# Radiation Therapy Planning by Multicriteria Optimisation

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**Abstract**

Radiation is one of the major forms of treatment in cancer therapy besides chemotherapy and surgery. The determination of a treatment plan is a complex task that involves finding directions of beams, beam intensities and a realisation of optimal intensities on the equipment. In this talk we focus on determination of beam intensities. Dose distributions must satisfy the conflicting goals of effectively destroying the tumour while at the same time avoiding dangerous overdosing in surrounding tissue and organs at risk. We present a multicriteria model of the problem and show how to find a solution in which deviations from prescribed dose levels is balanced for all organs under consideration. Such a solution can serve as a starting point for the search for a best treatment plan among a pre-computed representative set of "efficient" solutions in an on-line database environment.

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## 1 Introduction

Every year hundreds of thousands of patients around the world are diagnosed with cancer. About 50% of them receive radiation therapy, one of the three major forms of treatment besides surgery and chemotherapy. Radiotherapy is particularly useful, when the tumour is restricted to its primary site (no metastases) or when the site is inaccessible for surgery (brain tumours). Nevertheless, about one third of patients with forms of cancer that are deemed curable die with primary tumours still active at the original site.

Why does this occur? Radiation therapy planning has to find a precarious balance between ineffective underdosing of the tumour (the target volume) and dangerous overdosing of surrounding tissue (organs at risk). Current planning tools appear to be inadequate for achieving these conflicting goals.

Treatment plans are commonly based on desired dose levels, which are specified for the tumour and each organ at risk. These desired dose levels are chosen so that a high tumour control probability is realised (lower bound on dose levels in tumour cells), but also that probability of complications in any organ at risk is low (upper bound on dose level in healthy tissue). Desired dose levels (bounds) are specified in terms of the equivalent uniform dose (EUD), which is defined as that uniform dose in any given organ which has the same (harmful or beneficial) effect as the actual inhomogeneous dose that is delivered by radiation therapy equipment. The EUD can be determined based on organ structure using simulation methods and historical data [8]. A treatment plan is realised by irradiation from several directions using different intensity profiles.

Beams are focused on the centre of the tumour (isocentric geometry). This is illustrated in Figure 1.

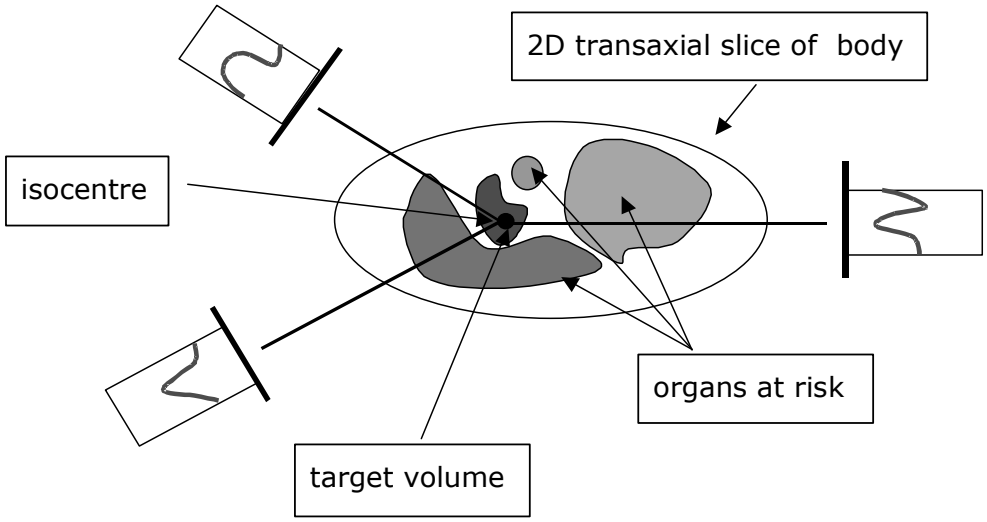


Figure 1: Illustration of the radiation therapy planning problem.[1]

Unfortunately, it is in general not possible to find a treatment plan, which satisfies all desired dose levels simultaneously. Therefore, some compromise between underdosing the target volume and overdosing the organs at risk has to be found. Mathematically, the problem can be formulated as an optimisation model to minimise functions of the deviation from desired dose levels. A satisfactory plan found by solving this problem yields beam intensities which are implemented on the radiation treatment equipment using multi-leaf collimators. [2] gives a survey on available methods.

