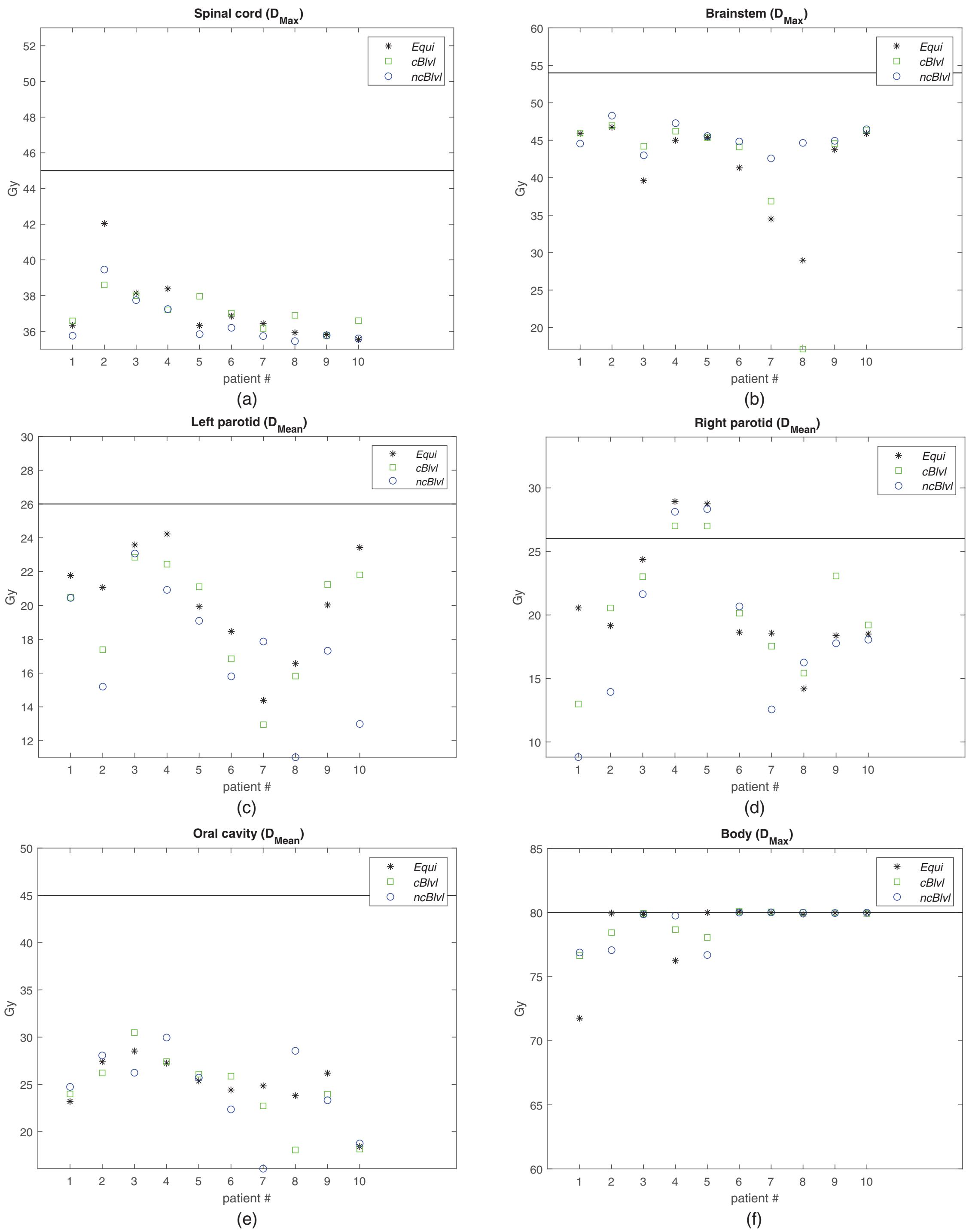

Fig. 2. Comparison of organ sparing metrics obtained by *ncBlvl*, *cBlvl*, and *Equi* treatment plans. The horizontal lines displayed represent the tolerance (mean or maximum) dose for each structure.

sparing and simultaneously maintain or increase PTV irradiation levels. These results show that the bi-level approach for the BAO problem is an effective tool for achieving higher quality treatment plans. While both plans obtained by the bi-level approach presented competitive results, the noncoplanar plans outperformed the remaining ones. This confirms the capability of noncoplanar approaches to improve treatment plans quality compared to the corresponding coplanar ones. In addition, the bi-level formulation relies on sparing OAR to perform beam selection, which resembles the manual process followed by physicists. Therefore, this tool can be of great value in supporting physicists' decisions and help them to better understand the optimization process in order to obtain better treatment plan.

