Interactive Multiobjective Optimization for 3D HDR Brachytherapy Applying IND-NIMBUS

Henri Ruotsalainen, Kaisa Miettinen, and Jan-Erik Palmgren

Abstract An anatomy based three-dimensional dose optimization approach for HDR brachytherapy using interactive multiobjective optimization is presented in this paper. In brachytherapy, the goals are to irradiate a tumor without causing damage to healthy tissue. These goals are often conflicting, i.e. when one target is optimized the other one will suffer, and the solution is a compromise between them. Our interactive approach is capable of handling multiple and strongly conflicting objectives in a convenient way, and thus, the weaknesses of widely used optimization techniques (e.g. defining weights, computational burden and trial-and-error planning) can be avoided. In addition, our approach offers an easy way to navigate among the obtained Pareto optimal solutions (i.e. different treatment plans), and plan quality can be improved by finding advantageous trade-offs between the solutions. To demonstrate the advantages of our interactive approach, a clinical example of seeking dwell time values of a source in a gynecologic cervix cancer treatment is presented.

1 Introduction

Radiation's delivery in high-dose-rate (HDR) intracavitary brachytherapy using an afterloading unit is realized by using temporarily implanted catheters: a programmable remote unit moves a single radioactive source along catheters. This system produces a high-dose region centered on the planning target volume while sparing the adjacent bladder and bowel. The flexibility of this system allows it to be tailored to a variety of different patient anatomy and cancer types because a wide variety of dose distributions can be generated from a given implant simply by adjusting the length of time (dwell time) that the source dwells at any location within a catheter (dwell position). In clinics, this flexibility allows the full benefit of the use

H. Ruotsalainen (✉)

Department of Physics, University of Kuopio, P.O. Box 1627, 70211 Kuopio, Finland
e-mail: Henri.Ruotsalainen@uku.fi

of three-dimensional (3D) planning system based on computer tomography (CT) or magnetic resonance imaging (MRI).

However, the increased flexibility in treatment applications and imaging increases also the complexity in the treatment planning. A patient domain can be divided into three different parts based on a patient anatomy: a planning target volume (PTV), dose sensitive organs at risk (OARs) and healthy normal tissue (NT). The OARs and NT are typically near the PTV, and thus, they may be unnecessarily overdosed. To maintain a complete coverage of the PTV and simultaneously reduce the dose to NT and OARs, the dose distribution should be as conformal as possible to the relevant anatomy.

Recently, there has been interest in using multiobjective optimization in brachytherapy treatment planning (e.g. Yu, 1997; Lahanas et al., 1999; Yu et al., 2000; Lessard et al., 2006). This is because the aim of brachytherapy is to treat the tumor without affecting healthy tissue but, naturally, increasing the dose in the tumor also increases the unwanted dose in surrounding healthy tissue. Thus, when one target is optimized, the other will suffer, and the solution is a compromise between them. This trade-off is complex, and optimization tools capable of handling multiple and conflicting objectives are naturally required. The multiobjective optimization approaches presented in the literature are based on using objective weights defined beforehand, where the final objective function is expressed as a weighted sum of the conflicting objectives (e.g. Milickovic et al., 2002; Lahanas and Baltas, 2003). In these cases, objectives are often formulated as using penalties where exceeding predefined upper limits for doses are penalized (e.g. Lahanas et al., 2003b). Unfortunately, it is typically hard to predefine the priorities or weights of the optimization targets. Moreover, sometimes information about objectives and even the practical relevance of the objective functions can become blurred if the objectives are expressed as a sum. Furthermore, penalizing only the overdose should not be the actual goal as we argue in this paper. Alternatively, evolutionary algorithms (e.g. Lahanas et al., 2001; Milickovic et al., 2001) have been used, too. These methods have their own difficulties because they are very time consuming requiring a lot of calculation when computing a large set of approximating solutions. The similar optimization methods and methods for comparing different solutions have been studied also in a similar context in intensity modulated radiotherapy (IMRT) treatment planning in Romeijn et al. (2004), Craft et al. (2005), Hoffmann et al. (2006), Holder (2006), Craft et al. (2007), Thieke et al. (2007), Monz et al. (2008), Craft and Bortfeld (2008) and Ehr Gott and Winz (2008).