In this paper, we present a multicriteria optimisation model for the radiation therapy treatment planning problem, which takes the inherently contradictory nature of the goals of the problem into account. This model has a set of "efficient" solutions rather than a single optimal solution. Each of these can be a candidate for a final plan to be chosen for the treatment. It is the task of the physician to search among the efficient plans. The main goal of the paper is to describe how a balanced solution of the problem can be found. Such a solution is often clinically relevant and will be located at the "centre" of the range of possible plans, so that it is very well suited as a starting point for the exploration of the efficient solutions.

## 2 Mathematical Model

In order to present our model, we first need to describe some fundamental assumptions. We will use a discretisation both of the body and the beams into equidistant volume elements "voxels" and beam elements "bixels", respectively. The discretisation of the body is based on MRI or CT scans. Let us assume that we have $K$ body parts, where $k = 1$ indicates the tumour and $k = 2, ..., K$ indicate organs at risk. Typically, $K$ will be of the order 3 to 7. Let $M = M_1 + ... + M_K$ be the number of voxels, where $M_k$ is the number of voxels in body part $k$, and let $N$ be the number of bixels ($N$ is equal to the

[1] Reproduced with permission from a presentation by Dr K.H. Küfer, Institut für Techno- und Wirtschaftsmathematik (ITWM), Kaiserslautern, Germany

number of irradiation directions multiplied by the number of bixels in the beam head). We shall assume that the directions are given and that an isocentric set-up is used. The dose distribution in the body is then described by a $K$-dimensional vector $D$. An $N$-dimensional beam intensity vector $x$ describes the intensity in each individual bixel and thus the intensity profiles applied from each direction. The discretisation is illustrated in Figure 2.