In most previous BAO studies, including our own, a score (e.g., the optimal value of an objective function embedding physical criteria) is minimized with the goal of obtaining a compromise solution considering two conflicting objectives: properly irradiate the PTV(s) and spare as much as possible the OAR. Knowing that tumor irradiation is possible from any beam angle direction, it is well known that organ sparing is the main role of BAO. This motivates the herein proposed bi-level approach that fully explores this idea of expliciting the role of BAO for OAR sparing: the solutions now obtained are driven by organ sparing alone, as long as tumor coverage is not compromised, while previous solutions aimed simultaneously at improving tumor coverage and organ sparing, possibly overshadowing the main goal of BAO that is organ sparing. Choosing PSM for the upper level was a natural choice due to its excellent performance in previous works when addressing highly nonconvex optimization problems. However, different strategies should be tested in the search step of PSM in order to further improve computational times. Moreover, alternative strategies/algorithms to PSM should also be tested within the proposed bi-level approach. This approach should also be tested for different cancer sites, particularly the ones where organ sparing might be particularly difficult to achieve. Moreover, it is also possible to consider algorithmic choices for the lower level optimization. In this work an interior-point method was used. In previous works, we have also used nonconstrained quadratic models and gradient based methods for fluence optimization. One of the future works that we plan on doing is to consider more expensive ways of calculating optimal fluences in the lower level, namely using fuzzy inference systems, but that also produce, in general, better solutions.

Acknowledgments

This work was supported by project grant POCI-01-0145-FEDER-028030 and by the Fundação para a Ciência e a Tecnologia (FCT) under project grants UIDB/05037/2020 and UIDB/00308/2020.

References

Alberto, P., Nogueira, F., Rocha, H., Vicente, L.N., 2004. Pattern search methods for user-provided points: application to molecular geometry problems. *Siam Journal of Optimization* 14, 1216–1236.

Aleman, D.M., Kumar, A., Ahuja, R.K., Romeijn, H.E., Dempsey, J.F., 2008. Neighborhood search approaches to beam orientation optimization in intensity modulated radiation therapy treatment planning. *Journal of Global Optimization* 42, 587–607.

Bangert, M., Oelfke, U., 2010. Spherical cluster analysis for beam angle optimization in intensity-modulated radiation therapy treatment planning. *Physics in Medicine and Biology* 55, 6023–6037.

Bard, J.F., 1998. *Practical Bilevel Optimization: Algorithms and Applications*. Springer Science + Business Media, Dordrecht.

Bertsimas, D., Cacchiani, V., Craft, D., Nohadani, O., 2013. A hybrid approach to beam angle optimization in intensity-modulated radiation therapy. *Computers & Operations Research* 40, 2187–2197.

Cabrera, G., Ehrgott, M., Andrew, J., Mason, A.J., Raith, A., 2018. A matheuristic approach to solve the multiobjective beam angle optimization problem in intensity-modulated radiation therapy. *International Transactions in Operational Research* 25, 243–268.

Carrasqueira, P., Rocha, H., Dias, J.M., Ventura, T., Ferreira, B.C., Lopes, M.C., 2021. An automated treatment planning strategy for highly noncoplanar radiotherapy arc trajectories. *International Transactions in Operational Research*. https://doi.org/10.1111/itor.12953.

Craft, D., 2007. Local beam angle optimization with linear programming and gradient search. *Physics in Medicine and Biology* 52, 127–135.

Dempe, S., 2002. *Foundations of Bilevel Programming*. Kluwer Academic Publishers, Dordrecht.

Dias, J., Rocha, H., Ferreira, B.C., Lopes, M.C., 2014. A genetic algorithm with neural network fitness function evaluation for IMRT beam angle optimization. *Central European Journal of Operations Research* 22, 431–455.

Dias, J., Rocha, H., Ferreira, B.C., Lopes, M.C., 2015. Simulated annealing applied to imrt beam angle optimization: a computational study. *Physica Medica* 31, 747–756.

