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Vorwort

Das Tätigkeitsfeld des Fraunhofer-Instituts für Techno- und Wirtschaftsmathematik ITWM umfasst anwendungsnahe Grundlagenforschung, angewandte Forschung sowie Beratung und kundenspezifische Lösungen auf allen Gebieten, die für Techno- und Wirtschaftsmathematik bedeutsam sind.

In der Reihe »Berichte des Fraunhofer ITWM« soll die Arbeit des Instituts kontinuierlich einer interessierten Öffentlichkeit in Industrie, Wirtschaft und Wissenschaft vorgestellt werden. Durch die enge Verzahnung mit dem Fachbereich Mathematik der Universität Kaiserslautern sowie durch zahlreiche Kooperationen mit internationalen Institutionen und Hochschulen in den Bereichen Ausbildung und Forschung ist ein großes Potenzial für Forschungsberichte vorhanden. In die Berichtreihe sollen sowohl hervorragende Diplom- und Projektarbeiten und Dissertationen als auch Forschungsberichte der Institutsmitarbeiter und Institutsgäste zu aktuellen Fragen der Techno- und Wirtschaftsmathematik aufgenommen werden.

Darüber hinaus bietet die Reihe ein Forum für die Berichterstattung über die zahlreichen Kooperationsprojekte des Instituts mit Partnern aus Industrie und Wirtschaft.

Berichterstattung heißt hier Dokumentation des Transfers aktueller Ergebnisse aus mathematischer Forschungs- und Entwicklungsarbeit in industrielle Anwendungen und Softwareprodukte – und umgekehrt, denn Probleme der Praxis generieren neue interessante mathematische Fragestellungen.

Prof. Dr. Dieter Prätzel-Wolters
Institutsleiter

Kaiserslautern, im Juni 2001

On the role of modeling parameters in IMRT plan optimization

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Abstract. Modeling and formulation of optimization problems in IMRT planning comprises the choice of various values such as function-specific parameters or constraint bounds. These values also affect the characteristics of the optimization problem and thus the form of the resulting optimal plans. This publication utilizes concepts of sensitivity analysis and elasticity in convex optimization to analyze the dependence of optimal plans on the modeling parameters. It also derives general rules of thumb how to choose and modify the parameters in order to obtain the desired IMRT plan. These rules are numerically validated for an exemplary IMRT planning problems.

AMS classification scheme numbers: 49K40, 90C25, 90C31, 90C90

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1. Introduction

1.1. Intensity modulated radiotherapy planning

The main goal of intensity modulated radiation therapy planning is to find a treatment plan that realizes sufficiently high doses in the tumor structures in order to destroy the cancerous cells with a high probability while keeping the dose deposit in the healthy structures reasonably low to bound the risk of future complications. A treatment plan is characterized by some configuration $\boldsymbol{x}$ of parameters like intensity values or beam positions, and its dose distribution $\boldsymbol{d}(\boldsymbol{x})$ is represented by dose values corresponding to the elements of a volume discretization. The large number of plan parameters and dose values makes a formulation as an optimization problem clearly favorable. For this purpose, the assessment of a dose distribution $\boldsymbol{d}$ with respect to planning structures is modeled with evaluation functions f. Reformulation of the planner's strict requirements on the dose distribution and aspired planning objectives with respect to these evaluation functions yields the optimization problem of intensity modulated radiotherapy planning.

1.2. The role of the modeling parameters

The many evaluation functions used in planning practice trace back to comparably few different types of functions, that just differ in the function parameters chosen according to the corresponding planning structures [Romeijn *et al.*, 2004].
In some software tools for IMRT planning, these function parameters are set to empirically derived default values. In some others, their individual choice is up to the physical planner, who will in general use well-approved values obtained from statistical analysis over many planning cases [Niemierko, 2006]. Both approaches suffer of some uncertainty in the exact choice of function parameters. This also affects the interpretation of the resulting function values $f(\boldsymbol{d})$.
The numerical solution of the IMRT planning problem also requires the reduction of a complex shaped dose distribution to a single value representing its radiobiological impact on a planning structure. This complicates the choice of appropriate value bounds and reference values to represent strict planning requirements and aspired planning objectives even more.
All these modeling parameters affect the optimization problem of IMRT planning and thus the resulting optimal treatment plan. This implies the following questions:

- Is the treatment plan sufficiently robust with respect to the parameter choice to compensate for the uncertainties in the choice of parameters, that is how does it vary under slight parameter changes?
- What is the influence of each modeling parameter on the treatment plan, that is how strongly does it depend on the individually chosen values?

This publication addresses these questions with the mathematical concepts of sensitivity and elasticity from convex optimization. These concepts allow for a profound

mathematical analysis, which provides clear statements about the importance of the different modeling parameters and simple rules of thumb for their appropriate choice.

2. Material and methods

2.1. Terminology and notation

Denote the volume elements (voxels) obtained from the discretization of the considered body volume by V_j ($j \in \mathcal{J}$), and represent dose distributions by the vectors

$$\boldsymbol{d} = (d(V_j))_{j\in\mathcal{J}} \in \mathbb{R}^{|\mathcal{J}|}$$

of corresponding dose values. Let the positions and geometry of the emitting beams be given. Treatment plans are then represented by the vectors

$$\mathbf{o} \leq \boldsymbol{x} = (x_i)_{i\in\mathcal{I}} \in \mathbb{R}^{|\mathcal{I}|},$$

where the value x_i represents the radiation emitted through the ith beamlet. For radiation modalities with linearly superposing dose absorption such as photons, the dose distribution corresponding to a treatment plan is then obtained with the linear *dose mapping*

$$\boldsymbol{d}: \ \boldsymbol{x} \ \longmapsto \ \boldsymbol{d}(\boldsymbol{x}) := \mathbf{P}\cdot\boldsymbol{x} = (\boldsymbol{p}(V_j))_{j\in\mathcal{J}}\cdot\boldsymbol{x}.$$