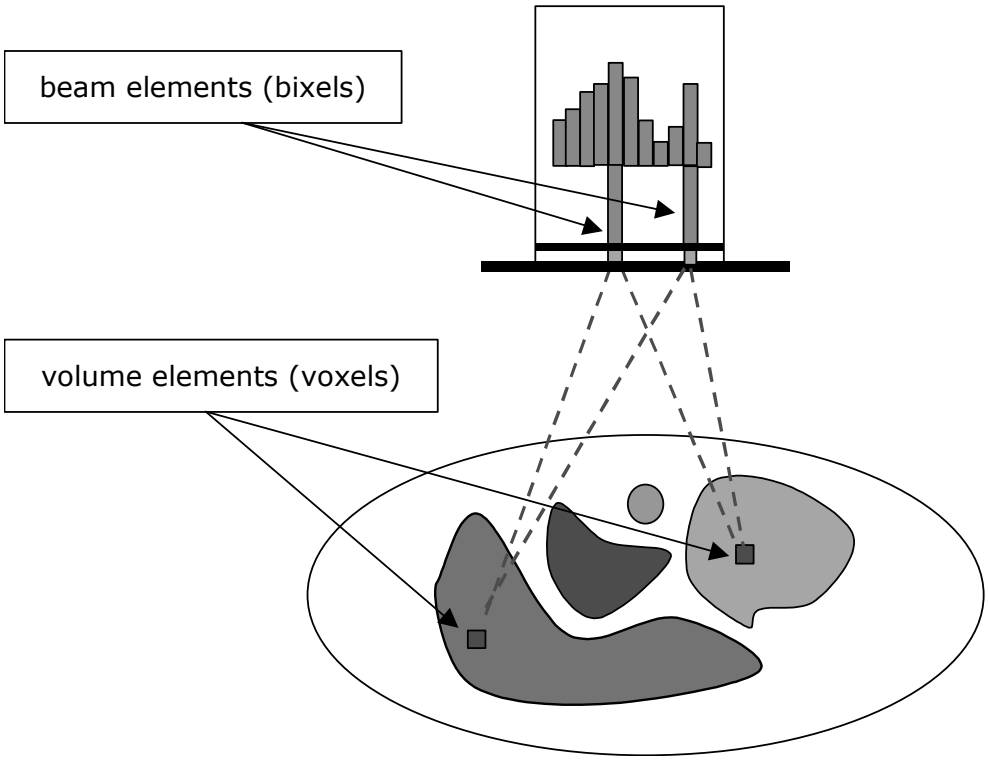


Figure 2: Discretisation of beams and body.[2]

$D$ can be calculated as

$$D=Px, \tag{1}$$

where $P$ is a matrix such that $p_{ij}$ denotes the dose in voxel $i$ resulting from unit intensity in bixel $j$. This commonly-used linear relationship is an approximation of the true behaviour of radiation [9]. $P$ depends on the energy spectrum of the radiation.

Equation (1) can also be rewritten for each body part $k$ as $D_k = P_k x$. For desired EUD levels $L_1$ (lower bound for the tumour) and $U_k$, $k = 2, \ldots K$, the problem of radiation therapy planning is to find an intensity profile vector $x$, which satisfies $P_1 x = D_1 \geq L_1 e$ and $P_k x = D_k \leq U_k e$, $k=2, \ldots, K$. As we pointed out earlier, such an $x$ does usually not exist.

It is therefore necessary to measure the deviation between actual and desired dose levels, which should be minimised. One possible way of doing this is to define

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$T_1(x) := (|| (L_1 e - D_1)_+ ||_2)^2$
$T_k(x) := (|| (D_k e - U_k)_+ ||_2)^2$, $k=2, ..., K$,

as the squared norm of deviation below the lower bound for the tumour and of deviation above the upper bound for organs at risk. Here $e$ represents a vector $e = (1, ..., 1)$ of appropriate dimension. Using thsi definition we can solve the nonlinear programming problem

$$\text{Min } F(x) = \mu_1 T_1(x) + \mu_2 T_2(x) + \ldots + \mu_K T_K(x), \text{ subject to } x \geq 0 \quad (2)$$

where the parameters $\mu_1, ..., \mu_K$ indicate relative importance of tumour and organs at risk [1].

Although used in current radiation therapy planning systems, this model has several drawbacks. The first is the use of the Euclidean norm. The Euclidean norm allows the averaging out of large deviations on a small volume by small or no deviations on a large volume. This is clearly undesirable for many organs (e.g. spinal chord, liver). It seems to be more reasonable to use the maximum norm or the max-and-mean model of [8]. Although the planning problem is formulated as an optimisation problem, this approach still involves a time-consuming trial and error search: Parameters $\mu_1, ..., \mu_K$ have to be fixed before the optimisation. Initially, values taken from a similar case might be used. If the resulting plan is unsatisfactory, a new set of parameters has to be specified and the process is repeated until a solution is considered good enough. This process is time consuming and does not even guarantee that a best plan has finally been chosen, as a lot of possible plans have never been explored.

In the next section we present an alternative model, based on multicriteria optimisation, in particular multiobjective linear programming (MOLP).

## 3 The Multicriteria Approach

The idea to use a multicriteria approach is a direct consequence from the observation that achieving high dose levels in the tumour whilst keeping levels in surrounding organs at risk low are contradictory objectives. In an appropriate model we should strive to minimise deviations from desired dose levels in every body part under consideration separately. The model presented here, on which our work is based, was first proposed in [5]. In a first step, we replace the inconsistent system