To overcome some shortcomings of currently used approaches, we exploit an interactive multiobjective optimization method for 3D HDR brachytherapy optimization in this paper. The real multiobjective nature of the problem is taken into account in the problem formulation and in the interactive solution process. For some reason, interactive multiobjective optimization methods have not been studied in the field of brachytherapy optimization before. The studies where brachytherapy treatment plan has been optimized are based on a priori methods or a posteriori methods. However, according to our knowledge, an interactive multiobjective optimization method is ideal for brachytherapy optimization, and we demonstrate the advantages

of our interactive approach by an example of a treatment plan of cervical cancer. In this study, our interactive approach is used to determine the dwell time values needed to fulfill the prescribed dose to the tumor and to minimize dose in each organ at risk. In our approach, the decision maker's (i.e. treatment planner's) knowledge and preferences are used during the iterative optimization process to direct the search in order to find the most preferred plan, that is, the best Pareto optimal solution, as it is called, between the conflicting treatment planning targets. This makes treatment planning times shorter, and good trade-offs between the targets can be found to improve the treatment plan's quality. Furthermore, the interactive approach improves the decision makers control over treatment: with this system, the treatment planner plays directly with the compromises between target coverage and protection of organs at risk instead of with dwell positions, dwell times, and objective weights. This approach brings the planning process near to the real clinical issues avoiding artificial simplifications, and when compared to the currently used trial-and-error method, our approach guarantees the mathematical optimality of the final solution, i.e. treatment plan. Here, by mathematical optimality we refer to Pareto optimality which means that any of the targets cannot be improved without impairing at least one other target at the same time. Pareto optimality is not guaranteed by trial-and-error method used at the clinics in which some of the targets could still be improved without deteriorating other targets. It is important to point out that these kinds of tools are designed to assist human treatment planners in their work, not to replace them.

2 Methods

2.1 Dose Calculation

Before optimization, the dose distribution in a patient needs to be calculated. The dose $D(x_i) = D_i$ at the i th sampling point x_i is calculated by

$$D_i = \sum_{j=1}^p t_j d_{ij}, \quad (1)$$

where p is the number of sources, t_j is the dwell time of the j th source dwell position and d_{ij} is the kernel value, i.e. dose value, for the i th dose calculation point and j th source dwell position. The dose rate matrix d_{ij} can be calculated using the following equation according to TG43 (Nath et al., 1995; Rivard et al., 2004):

$$d_{ij} = S_k \Lambda \Phi_{an}(\theta, r_{ij}) g(r_{ij}) / r_{ij}^2, \quad (2)$$

where S_k is the air kerma strength, Λ is the dose-rate constant, $\Phi_{an}(\theta, r_{ij})$ is the anisotropy function, $g(r_{ij})$ is the radial dose functions, and r_{ij} the distance between

the dwell position j and the dose calculation point i (point source). In this paper, we use (1) for dose calculations (anisotropy of a patient is neglected). In interactive multiobjective optimization, the dwell times t_j are the decision variables.

2.2 Objective Function Formulation

The aim of brachytherapy treatment planning is to obtain a plan which covers the PTV with at least some specified dose value D_{PTV} , which is case-specific depending on the type of the tumor. In addition to this, there is an upper bound for the dose in NT and the OAR which should not be exceeded. We denote these bounds by D_{NT} and D_{OAR} . Traditionally in optimization, dwell times t are sought so that the above-mentioned requirements are fulfilled, that is

$$\begin{aligned} D_i &\geq D_{\text{PTV}}, \quad i \in I_{\text{PTV}}, \\ D_i &\leq D_{\text{NT}}, \quad i \in I_{\text{NT}}, \\ D_i &\leq D_{\text{OAR}}, \quad i \in I_{\text{OAR}}, \end{aligned} \tag{3}$$

where I_{PTV} , I_{NT} and I_{OAR} present indexes of sampling points located in a region PTV, NT and OAR, respectively. In the literature, several different objective functions have been used to fulfill these requirements; variance based objective functions (e.g. Lahanas et al., 2003a) or dose volume histogram based objective functions (e.g. Lahanas et al., 2003b), for example. In addition, the formulation used in Lessard and Pouliot (2001) and Lessard et al. (2002) is well known. However, let us point out that even though (3) describes an acceptable solution, it is important to carefully think what should actually be optimized: the goal is that the dose in NT and OAR should be as low as possible (minimized), not only under the predefined bounds.