The row vectors $\boldsymbol{p}(V_j) = (p_i(V_j))_{i\in\mathcal{I}} \in \mathbb{R}^{1\times|\mathcal{I}|}$ describe the dose deposits for each unit of radiation $x_i = 1$ in the corresponding voxels V_j. The matrix $\mathbf{P} \in \mathbb{R}^{|\mathcal{J}|\times|\mathcal{I}|}$ thus describes the whole dose mapping and is therefore called the *dose information*.
Let each of the involved planning structures be given as a family of voxels V_j ($j \in \mathcal{J}'$), where $\mathcal{J}' \subseteq \mathcal{J}$. The quality of a dose distribution with respect to a planning structure is modeled by an *evaluation function*

$$\begin{aligned} f : \mathbb{R}^{|\mathcal{J}'|} &\longrightarrow \mathbb{R}, \\ \boldsymbol{d} \quad &\longmapsto f(\boldsymbol{d}), \end{aligned}$$

which is required to be convex and twice continuously differentiable in this context. For example, the following functions, which are well established in planning practice, fulfill these requirements:

- The radiobiological impact on a planning structure can be measured using the equivalent uniform dose (EUD) concept of Niemierko [Niemierko, 1999],
$$f_{\mathrm{EUD}}(\boldsymbol{d}) = \Big(\Big(\sum_{j\in\mathcal{J}'}|V_j|\Big)^{-1}\cdot\sum_{j\in\mathcal{J}'}|V_j|\cdot d(V_j)^{q_{\mathrm{EUD}}}\Big)^{q_{\mathrm{EUD}}^{-1}}, \tag{1}$$
where $|V_j|$ denotes the voxel volume and the parameter q_{EUD} is chosen 2 or larger for risk structures and less than 0 for target structures;
- The average underdose of a target structure below a certain dose value d_{under} can be measured with the function
$$f_{\mathrm{under}}(\boldsymbol{d}) = \Big(\Big(\sum_{j\in\mathcal{J}'}|V_j|\Big)^{-1}\cdot\sum_{j\in\mathcal{J}'}|V_j|\cdot\max\{0, d_{\mathrm{under}} - d(V_j)\}^{q_{\mathrm{under}}}\Big)^{q_{\mathrm{under}}^{-1}} \tag{2}$$
with $q_{\mathrm{under}} \geq 2$.

- The average exceedance of a certain dose value d_{over} in a planning structure, for example the inhomogeneity in a target structure, can be measured with the function

$$f_{\text{over}}(\boldsymbol{d}) = ((\sum_{j\in\mathcal{J}'}|V_j|)^{-1}\cdot\sum_{j\in\mathcal{J}'}|V_j|\cdot\max\{0,d(V_j)-d_{\text{over}}\}^{q_{\text{over}}})^{q_{\text{over}}^{-1}} \quad (3)$$

  with $q_{\text{over}}\geq 2$.

All these functions are of a very general form, but their individual characteristics may strongly depend on the individual choice of function parameters.

2.2. An exemplary IMRT optimization problem

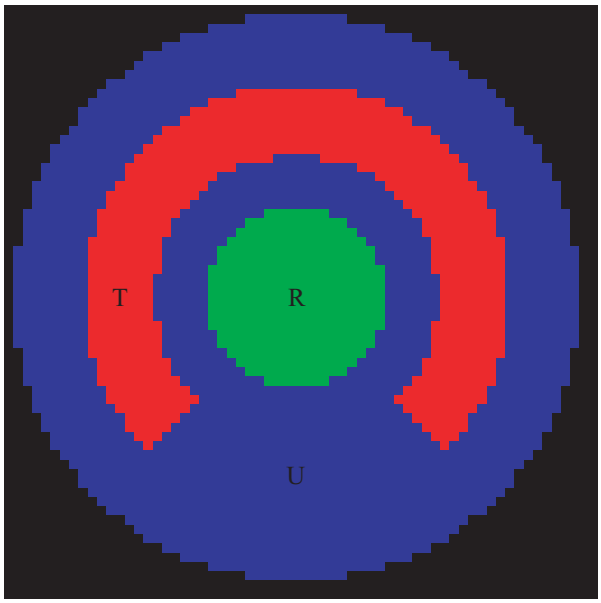

Figure 1. An exemplary horse shoe target case

Consider the following exemplary IMRT planning problem of a horse shoe target case as shown in Figure 1. The planning goal is to reduce the dose deposit in the risk structure as much as possible while simultaneously fulfilling the strict planning requirements of a sufficient high dose level in the surrounding target structure and keeping the inhomogeneities in the target structure and the high dose deposits in the remaining unclassified tissue acceptably low. The beam setup consists of five equidistantly located positions at 0, 72, 144, 216 and 288 degrees with 63 beamlets altogether. The corresponding optimization problem could then attain the form

$$\begin{aligned} f_{\text{EUD,R}}(\boldsymbol{d}(\boldsymbol{x})) &\rightarrow \min \quad s.t. \\ f_{\text{under,T}}(\boldsymbol{d}(\boldsymbol{x})) &\leq s_{\text{under,T}} \\ f_{\text{over,T}}(\boldsymbol{d}(\boldsymbol{x})) &\leq s_{\text{over,T}} \\ f_{\text{over,U}}(\boldsymbol{d}(\boldsymbol{x})) &\leq s_{\text{over,U}} \\ -\boldsymbol{x} &\leq \mathbf{o}, \end{aligned} \quad (4)$$

where the value bounds $s_{\text{under,T}}$, $s_{\text{over,T}}$ and $s_{\text{over,U}}$ describe the maximally acceptable underdose and overdose in the target and overdose in the unclassified tissue. Altogether, this problem has the modeling parameters

$$q_{\text{EUD,R}},\ q_{\text{under,T}},\ q_{\text{over,T}},\ q_{\text{over,U}},$$
$$d_{\text{under,T}},\ d_{\text{over,T}},\ d_{\text{over,U}},\ s_{\text{under,T}},\ s_{\text{over,T}},\ s_{\text{over,U}}.$$

2.3. Dose volume histogram and modeling parameters

A first understanding of these modeling parameters in terms of dose evaluation is obtained with the cumulative dose volume histogram (DVH). The planning problem of Figure 1 was treated as a paraspinal tumor case and the optimization problem (4) was thus computed for the following modeling parameters:
For the risk structure representing the spinal cord, $q_{\text{EUD,R}} = 13$ was chosen according to [Niemierko, 2006]. The underdose of the target structure was kept acceptably low by setting $d_{\text{under,T}} = 66\text{Gy}$ according to [Radiation Therapy Oncology Group (RTOG), 2006], $q_{\text{under,T}} = 2$ and $s_{\text{under,T}} = 0.5\text{Gy}$. In conjunction with the values $d_{\text{over,T}} = 72\text{Gy}$, $q_{\text{over,T}} = 2$ and $s_{\text{over,T}} = 0.5\text{Gy}$ for bounding the target inhomogeneity, this resulted in a dose distribution with a median target dose of 67Gy =: 100% and only moderate exceedances of the 98% and the 107% thresholds, see Figure 2. For the unclassified