$D_1 = P_1 x \geq L_1 e$
$D_k = P_k x \leq U_k e$, $k=2, \ldots, K$,
$x \geq 0$,

with one that is always consistent:

$$\begin{aligned} &D_1 = P_1 x \geq L_1(e - t_1) \\ &D_k = P_k x \leq U_k(e + t_k), \; k=2, ..., K \\ &x \geq 0 \\ &t_1, t_2, t_3, \ldots, t_K \geq 0 \end{aligned} \quad (3)$$

Variables $t_1, \ldots, t_K$ are vectors of the same dimension as $D_1, \ldots, D_k$ and denote deviation from desired dose levels voxel by voxel. With $x = 0$, $t_1 = e$, and $t_k = 0$, $k = 2, \ldots, K$, (3) is always feasible. The maximal deviation for each organ is now simply the largest entry in each $t_k$ vector. We can therefore define $T_k = ||t_k||_\infty = ||(D_k - L_k)_+||_\infty$. The multicriteria optimisation model based on maximal deviations from desired dose levels in each organ is then

$$\text{Min } T = (T_1, \ldots, T_K)$$

subject to the constraints (3), in which the $t_k$ can be replaced by $T_k e$, and nonnegativity is imposed on $T_k$. This is a multiobjective linear programme which is always feasible. In a multicriteria optimisation problem, optimal solutions are replaced by so called efficient or Pareto optimal solutions. A solution is efficient if there is no other solution which is at least as good for all objectives and strictly better for at least one. In the context of the radiation therapy problem, this means that in an efficient solution the deviation from desired dose levels for one organ can only be improved ($T_k$ decreased) if at the same time the deviation for at least one other body part is worsened ($T_k$ increased). Consequently an efficient solution is a candidate for final implementation, and the final solution has to be chosen from the set of all efficient solutions.

In fact, there are additional constraints that ensure a certain degree of homogeneity of the dose distribution in the tumour and that allow to specify percentages of the volumes of entities considered to exceed desired dose levels by a given percentage amount. These are not essential for the methodological development in this paper and left out. Details can be found in [5].

The next question to be addressed is how to technically solve the multicriteria LP. Multicriteria extensions of the Simplex methods are well known in the literature [7]. It is also interesting to note that the set of efficient solutions is identical with the set of optimal solutions of scalarised problems

$$\text{Min } \mu_1 T_1 + \ldots + \mu_K T_K$$

under the same constraints, for all possible choices of strictly positive weights $\mu_k$. (This is also true for the nonlinear but convex problem (2). For that case, however, algorithms to detect all efficient solutions are not known.)

These results are of a theoretical interest rather than of practical relevance for the problem. Due to the size of the MOLP (about 7 objectives (organs), hundreds of variables (bixels), and thousands of constraints (voxels)) there are an enormous number of efficient extreme points. It is a huge computational effort to evaluate them all and store them for later investigation. In addition, many of them are almost identical and not really different from a practical point of view. It is therefore reasonable to consider a representative subset of efficient solutions which covers the whole range of efficient solutions, but which contains only solutions which are noticeably different from each other. Hamacher and Küfer [5] describe one idea to generate a representative subset based on a concept of neighbour solutions.

This representative subset can be stored and accessed by the physician in an online interactive process. A starting solution will be presented together with a control panel which allows the physician to specify those body parts for which improvement is desired and those for which deteroration is acceptable. The efficient solution

corresponding to these requirements can then be retrieved from the database of representative solutions and displayed visually. This process continues until a satisfactory solution is found. This process avoids the time consuming trial-and-error approach of current systems and allows perusal of the whole range of possibilities for an efficient treatment plan.

In the following section we describe an approach to generate a solution which will serve as a good starting solution for the interactive phase of the treatment plan selection process. This solution can be characterised as unbiased or balanced, as deviation from desired dose levels will be as equal as possible. This solution is located "centrally" in the set of efficient solutions rather than at the extreme ends, where one $T_k$ value is large while others are very small. Therefore it tends to shorten the search process and is also often itself a clinically relevant solution.