Now, based on the fact that we want to minimize the dose in NT and OAR (i.e. not only the dose exceeding limits D_{NT} and D_{OAR}), objective functions can be formulated (in a discrete form) as

$$f_1(t) = \frac{|I_{\text{PTV}}|}{|I_{\text{PTV}}|}, \tag{4}$$

$$f_2(t) = \frac{1}{|I_{\text{NT}}|} \sum_{i \in I_{\text{NT}}} D_i, \tag{5}$$

$$f_3(t) = \frac{1}{|I_{\text{OAR}}|} \sum_{i \in I_{\text{OAR}}} D_i \tag{6}$$

and

$$f_4(t) = \max_{i \in I_{\text{PTV}}} D_i, \tag{7}$$

where t is a vector of dwell time values, and $|I_{PTV}|$, $|I_{OAR}|$ and $|I_{NT}|$ denote number of sampling points, i.e. size of the set, in a region (PTV, OAR and NT). Because of the computational reasons, all the sampling points are situated on the surface of the region, and thus a maximum dose inside the PTV is not an objective but it is controlled later. Here, $|I_{PTV}|$ represents the number of sampling points in the PTV that have a dose value bigger than the dose limit D_{PTV} . Thus, the function f_1 represents a percentual volume where the dose is higher or equally high to the prescribed dose D_{PTV} in the PTV, and it is maximized. The functions f_2 and f_3 are the averaged doses on the surface of NT and the OAR, respectively, to be minimized. If there are multiple OARs (as also here in the example), there are as many objective functions each similar to f_3 . The objective function f_4 describes the maximum dose on the surface between the PTV and NT (because the sampling points are situated on the surface of the PTV). With these objective functions, the unwanted dose in NT and the OAR is really minimized, not only penalized if it exceeds predefined upper limits for doses as it is often presented in the literature, see Lahanas et al. (2003b), for example.

2.3 Multiobjective Optimization

2.3.1 Multiobjective Optimization Problem

A multiobjective optimization problem can be defined as follows (Miettinen, 1999)

$$\begin{aligned} & \text{minimize } \{f_1(t), f_2(t), \dots, f_k(t)\} \\ & \text{subject to } t \in S, \end{aligned} \tag{8}$$

where t is a vector of decision variables from the feasible set $S \subset \mathbf{R}^n$ defined by linear, nonlinear and box constraints. We can denote an objective vector by $\mathbf{f}(t) = (f_1(t), f_2(t), \dots, f_k(t))^T$. Furthermore, we denote the image of the feasible set by $\mathbf{f}(S) = Z$ and call it a feasible objective set. In multiobjective optimization, optimality is understood in the sense of Pareto optimality (Miettinen, 1999). A decision vector $t' \in S$ is Pareto optimal if there does not exist another decision vector $t \in S$ such that $f_i(t) \leq f_i(t')$ for all $i = 1, \dots, k$ and $f_j(t) < f_j(t')$ for at least one index j . These Pareto optimal solutions form a Pareto optimal set. All the solutions are equally good from a mathematical point of view, and they can be regarded as equally valid compromise solutions of the problem. There exists no trivial mathematical tool in order to find the best solution in the Pareto optimal set because vectors cannot be ordered completely. That is why we need some additional information.

Typically, a decision maker, who is an expert in the field from where the problem has arisen (here, a treatment planner), is needed in order to find the best or most satisfying solution, called the final one. The decision maker can participate in the solution process, and, in one way or another, determine which of the Pareto optimal

solutions is the most satisfying to be the final solution. It can be useful for the decision maker to know the ranges of objective function values in the Pareto optimal set. An ideal objective vector $\mathbf{z}^* \in \mathbf{R}^k$ gives lower bounds for the objective functions in the Pareto optimal set and it is obtained by minimizing each objective function individually subject to the constraints. A nadir objective vector $\mathbf{z}^{\text{nad}}$ giving upper bounds of objective function values in the Pareto optimal set is usually difficult to calculate, and thus its values are usually only approximated by using pay-off tables, for example (see Miettinen, 1999 for details).

According to Miettinen (1999), the methods developed for multiobjective optimization can be divided into four classes depending on the role of the decision maker. There are methods for use when no decision maker is available. In these methods, the final solution is some neutral compromise solution. In the three other classes, the decision maker participates in the solution process beforehand, afterwards or iteratively; these methods are called the a priori, a posteriori and interactive methods, respectively. It can be difficult for the decision maker to specify preferences before the solution process has started and, on the other hand, generating many Pareto optimal solutions for the decision maker to compare can be computationally costly. It is also problematic to compare many solutions without setting too much cognitive load on the decision maker. Consequently, and encouraged by experiences reported in Ruotsalainen et al. (2006), we concentrate in this paper on interactive methods.