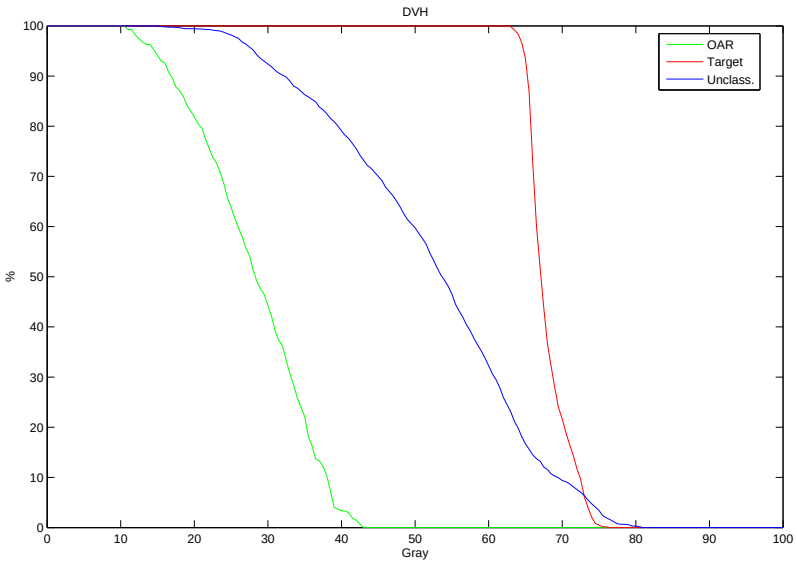

Figure 2. The dose volume histogram of the optimum

tissue, $d_{\text{over,U}} = 72\text{Gy}$, $q_{\text{over,U}} = 2$ and $s_{\text{over,U}} = 1\text{Gy}$. Altogether, these constraints resulted in a plan with an acceptable maximal dose in the risk structure of 42Gy, see [Wambersie and Landberg, 1999].
The dose value $d_{\text{under},T}$ determines which target voxels are actually considered to evaluate

the target underdose with the function (2). The higher this value is, the more voxels contribute to the function value $f_{\text{under,T}}(\boldsymbol{d}(\boldsymbol{x}))$. This function value somehow measures the area between the dose volume curve, the horizontal 100%-line and a vertical line at $d_{\text{under},T}$. The higher the function value is, the larger is this area and thus the target underdose. The value $q_{\text{under,T}}$ describes in which way voxels with a different underdose contribute to the function. It thus characterizes the preferable shape of the underdose: using a small value would favor dose volume curves with high volume percentages for dose values slightly below $d_{\text{under},T}$, and the higher the value is, the more preferable are dose volume curves that match with the 100% line as much as possible. The dose value $d_{\text{over},U}$ determines which voxels of the unclassified tissue actually contribute to the function value $f_{\text{over,U}}(\boldsymbol{d}(\boldsymbol{x}))$. This function value measures the area between the dose volume curve, the horizontal 0%-line and a vertical line at $d_{\text{over},T}$. The value $q_{\text{over,R}}$ again describes in which way voxels with a different overdose contribute to the function. The target overdose with $f_{\text{over,T}}$ is the same, and the EUD $f_{\text{EUD,R}}$, which "measures the exceedance" of 0Gy, is completely analogous.

2.4. Sensitivity and elasticity

The dependence of the optimization problem (4) on the corresponding modeling parameters implies the question, in which way their individual choice and possible modifications influence the resulting solution. For this purpose, define the vector

$$\begin{aligned}\boldsymbol{\Delta} := (&\Delta q_{\text{EUD,R}},\ \Delta q_{\text{under,T}},\ \Delta q_{\text{over,T}},\ \Delta q_{\text{over,U}},\\ &\Delta d_{\text{under,T}},\ \Delta d_{\text{over,T}},\ \Delta d_{\text{over,U}},\ \Delta s_{\text{under,T}},\ \Delta s_{\text{over,T}},\ \Delta s_{\text{over,U}})\end{aligned}$$

of parameter perturbations, denote for example the perturbed EUD function (1) by

$$f_{\text{EUD}}(\boldsymbol{d}(\boldsymbol{x}), \boldsymbol{\Delta}) = ((\sum_{j\in\mathcal{J}'} |V_j|)^{-1} \cdot \sum_{j\in\mathcal{J}'} |V_j| \cdot d(V_j)^{q_{\text{EUD}}+\Delta q_{\text{EUD}}})^{(q_{\text{EUD}}+\Delta q_{\text{EUD}})^{-1}}$$

and the other functions likewise. The optimization problem (4) under the parameter perturbation $\boldsymbol{\Delta}$ then attains the form

$$\begin{aligned} f_{\text{EUD,R}}(\boldsymbol{d}(\boldsymbol{x}), \boldsymbol{\Delta}) &\to \min \quad s.t. \\ f_{\text{under,T}}(\boldsymbol{d}(\boldsymbol{x}), \boldsymbol{\Delta}) &\leq s_{\text{under,T}} + \Delta s_{\text{under,T}} \\ f_{\text{over,T}}(\boldsymbol{d}(\boldsymbol{x}), \boldsymbol{\Delta}) &\leq s_{\text{over,T}} + \Delta s_{\text{over,T}} \\ f_{\text{over,U}}(\boldsymbol{d}(\boldsymbol{x}), \boldsymbol{\Delta}) &\leq s_{\text{over,U}} + \Delta s_{\text{over,U}} \\ -\boldsymbol{x} &\leq \mathbf{o}. \end{aligned} \tag{5}$$

There are several concepts to evaluate optimization problems with respect to such parameter perturbations, which may appear in literature under different names and meanings. This publication considers the following ones:

- *Sensitivity* basically describes, how an optimum varies under moderate parameter changes. Many sensitivity results trace back to the basic sensitivity theorem [Fiacco, 1976, Section 3.2]. This theorem assumes the involved functions to fulfill a

sufficiently high order of differentiability and the objective function and the active constraint functions to fulfill certain regularity conditions at the optimum $\mathbf{x}^*$ of the unperturbed problem. It then states, that (a) the optimum is uniquely determined even under small perturbations, (b) there exists a function describing its changes under such perturbations and (c) the active constraint functions stay the same under small perturbations.

