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EVOLUTIONARY MULTIOBJECTIVE OPTIMIZATION FOR INTENSITY MODULATED RADIATION THERAPY

Abstract

As cancer diseases take nowadays a heavy toll on societies worldwide, extensive research is being conducted to provide more accurate diagnoses and more effective treatments. In particular, Multiobjective Optimization has turned out to be an appropriate and efficient framework for timely and accurate radiotherapy planning.

In the paper, we sketch briefly the background of Multiobjective Optimization research to Intensity Modulated Radiation Therapy, and next we present a rudimentary formulation of the problem. We also present a generic methodology we developed for Multiple Criteria Decision Making, and we present preliminary results with it when applied to radiation treatment planning.

Keywords: Evolutionary multiobjective optimization, multiple criteria decision making, Intensity Modulated Radiation Therapy planning.

1 Introduction

Around the mid 1990s, precise techniques to deliver radiation to malicious tissues became available and then optimization techniques were harnessed to produce patient treatment plans timely and accurately. This resulted in a flow of research papers on the subject, estimated in several hundreds. About a decade later, the multiobjective optimization quite naturally turned out to be an adequate framework to represent trade-offs between the goal to irradiate the tumorous re-

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gions of the body with sufficiently high levels of radiation, and the requirement to protect healthy organs as much as possible.

The principle of radiation therapy is as follows. A number of high energy *beamlets* (rays), of order of tens of thousands (depending of the equipment), are radiated from a linear accelerator towards a patient positioned on a couch. The beamlets deposit radiation doses in the patient's tissue causing its ionization. When the radiation dose is over a certain level, the tissue is killed.

In the early stage of oncological radiation therapy (in the sequel, for short, *radiotherapy*), conformal radiotherapy was used. In this technique, all points of the radiated field receive the same dose and the shape of the field is formed with physical reflectors and dumpers (Bortfeld et al., 1994).

The first delivery using the *intensity modulated radiation therapy* (IMRT), was reported in 1994. From that time clinical evidences have been collected and reported in the literature that IMRT is remarkably well suited to multiobjective optimization (Küfer et al., 2005; Craft et al., 2012; Breedveld et al., 2012).

2 Intensity Modulated Radiation Therapy

The energy which can be deposited in a tissue by a beamlet is proportional to the time the beamlet is radiated. This time is controlled by a *collimator* – a set of iron blades which slide across a rectangular aperture in the *radiation head* (with a linear accelerator inside) with varied speed. When the aperture is fully open, all the beamlets carry the same energy. On the other end, when the aperture is fully closed, no radiation is emitted. In between, the collimator allows for a whole range of radiation energy patterns, called *fluency maps*. An example of a fluency map for 4 × 5 beamlets is given in Figure 1.

A collection of beamlets radiated from one position is called a *beam*. The radiation head, mounted on the *rotating gantry*, can be a source of many beams (say 36 beams with a 10° angle step).

The problem is to produce fluency maps whose superposition kills the malicious (tumor) tissue with the least harm to the organs which have to be especially protected (Organs At Risk) and limited doses to the normal tissue (not tumor or any OAR) of the patient. This is schematically presented in Figure 2.

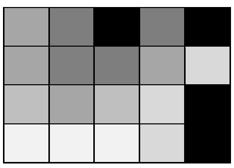

Figure 1. An example of a fluency map for 4 × 5 beamlets. The darker the colour is, the higher dose is deposited in a voxel

To control the radiation dose deposition in the irradiated region of the patient's body, this region is divided into small cubes (say, depending on the accuracy required, 2.5 mm × 2.5 mm × 10 mm), called *voxels*. The radiation dose deposited in a voxel by a beamlet radiated for one unit of time is specific to that voxel (this is calculated from a physical model) and denoted by d_{ij}, where i is the index of the voxel and j is the index of the beamlet. Thus, the dose deposited in voxel i is $d_i = \sum_j d_{ij} x_j$, where x_j is radiation time for beamlet j. This can be represented in the matrix form:

$$Dx = d ,$$

where $D = \{d_{ij}\}$ is the dose-influence matrix for all beams. Additivity of radiation doses deposited by individual beamlets is the standard assumption in the oncology radiotherapy.