2.3.2 The Interactive Multiobjective Optimization Method NIMBUS

In this paper, we integrate an anatomy based 3D HDR brachytherapy dose calculation model with an interactive multiobjective optimization method. The method we use is NIMBUS (Miettinen, 1999; Miettinen and Mäkelä, 2006, 1995). This method has been successfully used in external radiotherapy treatment planning optimization in an academic case with a simple pencil beam model in Ruotsalainen et al. (2006).

In interactive multiobjective optimization methods, the information given to and required from the decision maker must be easily understandable. The NIMBUS method is based on the idea of classification of objective functions. It is known that classification can be considered an acceptable task for human decision makers from a cognitive point of view (Larichev, 1992). In NIMBUS, the decision maker participates in the solution process iteratively and continuously. Finally, he/she decides which of the Pareto optimal solutions obtained is the most desired one. During the solution process, the decision maker classifies objective functions at the current Pareto optimal point into up to five classes. The classes are the following:

- I^{imp} functions whose values should be improved
- I^{asp} functions whose values should be improved up to a desired aspiration level $\hat{z}$
- I^{sat} functions whose values are satisfactory
- I^{bound} functions whose values can be impaired up to a given bound ϵ
- I^{free} functions whose values can change freely

Since all the solutions considered are Pareto optimal, the decision maker cannot make a classification where all the objective function values should improve without allowing at least one of the objective functions to be impaired. The aspiration levels and the bounds are elicited from the decision maker during the classification procedure if they are needed.

By classifying the objective functions, the decision maker gives preference information about how the current solution should be improved. Based on that, a scalarized single objective optimization problem (a subproblem, as we call it) can be formed, and it can be solved with an appropriate solver. Here, we use a synchronous NIMBUS method (Miettinen and Mäkelä, 2006). In this method, there are four different subproblems available, so the decision maker can choose whether to see one to four new solutions after each classification. Each subproblem generates a new Pareto optimal solution that satisfies the preferences given in the classification as well as possible, but the preferences are taken into account in slightly different ways (Miettinen and Mäkelä, 2002). The decision maker can use any solution obtained so far as a starting point for a new classification, and interesting solutions can also be saved in a database, so that the solution process can be continued later from any of them. Alternatively, the decision maker can generate a desired number of Pareto optimal intermediate solutions between any two solutions. This capacity differs from many other approaches used in treatment planning where intermediate solutions are only approximated, see, e.g. Monz et al. (2008). For more information about the NIMBUS algorithm, the scalarizations used and ways of aiding comparison of Pareto optimal solutions generated with different visualizations, see Miettinen and Mäkelä (2006).

3 Results

3.1 Problem Settings

Here, a clinical example of seeking dwell time values of a source in a gynecologic cervix cancer treatment is presented. In the example, Fletcher–Suit intracavitary applicator system was used to deliver the radiation, and there were 17 possible dwell positions (resolution of 5 mm in three applicators). Thus, the number of continuous decision variables was 17. In addition, the number of sampling points in computations was 508. The problem contained box constraints for the decision variables (i.e. dwell times). In the example, there were two OARs (bladder and rectum, sigma was not adjacent to the tumor), and thus, there were two objective functions similar to f_3 (f_3^{bladder} and f_3^{rectum}).

In the example, all the simulations were carried out with the mathematical software Matlab[®] R2006b after the patient geometry (anatomy and sampling points) was generated with a treatment planning software (BrachyVision[®], Varian Medical Systems, software version 7.3.10) at the Kuopio University Hospital. The optimization was done with a personal computer (Pentium[®] 4 CPU 3.00 GHz with

2 GB central memory). For interactive multiobjective optimization, an implementation of the NIMBUS method, called IND-NIMBUS[®] was used Miettinen (2006). A global optimization method (computation time was minutes per classification with the presented PC) was used to solve the formed subproblem in IND-NIMBUS. This optimization method does not require continuity of the objective functions.

3.2 Fletcher–Suit Applicator Example

The optimization problem used for the demonstration of the proposed interactive multiobjective optimization approach has the form

$$\begin{aligned} &\text{optimize } \{f_1(t), f_2(t), f_3^{\text{bladder}}(t), f_3^{\text{rectum}}(t), f_4(t)\} \\ &\text{subject to } t \in S, \end{aligned} \quad (9)$$

where t is a vector of continuous decision variables, and $S = [0, 100] \times [0, 100] \times \dots \times [0, 100] \subset \mathbf{R}^{17}$. Objective functions $f_1 - f_4$ are defined in Sect. 2.2: the value of f_1 represents the percentual value of sampling points in the PTV which has a dose value higher than the dose limit D_{PTV} (7 Gy), and values f_2 , f_3^{bladder} , f_3^{rectum} represent averaged dose values in NT, bladder, and rectum, respectively (in gray). Finally, f_4 is the maximum dose on the surface between the PTV and NT (in gray).