## 4 Finding a Balanced Solution

In this section we describe how to find a balanced solution of the inverse problem of radiation therapy planning. "Balanced" means achieving similar deviations from desired dose levels in all organs rather than achieving desired dose levels in one organ while others are far form desired bounds. This work has been carried out by the second author as a Year 4 Project in Engineering Science [3].

One might assume that this can be achieved with equal weights $\mu_k = 1/K$ for all body parts. This is not true, however, as the example presented later will show. This effect is partly caused by the influence of the irradiation geometry. If one irradiation direction centrally intersects an organ at risk, this organ is always more affected than one that is only marginally or not at all in the way of a beam direction. These effects of the set-up geometry are difficult to capture in the weights and illustrate the necessity of a careful selection of irradiation directions. The selection of beam directions is another aspect of the problem that gives rise to an optimisation problem which, however, is beyond the scope of this paper.

An unbiased solution will not have extremely high deviations in any one organ combined with no or small deviation occurring in others. To achieve this we minimise the largest of the deviation values $T_k$ using a minimax model:

$$\begin{aligned} &\text{Min Max } \{T_1, \ldots T_K\} \\ &D_1 = P_1 x \geq (L_1 - T_1)e \\ &D_k = P_k x \leq (U_k + T_k)e,\ k = 2, \ldots, K \\ &x \geq 0 \\ &T_1, \ldots, T_K \geq 0 \end{aligned} \tag{4}$$

However, an optimal solution of this problem need not be efficient (consider vectors (5,4,3) and (5,4,5), for example). Clearly we also require a solution which is efficient (thus avoiding (5,4,5) in the example). To obtain an efficient solution from the minimax problem we need to consider second largest, third largest values, etc. in case of ties. This extended minimax concept is known as lexicographic max-ordering in multicriteria optimisation [4].

Let $T = (T_1, \ldots T_K)$ be a vector. Then define $\theta(T) = (\theta_1(T), \ldots, \theta_K(T))$ as the ordered version of $T$: $\theta_1(T) \geq \theta_2(T) \geq \ldots \geq \theta_K(T)$. The problem to consider the individual values $T_k$ in an ordered sequence for minimisation is then formulated as

Lexmin $\theta(T)$ subject to the constraints in (4).

Lexicographic max-ordering guarantees to find an efficient solution and has several other desirable properties as discussed in [4]. From an implementation point of view, we need an additional variable $W$ to control the $T_k$ values. The lexicographic minimum is obtained through a sequence of optimisation problems. The first solves the minimax problem as follows:

$$
\begin{aligned}
&\text{Min } W \\
&D_1 = P_1 x \geq (L_1 - T_1)e \\
&D_k = P_k x \leq (U_k + T_k)e,\ k = 2, \ldots, K \\
&x \geq 0 \\
&T_1, \ldots, T_K \geq 0 \\
&W \geq T_k,\ k = 1, \ldots, K
\end{aligned}
\qquad (5)
$$

Assume that an optimal solution $T^* = (T_1^*, \ldots, T_j^*, \ldots, T_K^*)$ of (5) is found. We then identify the index j of the largest $T_k^*$ value and the corresponding constraint $W \geq T_j^*$ is replaced by $W = T_j^*$ (see [6] for details). This process is repeated $K$ times.

This approach was implemented and results compared with those obtained by scalarisation of the MOLP with equal weights. Below we show an example of a tumour in the nasal cavity with the organs at risk being left and right eyeballs and optical nerves. Desired dose levels are 10 grey for both organs at risk and 30 grey for the tumour. Figure 3 shows the result of the lexicographic max-ordering solution and corresponding deviation values. The picture illustrates the isodose curves resulting from the beam intensities that were obtained by solving the lexicographic max-ordering problem to find a balanced solution. Deviations from desired dose levels are colour coded using percentages, e.g. red in the tumour (tu) means at most 90% of the desired does was achieved, blue in an organ at risk (h1, h2) means up to 80% of the (maximal) dose level was achieved. Thus red and orange indicate violations of bounds, and blue and green indicate that dose bounds have been respected.