- *Elasticity* is derived from sensitivity analysis in the context of economics. It describes the ratio in limit of a relative change in one value caused by a relative change in a second value and this relative change. For example, the elasticity of the modeling parameter $q_{\mathrm{EUD,R}}$ with respect to the optimal value s^* of the problem (4) is defined as

$$E^{s^*}(q_{\mathrm{EUD,R}}) = \lim_{\Delta q_{\mathrm{EUD,R}} \to 0} \frac{\frac{\Delta s^*(\Delta q_{\mathrm{EUD,R}})}{s^*}}{\frac{\Delta q_{\mathrm{EUD,R}}}{q_{\mathrm{EUD,R}}}} \tag{6}$$

  If $|E^{s^*}(q_{\mathrm{EUD,R}})| > 1$ ($|E^{s^*}(q_{\mathrm{EUD,R}})| = \infty$), then $q_{\mathrm{EUD,R}}$ is *(perfectly) elastic*, if $|E^{s^*}(q_{\mathrm{EUD,R}})| < 1$ ($|E^{s^*}(q_{\mathrm{EUD,R}})| = 0$), it is *(perfectly) inelastic*. Hence, elasticity is a good concept to compare the importance of different parameters with each other, and may serve as a stability measure for the optimum, since smaller elasticity means higher stability of the optimum.

IMRT planning problems in general comprise several planning goals, which results in multi-criteria optimization problems [Yu, 1997; Küfer *et al.*, 2000; Cotrutz *et al.*, 2001]. For example, treating the homogeneity of the dose distribution in the target structure as a second objective function would turn problem (4) into a bi-criteria problem. The simultaneous minimization of multiple criteria may be conducted by various methods, see [Miettinen, 1999]. However, the following considerations and results, which focus on single-criteria problems, can be most naturally extended to the case of multi-criteria problems, see [Krause, 2007].

3. Results and Discussion

3.1. Sensitivity of the plan optimization problem

One application of sensitivity analysis is, that it allows for simulating small parameter changes with respect to a treatment plan, which is not satisfying. For example, take into account the function which is assigned to in the Basic Sensitivity Theorem. This function describes the optimum and corresponding Lagrangian multipliers in dependence of the perturbation and can be approximated in first order thoroughly, that is for the optimum

$$\mathbf{x}_{est}^{\boldsymbol{\Delta}} := \mathbf{x}^* + \frac{d}{d\boldsymbol{\Delta}}\mathbf{x}^*, \tag{7}$$

where $\frac{d}{d\boldsymbol{\Delta}}\mathbf{x}^*$ can be determined by *explicit* formulae which involve partial derivatives of first and second order of the Lagrangian and of the active constraint functions.

These are the constraints for which equality holds. Results of sensitivity analysis are restricted to a certain area, the sensitivity domain. This multi-dimensional cuboid gives an estimation for an interval for each modeling parameter, in which the parameter can be modified without altering the set of active constraints. The active constraints are in the example case - besides all of the constraint functions - $x_7, x_8, x_{32}, x_{45}, x_{56}$ and $x_{57} = 0$. According to [Büskens and Maurer, 2001, pp. 12-13], an approximation of a perturbation $\boldsymbol{\Delta} = (\mathbf{0}, \Delta_j, \mathbf{0})^t$ of the j-th parameter causing the k-th active constraint to leave the active set is given by

$$\Delta_j^k \approx -\frac{u_k^*}{\left(\frac{d}{d\Delta_j} u_k(\boldsymbol{\Delta})\right)\Big|_{\boldsymbol{\Delta}=\mathbf{0}}}.$$

This is derived from the corresponding Lagrange multiplier u_k equaling 0 in that case. Vice-versa, an approximation of a perturbation $\boldsymbol{\Delta} = (\mathbf{0}, \Delta_j, \mathbf{0})^t$ causing the inactive constraint f_k to enter the active set is given by

$$\Delta_j^k \approx -\frac{f_k(\mathbf{d}(\mathbf{x}^*), \mathbf{0})}{\left(\frac{d}{d\Delta_j} f_k(\mathbf{d}(\mathbf{x}^*), \boldsymbol{\Delta})\right)\Big|_{\boldsymbol{\Delta}=\mathbf{0}}},$$

which is due to the fact, that the constraint attains its bound. Note that the denominator is is required to be nonzero in both equations. An approximation of a domain, in which the set of active indices stays the same, is obtained when combining those considerations for each modeling parameter. For the example case we got the following sensitivity domain: Numerical experiments on the sensitivity domain show that the

$\Delta q_{\mathrm{EUD,R}}$	$\Delta q_{\mathrm{under,T}}$	$\Delta q_{\mathrm{over,T}}$	$\Delta q_{\mathrm{over,U}}$	$\Delta d_{\mathrm{under,T}}$	$\Delta d_{\mathrm{over,T}}$	$\Delta d_{\mathrm{over,U}}$
-9.75	-0.31	-1.07	-1.24	-1.51	-1.11	-4.16
7.19	0.35	1.26	1.20	1.13	1.50	3.98

$\Delta s_{\mathrm{under,T}}$	$\Delta s_{\mathrm{over,T}}$	$\Delta s_{\mathrm{over,U}}$
-0.19	-0.46	-1.16
0.18	0.56	1.07

Table 1. Sensitivity domain for the example case

approximation of first order (7) is a good estimation for the real optimum of the optimization problem with modified parameters. Consider for example perturbations of $s_{\mathrm{under,T}}$ to $s'_{\mathrm{under,T}} := 0.65$ and $s''_{\mathrm{under,T}} := 0.35$. The resulting changes in the dose-volume histograms for the optimum of the original problem and the optima of the perturbed problems are shown in Figure 3. For both perturbations, the DVHs of the estimate and the perturbed optimum are compared in Figures 4 and 5. In both cases, the dose-volume curves match almost exactly. A comparison of the estimates with the perturbed optima in terms of intensity vectors is done in Table 2. The changes of the optima in the Euclidean norm are significant in comparison with the norm of the original optimum. However, the deviations of the estimate from the real perturbed optimum is rather