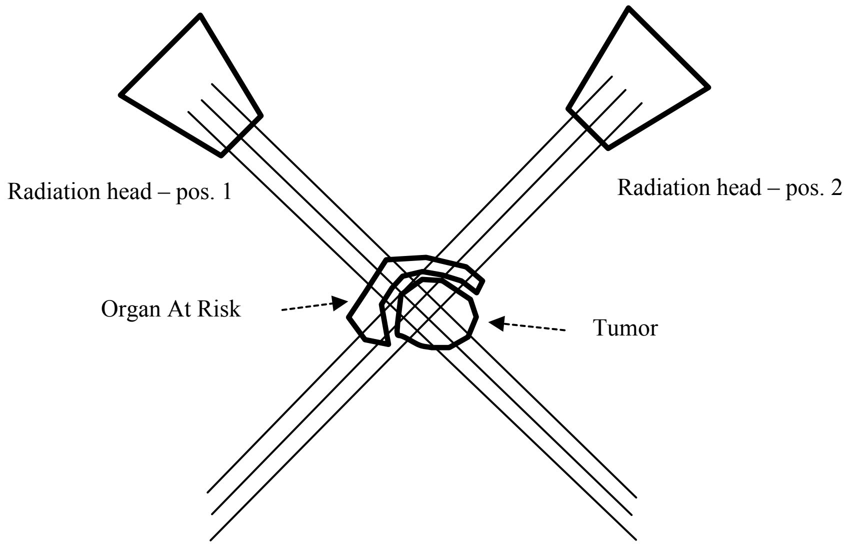

Figure 2. A schematic representation of radiation delivery to tumor and OAR by two beams

3 Multiobjective Optimization in IMRT

The distribution of energy doses to tumor, OARs and normal tissue, is the subject of optimization.

The rudimentary multiobjective optimization (specified up to objective functions) model for radiotherapy treatment planning is as follows:

$$\begin{gathered} f_l(d) \rightarrow \max\ (or\ min) \quad l = 1, \dots, k , \\ Dx = d, \\ l_{tumor} \le d_i \le u_{tumor} , i \in I_{tumor} , \\ d_i \le u_{OAR_t} , i \in I_{OAR_t} , t = 1, \dots, s , \\ d_i \le u_{normal\ tissue} , i \in I_{normal\ tissue} , \end{gathered} \tag{1}$$

where x is the vector of beamlet radiation times, I_{tumor}, I_{OAR_t} and $I_{normal\ tissue}$ are the sets of indices of voxels belonging to the respective areas, s is the number of OARs. Radiation doses deposited in tumor voxels are bounded from below by l_{tumor} and from above by u_{tumor} . For voxels of OARs and of the normal tissue only upper bounds u_{OAR_t} and $u_{normal\ tissue}$, respectively, are imposed.

The interplay between objective function values defines doses delivered to the tumor, to OARs and to the normal tissue. Dosed delivered to tumor should be maximized and doses delivered to OAR and the normal tissue should be minimized. To fulfil these general goals, various objective functions are used.

As an alternative, two-sided constraints on doses deposited in tumor voxels can be replaced by a weaker requirement, namely that the deviation of the average dose deposited in a voxel of the tumor from the dose prescribed be within a band around zero.

It should be stressed here that multiobjective optimization models solved for optimization of radiotherapy planning are large-scale, with the number of voxels reaching hundreds of thousands and the number of beamlets reaching tens of thousands.