3.2.1 Interactive Solution Process

The interactive solution process (i.e. moving from one Pareto optimal solution to another) was guided by preference information of a treatment planner, who was acting as a decision maker. Before the solution process, the decision maker had the following desires: the percentual value of sampling points in the PTV that have a dose value higher than the dose limit D_{PTV} should be maximized (f_1). At the same time, the averaged doses in NT and both OARs should be minimized (f_2 , f_3^{bladder} , f_3^{rectum}). Since the objective function f_4 shows the maximum dose on the surface between the PTV and NT, the decision maker wanted to minimize it, too. At the very beginning, the objective functions had the initial values (generated by IND-NIMBUS) $f_1 = 0.58$, $f_2 = 9.89$, $f_3^{\text{bladder}} = 1.96$, $f_3^{\text{rectum}} = 3.13$ and $f_4 = 96.80$ (initial solution $\mathbf{f}(t^1)$). As can be seen from the initial objective function values $\mathbf{f}(t^1)$, the f_1 value was certainly too low ($f_1 = 0.58$, i.e. 58% of the PTV received higher dose than D_{PTV} which was 7 Gy). Nevertheless, the objective functions f_2 , f_3^{bladder} and f_3^{rectum} were in a good level and, thus, the dose in NT and the OARs was low but, as said, at the same time the dose in the PTV was too low and the tumor would not be treated properly. Thus, the decision maker wanted to search for a better solution in an iterative way. He started to classify the functions and generated new solutions (see classes in Sect. 2.3.2), and in this way declared his preferences and steered the solution process interactively and iteratively towards the most satisfying Pareto optimal solutions.

Table 1 Summary of interactive solution process. Bounds and aspiration levels used are denoted as superscripts in the classification notation

Solution	$f_1(-)$	$f_2(\text{Gy})$	$f_3^{\text{bladder}}(\text{Gy})$	$f_3^{\text{rectum}}(\text{Gy})$	$f_4(\text{Gy})$
Ideal	1	0	0	0	0
Nadir	0	25.82	4.64	7.72	744.33
Initial solution					
$\mathbf{f}(t^1)$	0.58	9.89	1.96	3.13	96.80
1st classification	$I^{\text{asp } 0.70}$	I^{free}	$I^{\text{bound } 2.00}$	$I^{\text{asp } 2.00}$	I^{free}
$\mathbf{f}(t^2)$	0.58	9.55	1.98	2.74	135.89
2nd classification	I^{imp}	I^{free}	$I^{\text{bound } 2.00}$	$I^{\text{asp } 2.00}$	I^{free}
$\mathbf{f}(t^3)$	0.83	11.18	2.67	3.29	55.18
$\mathbf{f}(t^4)$	1.00	15.86	3.34	4.05	109.89
$\mathbf{f}(t^5)$	0.79	11.57	2.55	3.24	76.85
Intermediate sol. ^a					
$\mathbf{f}(t^6)$	0.64	9.87	2.12	2.86	64.23
$\mathbf{f}(t^7)$	0.69	10.02	2.24	2.90	62.11
$\mathbf{f}(t^8)$	0.71	10.44	2.36	3.04	52.23
$\mathbf{f}(t^9)$	0.73	10.50	2.35	3.15	52.23
$\mathbf{f}(t^{10})$	0.76	10.87	2.45	3.22	54.00