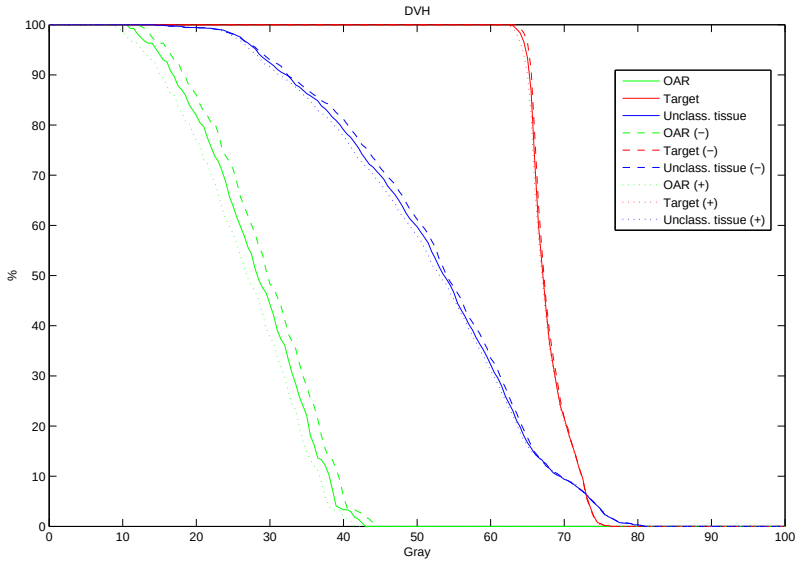

Figure 3. DVHs for the unperturbed problem and the perturbed problems with $\Delta s'_{\text{under,T}} = +0.15$ and $\Delta s''_{\text{under,T}} = -0.15$

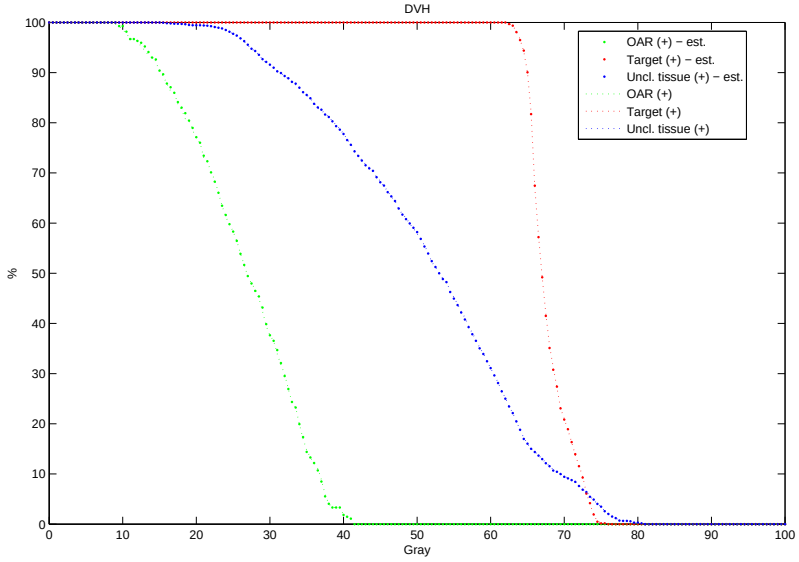

Figure 4. Original and estimated DVH for $s'_{\text{under,T}} = 0.65$

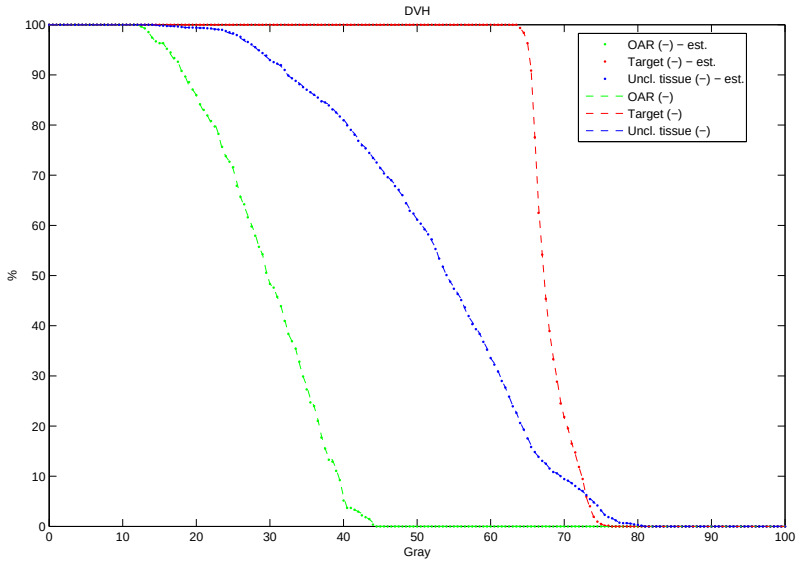

Figure 5. Original and estimated DVH for $s''_{\text{under,T}} = 0.35$

small. This also indicates, that the concept of sensitivity facilitates very good guesses, how the optimum changes under parameter perturbations. Also, the corresponding

$s_{\text{under,T}}$	$\|\mathbf{x}^*\|_2$	$\|\mathbf{x}^* - \mathbf{x}^{*,\boldsymbol{\Delta}}\|_2$	$\|\mathbf{x}^{*,\boldsymbol{\Delta}}_{est} - \mathbf{x}^{*,\boldsymbol{\Delta}}\|_2$
0.35	167.21	11.29	1.99
0.65	167.21	11.28	2.43

Table 2. The norm differences of the real and the perturbed optima and between estimates and perturbed optima

optimal value of the estimate $\mathbf{x}_{est}$ gives a good approximation of the optimal value of the real perturbed optimization problem: In Table 3 we compare the optimal values for the perturbed problems with $s'_{\text{under,T}}$ and $s''_{\text{under,T}}$. Alternative approximations for the

$s_{\text{under,T}}$	$f_{\text{EUD,R}}(\mathbf{0}, \mathbf{x}^*)$	$f_{\text{EUD,R}}(\boldsymbol{\Delta}, \mathbf{x}^{*,\boldsymbol{\Delta}})$	$f_{\text{EUD,R}}(\boldsymbol{\Delta}, \mathbf{x}^{*,\boldsymbol{\Delta}}_{est})$
0.35	34.67	33.52	33.47
0.65	34.67	35.94	35.89