As we see from the rudimentary multiobjective optimization model, the only element which can differentiate between models are objective functions. In the radiology literature there are many objective functions proposed. They can be of the statistical type, i.e. describing the dose distributions in organs considered, and of the biophysical type, describing the effect of radiation on the radiated cells. The latter are as a rule nonlinear. Taking this in mind, and wanting to be independent of solvers devoted to a particular class of problems and to have freedom to switch from one type of criteria function to another without having to pay attention to their analytical properties, one can opt for multiobjective evolutionary optimization (Deb, 2001; Deb et al., 2003; Coello Coello et al., 2002; Bokrantz, 2013). Bellow we follow this option.

However, switching to evolutionary computations, which are in principle heuristics with no performance guarantee, one loses a grip on the concept of optimality. In the next section, we show how one can cope with this issue.

4 The Proposed Multiple Criteria Decision Making Methodology

For the sake of consistency, we present here the proposed methodology in terms specific to radiotherapy planning. However, the method, originally described in Kaliszewski et al. (2012), is general and can be applied to any multiple criteria decision making problem.

Let x denote a vector of beamlet intensities of length n . By the physical interpretation, set X_0 of feasible x is a subset of R_+^n, the nonnegative orthant of R^n .

The underlying Multiobjective Optimization model for *Multiple Criteria Decision Making* is[1]:

$$"max"f(x), \tag{2}$$

where $f: R_+^n \to R^k$, $f = (f_1, \dots, f_k)$, $f_l : R_+^n \to R, l = 1, \dots, k, k \geq 2$, f_l are *objective functions, "max"* denotes the operator of deriving all Pareto optimal solutions (in the sense of Pareto) in X_0.

We assume that Pareto optimal solutions are derived by solving the following optimization problem:

$$min_{x \epsilon X_0} \, max_l \, \lambda_l(y^* - f_l(x)), \tag{3}$$

where y^* is such that $f(x) < y^*$ for any $x \in X_0$. The set $f(x)$, where x are all Pareto optimal solutions, is called the *Pareto front.*

We have selected optimization problem (3) as a Pareto optimal solution generator because it has the ability to provide all Pareto optimal solutions[2] to a given problem, the only condition being the existence of element y^* (for details, see e.g. Kaliszewski et al., 2012; Kaliszewski, 2006; Ehrgott, 2005; Miettinen, 1999).

Under the assumption that all objectives are of the "max" type, for a given element y^*, the optimization problem realizes a line search along the so-called *compromise half line* (Kaliszewski et al., 2012), provided that the compromise half line $y = y^* - t\,\tau, \tau_l > 0, t \geq 0$, intersects set $f(X_0)$, but it yields a Pareto optimal solution in any case. This argument is graphically represented in Figure 3.

The relation between search directions τ (called in Kaliszewski et al., 2012 *directions of concessions*) and parameters λ in the objective function of optimization problem (2), is given by formula:

$$\lambda_l = (\tau_l)^{-1}, l = 1, \dots, k. \tag{4}$$

All components of search directions τ_l are positive, hence $\lambda_l > 0, l = 1, \dots, k$ (Kaliszewski et al., 2012).

Formula (4) establishes a clear relationship between technical parameters λ in the optimization problem (3), and the realm of decision making where vectors of concessions τ are easily interpretable. Indeed, vector τ represents a simple form of *preference carrier* which can be used to encapsulate the radiotherapy planner's (in general: the decision maker's) preferences[3].

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[1] For the sake of brevity of presentation we assume here that all objectives are of, or are converted to, the "max" type.

[2] In fact, this optimization problem provides a characterization of weakly Pareto optimal solutions, but for the problems considered in this work such a distinction is immaterial.

[3] For the complete treatment of this problem see: Kaliszewski (2006); Ehrgot (2005); Miettinen (1999).