Fiege, J., McCurdy, B., Potrebko, P., Champion, H., Cull, A., 2011. Pareto: a novel evolutionary optimization approach to multiobjective IMRT planning. *Medical Physics* 38, 5217–5229.

Freitas, J.C., Florentino, H.O., Benedito, A.S., Cantane, D.R., 2019. Optimization model applied to radiotherapy planning problem with dose intensity and beam choice. *Applied Mathematics and Computation* 387. https://doi.org/10.1016/j.amc.2019.124786.

Jeroslow, R.G., 1985. The polynomial hierarchy and a simple model for competitive analysis. *Mathematical Programming* 32, 146–164.

Li, Y., Yao, D., Yao, J., Chen, W., 2005. A particle swarm optimization algorithm for beam angle selection in intensity-modulated radiotherapy planning. *Physics in Medicine and Biology* 50, 3491–3514.

Lim, G.J., Cao, W., 2012. A two-phase method for selecting IMRT treatment beam angles: branch-and-prune and local neighborhood search. *European Journal of Operational Research* 217, 609–618.

Llacer, J., Li, S., Agazaryan, N., Promberger, C., Solberg, T.D., 2009. Non-coplanar automatic beam orientation selection in cranial IMRT: a practical methodology. *Physics in Medicine and Biology* 54, 1337–1368.

Nazareth, D.P., Brunner, S., Jones, M.D., Malhotra, H.K., Bakhtiari, M., 2015. Optimization of beam angles for intensity modulated radiation therapy treatment planning using genetic algorithm on a distributed computing platform. *Journal of Medical Physics* 34, 129–132.

Obal, T.M., Irawan, C.A., Jones, D., Ouelhadi, J., Florentino, H.O., Gryczak, V., Volpi, N.M.P., Wilhelm, V.E., 2018. Development and evaluation of a matheuristic for the combined beam angle and dose distribution problem in radiotherapy planning. *IMA Journal of Management Mathematics* 30, 413–430.

Pugachev, A., Li, G.L., Boyer, A.L., Hancock, S.L., Le, Q.T., Donaldson, S.S., Xing, L., 2001. Role of beam orientation optimization in intensity-modulated radiation therapy. *International Journal of Radiation Oncology-Biology-Physics* 50, 551–560.

Rocha, H., Dias, J., Ferreira, B.C., Lopes, M.C., 2013a. Beam angle optimization for intensity-modulated radiation therapy using a guided pattern search method. *Physics in Medicine and Biology* 58, 2939–2953.

Rocha, H., Dias, J., Ferreira, B.C., Lopes, M.C., 2013b. Pattern search methods framework for beam angle optimization in radiotherapy design. *Applied Mathematics and Computation* 219, 10853–10865.

Rocha, H., Dias, J., Ferreira, B.C., Lopes, M.C., 2013c. Selection of intensity modulated radiation therapy treatment beam directions using radial basis functions within a pattern search methods framework. *Journal of Global Optimization* 57, 1065–1089.

Rocha, H., Dias, J., Ventura, T., Ferreira, B.C., Lopes, M.C., 2016. A derivative-free multistart framework for an automated noncoplanar beam angle optimization in IMRT. *Medical Physics* 43, 5514–5526.

Rocha, H., Dias, J., Ventura, T., Ferreira, B.C., Lopes, M.C., 2019. Beam angle optimization in IMRT: are we really optimizing what matters? *International Transactions in Operational Research* 26, 908–928.

Schreibmann, E., Lahanas, M., Xing, L., Baltas, D., 2004. Multiobjective evolutionary optimization of the number of beams, their orientations and weights for intensity-modulated radiation therapy. *Physics in Medicine and Biology* 49, 5, 747–770.

Wachter, A., Biegler, L.T., 2006. On the implementation of an interior-point filter line-search algorithm for large-scale nonlinear programming. *Mathematical Programming* 106, 25–57.

Wieser, H.P., Cisternas, E., Wahl, N., Ulrich, S., Stadler, A., Mescher, H., Muller, L.R., T., K., Gabrys, H., Burigo, L., Mairani, A., Ecker, S., Ackermann, B., Ellerbrock, M., Parodi, K., Jakel, O., Bangert, M., 2017. Development of the open-source dose calculation and optimization toolkit matrad. *Medical Physics* 44, 2556–2568.