Table 3. Value comparisons for the two perturbations of $s_{\text{under,T}}$

perturbed optimal value can be obtained by using Taylor's series expansion:

$$f_{\text{EUD,R}}(\boldsymbol{\Delta}, \mathbf{x}(\boldsymbol{\Delta})) \approx \quad f_{\text{EUD,R}}(\mathbf{0}, \mathbf{x}^*) + \left(\frac{d}{d\boldsymbol{\Delta}} f_{\text{EUD,R}}(\boldsymbol{\Delta}, \mathbf{x}(\boldsymbol{\Delta}))|_{\boldsymbol{\Delta}=\mathbf{0}} \right)^t \cdot \boldsymbol{\Delta}$$
$$+ \frac{1}{2} \cdot \boldsymbol{\Delta}^t \cdot \left(\frac{d^2}{d\boldsymbol{\Delta}^2} f_{\text{EUD,R}}(\boldsymbol{\Delta}, \mathbf{x}(\boldsymbol{\Delta}))|_{\boldsymbol{\Delta}=\mathbf{0}} \right) \cdot \boldsymbol{\Delta} + \dots$$

From the Lagrange condition, one can explicitly determine the total derivatives with respect to $\boldsymbol{\Delta}$. The approximations are compared with each other in Table 4, where $f_{\mathrm{EUD,R}}^{est,1st}$ refers to the first order approximation and $f_{\mathrm{EUD,R}}^{est,2nd}$ to the second order approximation. All approaches yield good estimates, so it may be a question of

$s_{\mathrm{under,T}}$	$f_{\mathrm{EUD,R}}(\boldsymbol{\Delta}, \mathbf{x}^{*,\boldsymbol{\Delta}})$	$f_{\mathrm{EUD,R}}(\boldsymbol{\Delta}, \mathbf{x}_{est}^{*,\boldsymbol{\Delta}})$	$f_{\mathrm{EUD,R}}^{est,1st}(\boldsymbol{\Delta}, \mathbf{x}^{*,\boldsymbol{\Delta}})$	$f_{\mathrm{EUD,R}}^{est,2nd}(\boldsymbol{\Delta}, \mathbf{x}^{*,\boldsymbol{\Delta}})$
0.35	33.52	33.47	33.47	33.52
0.65	35.94	35.89	35.88	35.93

Table 4. Different optimal value estimates for the two perturbations of $s_{\mathrm{under,T}}$

preference and suitability which one to choose.

3.2. Elasticity of the plan optimization problem

[Krause, 2007] has shown, that the elasticity (6) of a parameter with respect to the optimal value s^* attained for an optimum $\boldsymbol{x}^*$ and Lagrangian multipliers $\boldsymbol{u}^*$ is the product of the partial derivative of the Lagrangian function with respect to the parameter and the quotient of the parameter and the optimal value. The following elasticity computations focus on the the particular case of the problem (4) with the parameters settings of Section 2.3. However, the results can be most naturally transferred to other planning cases.

3.2.1. Elasticity in the risk EUD Consider the parameter $q_{\mathrm{EUD,R}}$ in the objective function $f_{\mathrm{EUD,R}}$. To also take the shape of the dose distribution over the voxels of the risk structure into account, each dose value is rewritten as

$$d(V_j) = s^* \cdot (1 + \delta(V_j)) \quad (j \in \mathcal{J}_{\mathrm{R}}),$$

where $\delta(V_j)$ denotes its relative deviation from the equivalent uniform dose. The elasticity of $q_{\mathrm{EUD,R}}$ with respect to s^* then follows as

$$E^{s^*}(q_{\mathrm{EUD,R}}) = (1 + \ln(q_{\mathrm{EUD,R}} \cdot s^*)) \cdot \sum_{j \in \mathcal{J}_{\mathrm{R}}} \frac{|V_j| \cdot \delta(V_j)}{\sum_{j \in \mathcal{J}_{\mathrm{R}}} |V_j|} + \boldsymbol{O}\Big(\|(\delta(V_j))_{j \in \mathcal{J}_{\mathrm{R}}}\|^2 \Big)$$

for $\|(\delta(V_j))_{j \in \mathcal{J}_{\mathrm{R}}}\| \to 0$. Hence, $q_{\mathrm{EUD,R}}$ is in general inelastic and tends to be perfectly inelastic for increasingly homogeneous dose distributions in the risk structure. This means, the plan quality with respect to the risk structure is rather stable in the value of the EUD parameter.

For the optimum of Section 2.3, the elasticity attains the value $E^{s^*}(13) = 0.106$. Exemplary computations for different values of $q_{\mathrm{EUD,R}}$ validate the small influence of this parameter. Table 5 gives the resulting optimal values and Figure 6 shows the corresponding dose-volume histograms. The resulting optimal values and the dose-volume curves for the risk structure are almost the same. Only the value $q_{\mathrm{EUD,R}} = 3$ yields a slightly different result, which is also confirmed by the different elasticity $E^{s^*}(3) = 0.193$. The elasticities for the other parameter choices of $q_{\mathrm{EUD,R}}$ are pretty

$q_{\mathrm{EUD,R}}$	3	8	13	18
s^* [Gy]	27.9	32.7	34.7	35.8

Table 5. The optimal values for different $q_{\mathrm{EUD,R}}$

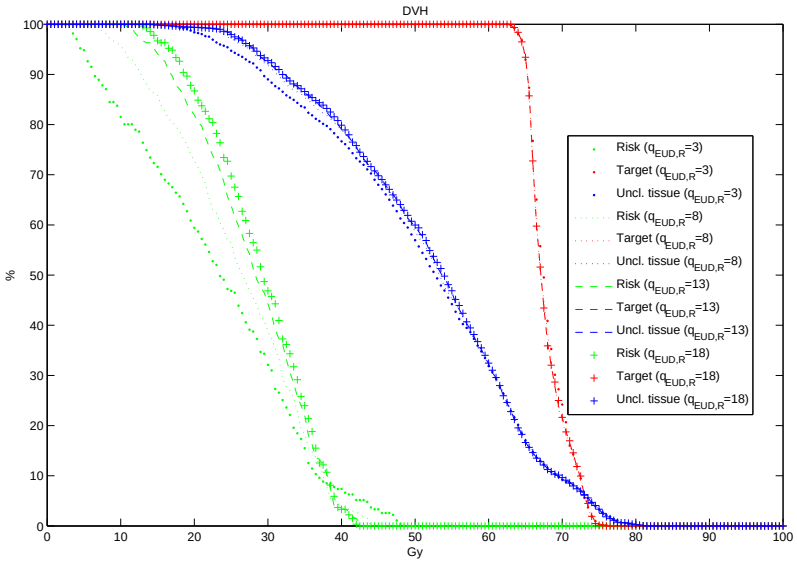

Figure 6. The dose-volume curves of the optima for different $q_{\mathrm{EUD,R}}$

similar. The elasticities of the other modeling parameters vary only moderately over the optima, which is also the same for the subsequent computations.