With vectors of concessions we can do more than that. With two sets of elements: feasible S_L – *lower shell* and infeasible A_U – *upper approximation*, with images $f(\cdot)$ located, respectively, below and above set $f(x)$, where x are Pareto optimal solutions, for a given vector of concessions τ we can calculate $L_l(\tau, S_L)$ and $U_l(\tau, A_U)$, such that:

$$L_l(\tau, S_L) \leq f_l(x) \leq U_l(\tau, A_U),\ l = 1,\dots,k,$$

where x is the solution which would be derived if the optimization problem was solved with $\lambda_l = (\tau_l)^{-1}$, $l = 1,\dots, k$. We can now estimate unknown $f_l(x)$ indirectly, by lower and upper bounds $L_l(\tau, S_L)$ and $U_l(\tau, A_U)$, $l = 1,\dots, k$ (Kaliszewski et al., 2012).

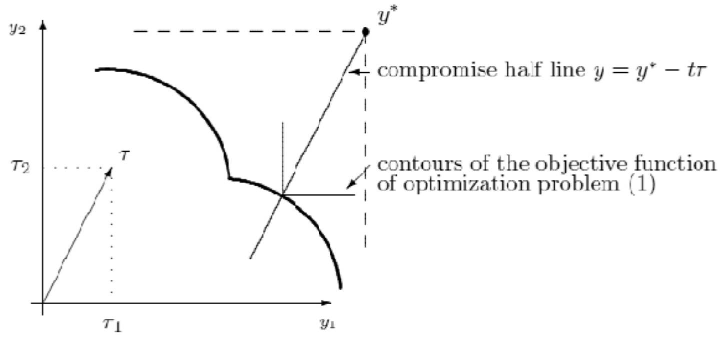

Figure 3. A graphical interpretation of vector of concessions τ and optimization problem (2)

Sets S_L and A_U are to be derived by specific evolutionary multiobjective optimization algorithms (Kaliszewski et al., 2012).

5 Preliminary Results

We have solved a number of test problems extracted from anonymized clinical data. The largest problem solved (Head & Neck tumor case) has 3 beams, 8064 beamlets, 181292 voxels. An approximation of the Pareto front was obtained with the NSGA-II evolutionary algorithm with 300 iterations and population size equal to 100. The number of elements in the approximation was 76. Computations on an AMD Dual Core E2-1800, 1.7 GHz desktop computer running under the Linux operating system took 10 min. In this particular case, the formulation of the rudimentary problem (1) presented in Section 3 was as follows:

$$\frac{1}{|I_{tumor}|}\sum_{i \in I_{tumor}} d_i \to max,$$

$$\max\{max_{i \in I_{SPINE}} d_i,\ max_{i \in I_{JAW}} d_i\} \to min,$$

$$Dx = d,$$

$$0.18 \times 66\ Gy \leq d_i \leq 1.15 \times 66\ Gy,\ i \in I_{tumor},$$

$$d_i \leq 45\ Gy,\ i \in I_{SPINE},$$

$$d_i \leq 70\ Gy,\ i \in I_{JAW},$$

where Gy (gray) is a unit of radiation dose, SPINE and JAW are OARs, $|\cdot|$ denotes the cardinality of a set. The first objective function represents the average dose per voxel deposited in the tumor, and this value has to be maximized. The second objective function represents the maximum of doses deposited in voxels of two organs to be spared, namely spine and jaw, and this value has to be minimized.

It is worth observing that even for the size of the largest problem it was possible to derive an approximation of the whole Pareto front (in Figure 4, to be consistent with multiobjective optimization model (2), the second objective function is multiplied by -1 and maximized). To our best knowledge, solving multiobjective optimization problems of such sizes have not been reported in the literature. The only paper which discusses the issue of solving large-scale multiobjective optimization problems by evolutionary computations is Antonio, Coello Coello (2013). However, that paper presents results for artificial test problems scalable to any size. The paper reports solving problems with up to 5000 variables and only box constraints.