^a Intermediate solutions between $\mathbf{f}(t^2)$ and $\mathbf{f}(t^3)$

In the *1st classification*, as said, he wanted to obtain a better value to f_1 (aspiration level 0.70) and simultaneously maintain the good values of f_3 and f_4 (save the OARs). Thus, he set a bound to f_3^{bladder} , and an aspiration level to f_3^{rectum} . The bound and aspiration level both were 2.00. At the same time, he had to allow some other targets (f_2 and f_4) to get worse. That is, the classification was $f_1 : I^{\text{asp } 0.70}$, $f_2 : I^{\text{free}}$, $f_3^{\text{bladder}} : I^{\text{bound } 2.00}$, $f_3^{\text{rectum}} : I^{\text{asp } 2.00}$ and $f_4 : I^{\text{free}}$, and he wanted to generate one new solution (solutions are collected in Table 1). After the first classification, the decision maker obtained a better solution ($\mathbf{f}(t^2)$) because the rectum ($f_3^{\text{rectum}} = 2.74$), which he considered very important, obtained smaller dose value than in solution $\mathbf{f}(t^1)$, but still f_1 was too low according to his preferences. Because of this reason, he decided to do a *2nd classification* using the solution $\mathbf{f}(t^2)$ as a starting point of the classification. In this classification, the decision maker wanted to improve f_1 as much as possible, and again, he set a bound to f_3^{bladder} , and an aspiration level to f_3^{rectum} to maintain the good levels of these objectives. In addition, the decision maker allowed f_2 and f_4 to change freely. Therefore, the classification was $f_1 : I^{\text{imp}}$, $f_2 : I^{\text{free}}$, $f_3^{\text{bladder}} : I^{\text{bound } 2.00}$, $f_3^{\text{rectum}} : I^{\text{asp } 2.00}$ and $f_4 : I^{\text{free}}$. After the second classification, the decision maker obtained three new solutions having excellent f_1 values, but, at the same time, values of other objectives were not so good (Table 1). That is why he wanted to generate five *intermediate solutions* between the solutions $\mathbf{f}(t^2)$ and $\mathbf{f}(t^3)$, which had good values of objectives f_3^{bladder} and f_3^{rectum} , and f_1 , respectively. Intermediate solutions represent compromise solutions between the conflicting treatment planning targets, and the decision maker was

able to choose the best Pareto optimal solution according to his knowledge to be the final solution, i.e. the final treatment plan. That solution was $\mathbf{f}(t^9)$, in which the objective values were $f_1 = 0.73$, $f_2 = 10.50$, $f_3^{\text{bladder}} = 2.35$, $f_3^{\text{rectum}} = 3.15$ and $f_4 = 52.23$. As can be seen in Figs. 1 (left) and 2, all the requirements of the

Fig. 1 *Left*, the final dose distribution with interactive multiobjective optimization (solution $\mathbf{f}(t^9)$) from three different point of views (x , y , and z -direction), and *right*, for comparison, solution obtained with BrachyVision[®] optimization

Fig. 2 For comparison, dose volume histograms of OARs. Dose volume histogram values start to decrease faster in IND-NIMBUS solution than in solution obtained with Brachyvision[®]

treatment plan were taken into account as well as possible: harmful dose in rectum and bladder was minimized and the prescribed dose in the PTV was delivered. Thus, the treatment plan was clinically acceptable.

All the solutions obtained and steps taken by the decision maker during the solution process are collected in Table 1. In this table, the starting point of a new classification and the final solution are given in bold face. Let us add that a more thorough description of a typical process of classifying objective functions in a radiotherapy case and steering the optimization process is presented in Ruotsalainen et al. (2006).

3.2.2 Comparison and Discussion

In this example, we have shown how our interactive approach can handle the strongly conflicting objective functions in a cervix cancer case. As can be seen in Fig. 3 (a display of IND-NIMBUS software), the solutions obtained can be compared and carefully studied during the interactive solution process. Thus, the decision maker is better prepared to make the final decision, i.e. choose the final treatment plan, after analyzing the isodose maps (Fig. 1), dose volume histograms (Fig. 2), graphical information (Fig. 3), and numerical information (Table 1 and

Fig. 3 All the solution obtained during the optimization process can be compared also with a graphical tool in IND-NIMBUS. On the *left*, the final solution $\mathbf{f}(t^9)$ presented with bars describing objective function values, and, on the *right*, all 10 solutions generated. On the *lower-right*, best candidates, that is, solutions used in classifications and generating intermediate solutions

Fig. 3). Compared to the trial and error method or methods demanding a large database of Pareto optimal solutions, our approach makes treatment planning times shorter, and a good trade-offs between the objectives can be found to improve the treatment plan's quality. A good example of this trade-off information can be seen in Table 1: when comparing solutions $\mathbf{f}(t^1)$ and $\mathbf{f}(t^2)$, the dose in the rectum could be decreased without losing the target coverage, for example.

For comparison, in Figs. 1 (right) and 2, a treatment plan obtained with the BrachyVision[®] optimization tool is presented. Further, in Table 2, there are target's 90% dose value and OARs's 2 cm³ dose volume histogram point values presented. When comparing the two solutions, it can be seen from Fig. 2 that dose volume histogram values start to decrease faster in IND-NIMBUS solution than in BrachyVision[®] solution. However, from Table 2 we can see that dose (2 cm³) in bladder and rectum is smaller in solution obtained with BrachyVision[®], but, at the same time, the PTV (90%) is covered with radiation better and the dose in sigma (2 cm³) is smaller in the solution obtained with interactive multiobjective optimization. These results are one evidence more showing that the radiotherapy objectives are in conflict, and tools capable to help the decision maker (treatment planner) in navigating among different optimal treatment plans are needed.