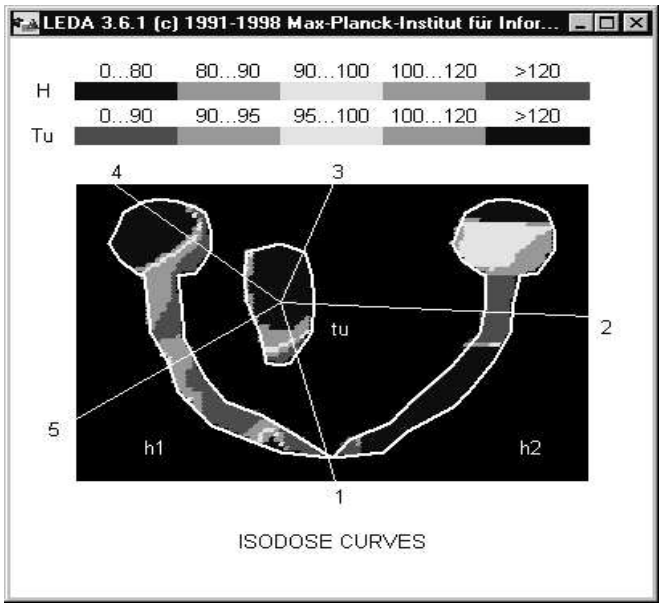


Figure 3: Balanced solution of example problem, T=(4.1,4.1,4.1).

Figure 4 shows a sequence of dose distribution diagrams obtained by the MOLP model using equal weights $\mu_k = 1/3$ to obtain the first solution. The first solution gives T=(11.68,0,0), i.e. deviations from required levels are very uneven despite the equal weights. In particular, the deviation in the tumour is large (cf. the red area in the tumour in the first picture). The subsequent pictures show two dose distributions obtained using the neighbour solution representation of [5], where the tumour was chosen as the organ for which improvement is desired, and results for both organs at risk were allowed to deteriorate. Additional steps through neighbour solutions are needed to achieve the levels of the balanced solution. It is obvious that starting from the balanced solution the search process can be expected to be much faster than from a solution obtained from a scalarisation of the MOLP model.