With elements of Pareto front approximations derived, we are able to apply our methodology, as outlined in Section 4. Let us illustrate how it can work with the largest problem solved for the Head & Neck cancer case. We can proceed according to two scenarios. Both scenarios are hypothetical because the preliminary results we have obtained are of no real clinical value. Radiotherapy plans with the IMRT technique applied to patients involve at least five beams. Therefore the results we have obtained so far are to be regarded only as a proof of the concept.

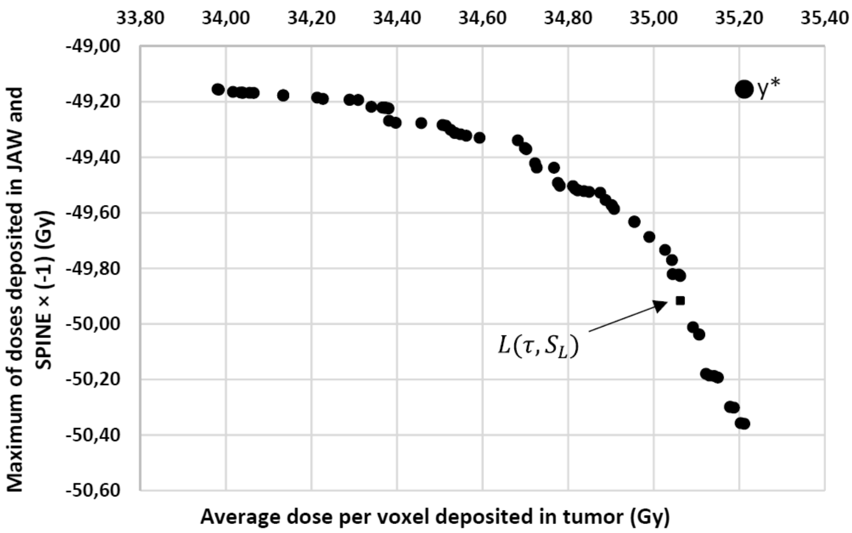

Figure 4. A Pareto front approximation of Head & Neck tumor case with three beams

Decision making scenario 1

Let us regard the approximation of the Pareto front derived as an accurate representation of the Pareto front, sufficient for radiotherapy planning.

Presenting 76 elements of the Pareto front to the radiotherapy planner (medical physicist) or the oncology physician leaves him unsupported.

Here comes the proposed multiple criteria decision making methodology presented in Section 4. We calculate element $y_l^* = max_{x \in \{Pareto\ front\}} f_l(x) + \varepsilon, \varepsilon > 0, l = 1,2$, and for $\varepsilon = 0.5$ (selected arbitrarily) we get $y^* = (35.71, -49.15)$.

For selected vectors of concessions τ, using formula (4) we can find, in the 76-element representation of the Pareto front, the element with the minimal value of the objective function in problem (3). With τ representing the decision maker's preferences, the selected elements correspond best to those preferences (in the sense of the objective function in problem (3)).

Table 1 presents selected elements for five vectors τ (in the table vectors τ are normalized). To be consistent with the assumption made in Section 4, the second objective function was converted to the "max" type by multiplication of its values by -1.

Table 1: Selected elements for a pair of vectors τ

τ_1	τ_2	$f_1(x)$	$f_2(x)$	$L_1(\tau, S_L)$	$L_2(\tau, S_L)$
0.1	0.9	35.21	-50.36	35.21	-53.15
0.25	0.75	35.18	-50.30	35.16	-50.30
0.5	0.5	34.85	-49.52	34.84	-49.52
0.75	0.25	34.13	-49.18	34.13	-49.18
0.90	0.10	33.98	-49.15	31.21	-49.15

Table 1 also provides bounds on solutions of problem (3) which would be derived if problem (3) was solved with a given τ. It is of interest to note, that, in full accordance with the methodology, in some cases lower bounds on components can be higher than components of minimizers of the objective in problem function (2). For example, for $\tau = (0.1, 0.9)$, the lower bound on the second component is -53.15, whereas the second component of the element derived for that τ is -53.36.