3.2.2. Elasticity in the target underdose The elasticity in the dose value $d_{\mathrm{under,T}}$ is

$$\begin{aligned} E^{s^*}(d_{\mathrm{under,T}}) = {} & \frac{u_{\mathrm{under,T}} \cdot d_{\mathrm{under,T}}}{s^*} \cdot \Big(\frac{\sum_{j\in\mathcal{J}_{\mathrm{T}}} |V_j|}{\sum_{j\in\mathcal{J}_{\mathrm{T}}^<} |V_j|} \Big)^{q_{\mathrm{under,T}}^{-1}} \\ & + \frac{u_{\mathrm{under,T}} \cdot d_{\mathrm{under,T}} \cdot (q_{\mathrm{under,T}} - 1)}{s^*} \cdot \Big(\frac{\sum_{j\in\mathcal{J}_{\mathrm{T}}} |V_j|}{\sum_{j\in\mathcal{J}_{\mathrm{T}}^<} |V_j|} \Big)^{q_{\mathrm{under,T}}^{-1}} \\ & \cdot \sum_{j\in\mathcal{J}_{\mathrm{T}}^<} \frac{|V_j| \cdot \delta(V_j)}{\sum_{j\in\mathcal{J}_{\mathrm{T}}} |V_j|} + \boldsymbol{O}\Big(\|(\delta(V_j))_{j\in\mathcal{J}_{\mathrm{T}}^<}\|^2 \Big), \end{aligned} \tag{8}$$

where $\mathcal{J}_{\mathrm{T}}^<$ refers to the voxels with dose values

$$\begin{aligned} d_{\mathrm{under,T}} > {} & d(V_j) \\ := {} & \Big[d_{\mathrm{under,T}} - f_{\mathrm{under,T}}(\boldsymbol{d}(\boldsymbol{x}^*)) \cdot \Big(\frac{\sum_{j\in\mathcal{J}_{\mathrm{T}}} |V_j|}{\sum_{j\in\mathcal{J}_{\mathrm{T}}^<} |V_j|} \Big)^{q_{\mathrm{under,T}}^{-1}} \Big] \cdot (1 + \delta(V_j)). \end{aligned} \tag{9}$$

Hence, $d_{\mathrm{under,T}}$ is in general elastic and tends to be perfectly elastic for increasingly homogeneous underdose occurring in a small volume fraction $\sum_{j\in\mathcal{J}_{\mathrm{T}}^<} |V_j| \cdot (\sum_{j\in\mathcal{J}_{\mathrm{T}}} |V_j|)^{-1}$ of the target structure. Shifting this dose value is thus a very efficient means to influence

the dose quality with respect to the risk structure. This fact is well-known from clinical routine: reduction of the dose value aspired for most of the target volume provides new possibilities to spare vicinal risk structures.
For the considered optimum, $E^{s^*}(d_{\text{under,T}}) = 5.88$. This indicates a strong influence of this parameters, which is confirmed by exemplary computations, see Table 6 and Figure 7. In the case, the optimal values and dose-volume curves for the risk structure

$d_{\text{under,T}}$ [Gy]	61	66	71
s^* [Gy]	20.8	34.7	52.3

Table 6. The optimal values for different $d_{\text{under,T}}$

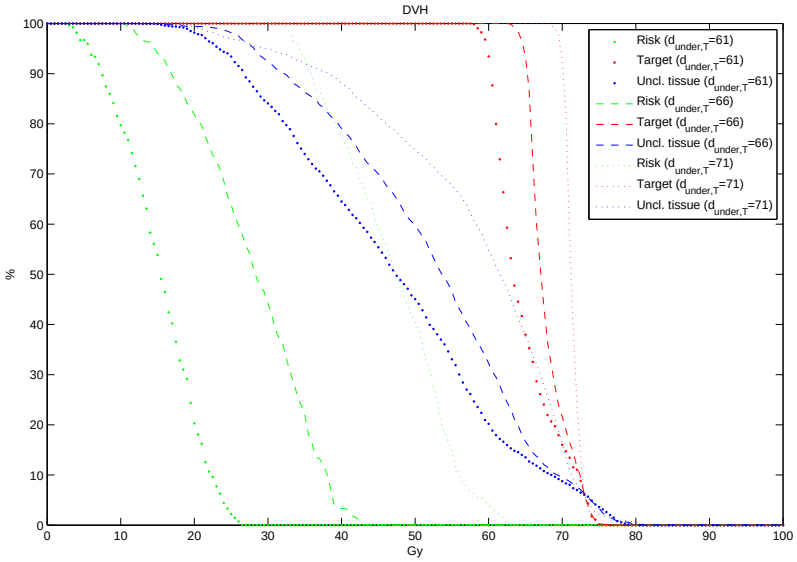

Figure 7. The dose-volume curves of the optima for different $d_{\text{under,T}}$

show major shifts. Again, the elasticities attain their highest values for the case $d_{\text{under,T}} = 61\text{Gy}$, for example $E^{s^*}(d_{\text{under,T}}) = 7.24$, which provides the most degrees of freedom to influence the shape of the dose distribution in the risk structure.
The elasticity in the exponent $q_{\text{under,T}}$ is