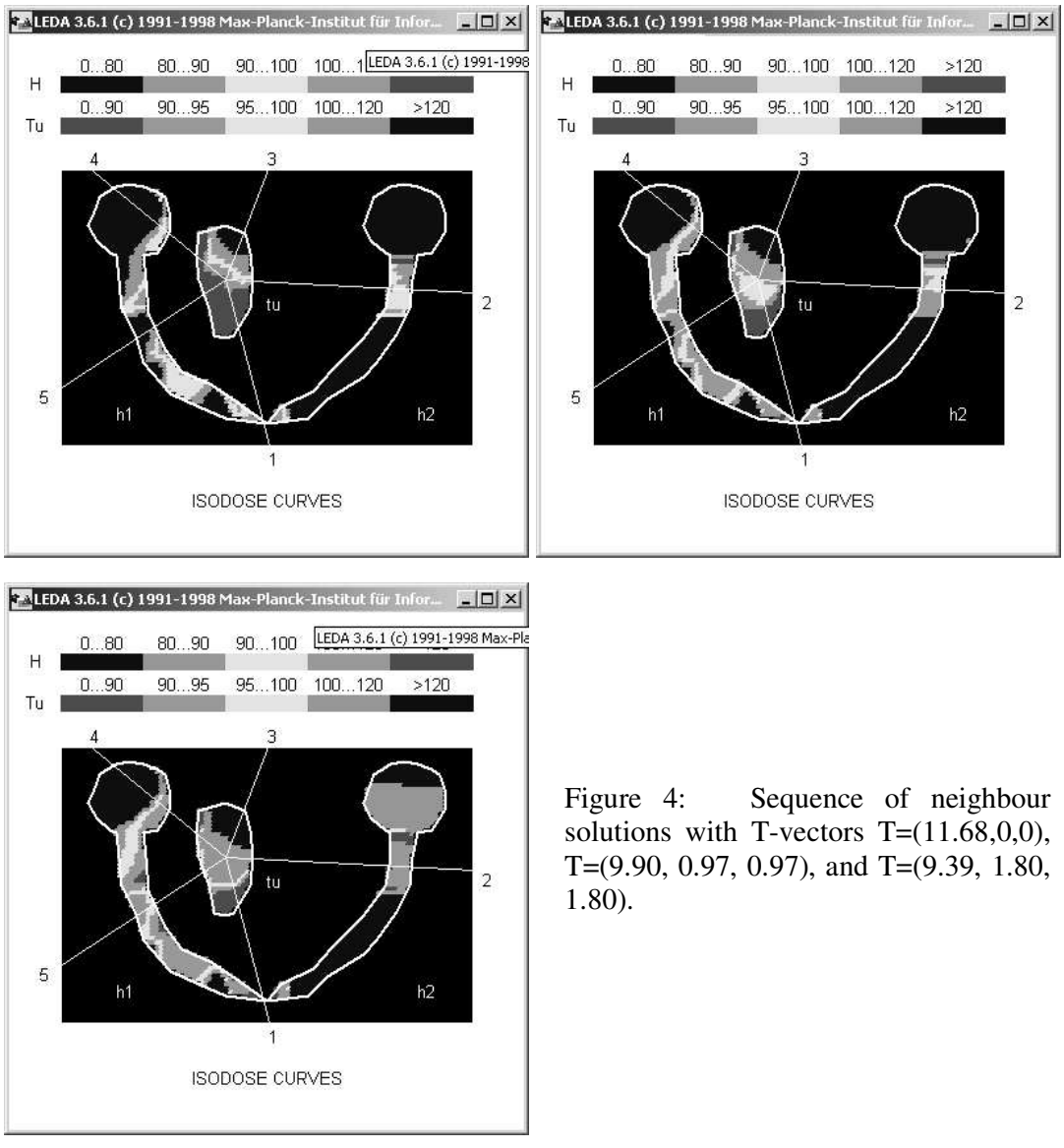


Figure 4: Sequence of neighbour solutions with T-vectors T=(11.68,0,0), T=(9.90, 0.97, 0.97), and T=(9.39, 1.80, 1.80).

## 5 Conclusions and Future Research

In this paper we have shown that a multicriteria optimisation approach is an appropriate tool to solve the inverse planning problem of radiation therapy treatment. Through explicit consideration of the contradictory objectives of maximising tumour control whilst minimising harmful effects on surrounding tissue the approach captures the

problem structure better than previous models. It allows an exploration of the whole range of possibly efficient solutions (which are the only ones relevant for the final choice of treatment plan) by separating the computation phase, which does not need interaction and can be carried out off-line, and the selection phase, which requires interaction with physician and/or dosimetrist. In this phase the pre-computed representative set of solutions can easily be accessed using a database environment. Visual aids help assessment of solutions and navigation among solutions. Considerable gains in the quality of the planning process can be expected. We presented the lexicographic extension of the minimax problem as a tool to find an unbalanced solution from which the search process can be started. The search process can be speeded up considerably using this approach.

In future research we will investigate the problem of finding a representation of the set of efficient solutions. This topic has received little attention in the multicriteria optimisation literature. It is, however, key to the success of the proposed methodology. Other topics that need further attention are the navigation among the set of representative solutions: given the desired changes from a current plan, one that best matches the requested changes needs to be found. Interactive methods of multicriteria decision aid provide appropriate tools. There are other optimisation problems related to radiation therapy planning: In a phase prior to determination of optimal beam intensities a set-up geometry needs to be (optimally) chosen. We assumed the geometry to be fixed in our model in this paper. Finally, the realisation of beam intensities on multi-leaf collimators has to be addressed. Integer programming models can be used. Solving these problems individually provides considerable challenges for the application of optimisation methods. As all three problems are closely interrelated, however, an integrated model should be the ultimate goal.

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