Table 2 Comparison of target 90% values and OAR 2 cm³ values

	Interactive method (Gy)	BrachyVision [®] (Gy)
Target 90%	7.32	7.23
Bladder 2 cm ³	5.24	5.06
Rectum 2 cm ³	5.64	5.01
Sigma 2 cm ³	1.38	1.61

4 Conclusions

In this paper, we have presented a new interactive multiobjective optimization approach for anatomy based 3D HDR brachytherapy optimization. In this research, the multiobjective nature of the problem has been genuinely taken into account in the problem formulation and in the interactive solution process which was directed by a treatment planner. We have demonstrated the advantages of our interactive approach by an example of a clinical gynecologic cancer.

In this study, our interactive approach has been used to determine the dwell time values needed to fulfill the prescribed dose to the tumor and to minimize dose in each organ at risk. In our approach, the decision maker’s (i.e. treatment planner’s) knowledge and preferences are used during the iterative optimization process to direct the search in order to find the most preferred treatment plan. This can make treatment planning times shorter and improve the treatment plan’s quality. In addition, let us point out that our interactive approach is capable of handling multiple and strongly conflicting objectives in a convenient way, and thus, it offers a possibility to navigate among the obtained Pareto optimal solutions (i.e. different treatment plans).

In the presented example, there were 17 continuous decision variables and 508 sampling points. The amount of variables can easily be increased even to hundreds in more complex cases and there can be thousands of sampling points. In addition, there were only box constraints for variables. However, it is easy to add any other constraints to our interactive multiobjective optimization approach if needed. In addition, the idea of classifying objective functions is practical and computation is fast also with different numbers of objective functions. The number of objective functions can be increased, but naturally the cognitive load of the decision maker increases.

Finally, let us add that this approach brings the planning process near to the real clinical issues: with this system, the treatment planner plays directly with the compromises between a target coverage and protection of organs at risk instead of with dwell positions, dwell times, and objective weights. Whenever a trial-and-error method is used, there are no guarantees for the (Pareto) *optimality* of the final solution. Opposite to this, our approach avoids this shortcoming. These kinds of tools are not intended to replace human treatment planners, but to support them in their work.