Decision making scenario 2

Let us regard the approximation of the Pareto front derived as an inaccurate representation of the Pareto front, insufficient for radiotherapy planning. In that case we can use it as a shell S_L (see Section 4) to calculate lower bounds on components of unknown $f(x)$, selected implicitly by DM's preferences represented by vectors τ. For example, in Figure 4 there is a region not well covered by elements of S_L in the segment $[-50.00, 49.80]$ of the horizontal axis. We can probe that region with the compromise half line with $\tau = (0.34, 0.66)$. Without solving problem (3) we get lower bounds for the solution of this problem for $\lambda_l = (\tau_l)^{-1}, l = 1,2$, as shown in Table 2. In this way, we can probe any fragment of the Pareto front.

We could also get an upper bound for this solution, but for this aim we would need an upper approximation A_U. As the problem considered here has no clinical value and is used here as an illustration, we did not calculate upper bounds. But for more realistic, hence larger problems, we will calculate two-sided bounds which is a reasonable way to avoid solving problem (3) explicitly.

Table 2: Two-sided bounds

τ_1	τ_2	$f_1(x)$	$f_2(x)$	$L_1(\tau, S_L)$	$L_2(\tau, S_L)$
0.34	0.66	*unknown*	*unknown*	35.06	-49.92

6 Concluding Remarks and Direction of Further Research

This paper reports on our efforts to establish practical connections between multiobjective optimization and radiotherapy planning. To this aim we are strongly supported by cooperating radiotherapy planners who:

1) have shown deep interest in the issue,
2) provided us with clinical data,
3) verify results of our computations,
4) declare to use our results in clinical practice if we provide comparative or better results than those produced by treatment planning systems currently in use.

The preliminary results we have obtained indicate that problems with a limited number of beams, but nevertheless large-scale problems, can be solved with general purpose Evolutionary Multiobjective Optimization methods, where the solution takes the form of a (hopefully fair) representation of the Pareto front. That is a novelty in the literature on the multiobjective optimization.

As radiotherapy plans quality increases with the increasing number of beams, we expect that the derivation of representations of the whole Pareto front, given a reasonable time budget, will not be possible. In fact, we have never intended to propose this. Instead, with the relation (4) the radiotherapy planner is in the position to direct the derivation of radiotherapy treatment plans to the regions of the Pareto front of his/her direct interest. To arrive at a feasible and Pareto optimal treatment plan, the planner has to compromise on unattainable values of components of y^* and he/she can easily do so in terms of vectors of concessions.

Encapsulation of preferences in terms of vectors of concessions is a simple but sufficient tool to interface the decision making realm with optimization engines, the latter of no or little interest for a general decision maker. The approach and tool we propose and advocate sets a very low cognitive barrier for entering into Multiple Criteria Decision Making. In radiotherapy planning, where planners (medical physicists by profession) work in the regime of daily routines, under stress and time pressure to deliver patient radiation plans timely, this is a key factor for the successful adoption of the multiple criteria perspective.

However, the ultimate goal, as it is suggested by radiotherapy practitioners we cooperate with, should be to actively include physicians-oncologists, who are the last and decisive link in the decision making chain, in the multiple criteria decision making processes. For this aim, a low cognitive barrier to enter will be of paramount importance.

Providing clean radiotherapy data, in formats suitable for optimization, requires a great amount of work. It has taken us two years to produce preliminary results. In addition, some physical models have been built to provide data, which cannot be otherwise obtained from commercial systems currently in operation in oncology centres.

We would like to stress again that the approach to multiple criteria decision making outlined in this paper, being general, is applicable to any problem with multiobjective optimization as the underlying model. It has been already successfully applied to problems in engineering design (Kaliszewski et al., 2015) and to the airport gate assignment problem (Kaliszewski et al., 2013).

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