References

- Craft D, Bortfeld T (2008) How many plans are needed in an IMRT multi-objective plan database? *Phys Med Biol* 53:2785–2796
- Craft D, Halabi T, Bortfeld T (2005) Exploration of tradeoffs in intensity-modulated radiotherapy. *Phys Med Biol* 50:5857–5868
- Craft D, Halabi T, Shih HA, Bortfeld T (2007) An approach for practical multiobjective IMRT treatment planning. *Int J Radiat Oncol Biol Phys* 69:1600–1607
- Ehrgott M, Wenz I (2008) Interactive decision support in radiotherapy treatment planning. *OR Spectrum* 30:311–329
- Hoffmann AL, Siem AYD, den Hertog D, Kaanders JHAM, Huizenga H (2006) Derivate-free generation and interpolation of convex Pareto optimal IMRT plans. *Phys Med Biol* 51:6349–6369
- Holder A (2006) Partitioning multiple objective optimal solutions with applications in radiotherapy design. *Optim Eng* 7:501–526
- Lahanas M, Baltas D (2003) Are dose calculations during dose optimization in brachytherapy necessary? *Med Phys* 30(9):2368–2375
- Lahanas M, Baltas D, Zamboglou N (1999) Anatomy-based three-dimensional dose optimization in brachytherapy using multiobjective genetic algorithms. *Med Phys* 26:1904–1918
- Lahanas M, Milickovic N, Papagiannopoulou M, Baltas D, Zamboglou N, Karouzakis K (2001) Application of a hybrid version of NSGA-II for multiobjective dose optimization in brachytherapy. In: Giannakoglou KC, Tsahalis DT, Périaux J, Papailiou KD, Fogarty T (eds) *Evolutionary methods for design, optimization and control with applications to industrial problems*. International Center for Numerical Methods in Engineering (CIMNE), Athens, Greece, pp 299–304
- Lahanas M, Baltas D, Giannouli S (2003a) Global convergence analysis of fast multiobjective gradient based dose optimization algorithms for high dose rate brachytherapy. *Phys Med Biol* 48:599–617
- Lahanas M, Baltas D, Zamboglou N (2003b) A hybrid evolutionary algorithm for multiobjective anatomy based dose optimization in HDR brachytherapy. *Phys Med Biol* 48:399–415
- Larichev O (1992) Cognitive validity in design of decision aiding techniques. *J Multicriteria Decis Anal* 1:127–138
- Lessard E, Pouliot J (2001) Inverse planning anatomy-based dose optimization for HDR-brachytherapy of the prostate using fast simulated annealing algorithm and dedicated objective function. *Med Phys* 28:773–779
- Lessard E, Hsu I, Pouliot J (2002) Inverse planning for interstitial gynecologic template brachytherapy: truly anatomy-based planning. *Int J Rad Oncol Biol Phys* 54:1243–1251
- Lessard E, Hsu I, Aubry J, Pouliot J (2006) SU-FF-T-337: multiobjective inverse planning optimization: adjustment of dose homogeneity and urethra protection in HDR-brachytherapy of the prostate. *Med Phys* 33:2124
- Miettinen K (1999) *Nonlinear multiobjective optimization*. Kluwer, Boston
- Miettinen K (2006) IND-NIMBUS for demanding interactive multiobjective optimization. In: Trzaskalik T (ed) *Multiple criteria decision making '05*. The Karol Adamiecki University of Economics, Katowice, pp 137–150
- Miettinen K, Mäkelä MM (1995) Interactive bundle-based method for nondifferentiable multiobjective optimization: NIMBUS. *Optimization* 34:231–246
- Miettinen K, Mäkelä MM (2002) On scalarizing functions in multiobjective optimization. *OR Spectrum* 24:193–213
- Miettinen K, Mäkelä MM (2006) Synchronous approach in interactive multiobjective optimization. *Eur J Oper Res* 170:909–922
- Milickovic N, Lahanas M, Papagiannopoulou M, Baltas D, Zamboglou N, Karouzakis K (2001) Application of multiobjective genetic algorithms in anatomy based dose optimization in brachytherapy and its comparison with deterministic algorithms. In: Giannakoglou KC, Tsahalis DT, Périaux J, Papailiou KD, Fogarty T (eds) *Evolutionary methods for design,*

- optimization and control with applications to industrial problems. International Center for Numerical Methods in Engineering (CIMNE), Athens, Greece, pp 293–298
- Milickovic N, Lahanas M, Papagiannopoulou M, Zamboglou N, Baltas D (2002) Multiobjective anatomy-based dose optimization for HDR-brachytherapy with constraint free deterministic algorithms. *Phys Med Biol* 47:2263–2280
- Monz M, Küfer KH, Bortfeld TR, Thieke C (2008) Pareto navigation – algorithmic foundation of interactive multi-criteria IMRT planning. *Phys Med Biol* 53:985–998
- Nath R, Anderson LL, Luxton G, Weaver KA, Williamson JF, Meigooni AS (1995) Dosimetry of interstitial brachytherapy sources: recommendations of the AAPM radiation therapy committee task group no. 43. *Med Phys* 22:209–234
- Rivard MJ, Coursey BM, DeWerd LA, Hanson WF, Saiful Huq M, Ibbott GS, Mitch MG, Nath R, Williamson JF (2004) Update of AAPM task group no. 43 report: a revised AAPM protocol for brachytherapy dose calculations. *Med Phys* 31:633–674
- Romeijn HE, Dempsey JF, Li JG (2004) A unifying framework for multi-criteria fluence map optimization models. *Phys Med Biol* 49:1991–2013
- Ruotsalainen H, Boman E, Miettinen K, Hämäläinen J (2006) Interactive multiobjective optimization for IMRT. Working Papers W-409. <http://hsepubl.lib.hse.fi/pdf/wp/w409.pdf>
- Thieke C, Küfer KH, Monz M, Scherrer A, Alonso F, Oelfke U, Huber PE, Debus J, Bortfeld T (2007) A new concept for interactive radiotherapy planning with multicriteria optimization: first clinical evaluation. *Radiother Oncol* 85:292–298
- Yu Y (1997) Multiobjective decision theory for computational optimization in radiation therapy. *Med Phys* 24:1445–1454
- Yu Y, Zhang JB, Cheng G, Schell MC, Okunieff P (2000) Multi-objective optimization in radiotherapy: applications to stereotactic radiosurgery and prostate brachytherapy. *Artif Intell Med* 19:39–51