$$\begin{aligned} E^{s^*}(q_{\text{under,T}}) = {} & \frac{u_{\text{under,T}} \cdot f_{\text{under,T}}(\boldsymbol{d}(\boldsymbol{x}^*))}{s^* \cdot q_{\text{under,T}}} \cdot \ln \frac{\sum_{j \in \mathcal{J}_{\text{T}}} |V_j|}{\sum_{j \in \mathcal{J}_{\text{T}}^<} |V_j|} \\ & + \frac{u_{\text{under,T}} \cdot f_{\text{under,T}}(\boldsymbol{d}(\boldsymbol{x}^*))}{s^*} \cdot \frac{\sum_{j \in \mathcal{J}_{\text{T}}} |V_j|}{\sum_{j \in \mathcal{J}_{\text{T}}^<} |V_j|} \\ & \cdot \left(1 + q_{\text{under,T}} \ln f_{\text{under,T}}(\boldsymbol{d}(\boldsymbol{x}^*)) - \ln \frac{\sum_{j \in \mathcal{J}_{\text{T}}} |V_j|}{\sum_{j \in \mathcal{J}_{\text{T}}^<} |V_j|}\right) \end{aligned}$$

$$\cdot \sum_{j \in \mathcal{J}_{\mathrm{T}}^{<}} \frac{|V_j| \cdot \delta(V_j)}{\sum_{j \in \mathcal{J}_{\mathrm{T}}} |V_j|} \; + \; \boldsymbol{O}\Big(\|(\delta(V_j))_{j \in \mathcal{J}_{\mathrm{T}}^{<}}\|^2 \Big).$$

This indicates, that $q_{\mathrm{under,T}}$ is in general inelastic, in particular for increasingly homogeneous underdose occurring in a large volume fraction $\sum_{j \in \mathcal{J}_{\mathrm{T}}^{<}} |V_j| \cdot (\sum_{j \in \mathcal{J}_{\mathrm{T}}} |V_j|)^{-1}$ of the target structure. Hence, modifications of this parameter do not really change the quality of the dose distribution in the risk structure.
For the considered optimum, the elasticity attains the value $E^{s^*}(q_{\mathrm{under,T}}) = 0.132$, which is by one magnitude smaller than $E^{s^*}(d_{\mathrm{under,T}})$. The possibilities to influence the optimal value and the dose-volume histogram by changes of this parameter are thus as limited as in Section 3.2.1.
The case is similar for the elasticity of the bound value $s_{\mathrm{under,T}}$,

$$E^{s^*}(s_{\mathrm{under,T}}) = -\frac{u_{\mathrm{under,T}} \cdot s_{\mathrm{under,T}}}{s^*}, \tag{10}$$

which in general attains values less than 1 indicating inelasticity, for example $E^{s^*}(s_{\mathrm{under,T}}) = -0.116$ for the considered optimum. Hence, modifications of this parameter also affect the dose distribution in the risk structure only in a minor way.

3.2.3. Elasticity in target overdose and unclassified tissue The elasticities of $d_{\mathrm{over,T}}$ and $d_{\mathrm{over,U}}$ differ from (8) just by minus signs instead of plus, the different subscripts and substitutions analogous to (9). The drawn conclusions are thus also the same. For the considered optimum, the elasticity of $d_{\mathrm{over,T}}$ attains the value $E^{s^*}(72\mathrm{Gy}) = -3.64$, which indicates strong influence on the EUD objective function in the risk structure. This validates the rule of thumb from clinical routine, that the steeper dose-volume curves for target structures result shall be, the worse the situation in vicinal risk structures gets.
The elasticity in the parameter $d_{\mathrm{over,U}}$ attains the smaller value $E^{s^*}(72\mathrm{Gy}) = -0.976$, which gives no clear statement about its influence for this particular case. Computations for other parameter settings indicated moderate inelasticity for problems with stricter planning requirements and moderate elasticity for more relaxed optimization problems. However, the major difference to the elasticity in $d_{\mathrm{over,T}}$ remained due to the intuitive fact, that a homogeneity requirement on the dose distribution in the target structure contradicts with the dose quality in the risk structure much more than a requirement on the overdose in the unclassified tissue.
This behavior is also reflected by the corresponding Lagrangian multipliers. The larger a multiplier is, the more the corresponding constraint opposes the objective function. For the considered optimum, the Lagrangian multiplier of the target overdose is $u_{\mathrm{over,T}} = 6.16$, whereas the multiplier for the unclassified tissue is just $u_{\mathrm{over,U}} = 2.07$. In comparison, the value of $u_{\mathrm{under,T}} = 8.04$ shows, that attaining a sufficiently high target dose is the strongest opponent of sparing the risk structure.
The elasticities of $q_{\mathrm{over,T}}$ and $q_{\mathrm{over,U}}$ are the same as (10) with different subscripts and imply the same conclusions. The elasticity of $q_{\mathrm{over,T}}$ attains the value $E^{s^*}(2) = 0.123$ and the elasticity in $q_{\mathrm{over,U}}$ is $E^{s^*}(2) = 0.097$, which both indicate their small influence

on the EUD in the risk structure.
The elasticities of $s_{\text{over,T}}$ and $s_{\text{over,U}}$ are the same as (10) with different subscripts. The conclusions are the same, as verified for the considered optimum with the elasticity value $E^{s^*}(2) = -0.089$ in $s_{\text{over,T}}$ and $E^{s^*}(2) = -0.060$ in $s_{\text{over,U}}$. Both values indicate their small influence on the EUD in the risk structure, see for example Table 7.

$s_{\text{over,T}}$ [Gy]	0.5	1.0	1.5
s^* [Gy]	36.6	34.7	33.8

Table 7. The optimal values for different $s_{\text{over,U}}$

3.2.4. Elasticities of differently shaped planning structures An aspect with major influence on the case-specific limitations of IMRT treatment planning is the geometry of the considered planning structures. The possibilities to give a dose distribution the desired shape are to some extent predefined by the relative position of target and risk structures with respect to each other, a fact that must not be underestimated in the choice of modeling parameters. This influence is in general impossible to quantify, however, the concept of elasticity, which numerically describes the influence of modeling parameters, may provide some deeper insight.
In the exemplary planning case of Figure 1, the ring-shaped target structure had a sparing of 90°. Consider the family of planning cases shown in Figure 8.

Figure 8. Horse shoe planning cases with different spared angle segments

The target structures of these cases differ in the spared angle segments of 45, 90, 135, 180 and 225 degrees. Consider the optimization problem (4) with the parameter settings of Section 2.3 on these cases. The more the risk structure is surrounded by the target structure, the more difficult it is to spare. This means, in cases with smaller spared angle segments the shape of the optimal dose distribution is almost predefined by the geometry of the planning structure and the influence of the modeling parameters is rather small. This is confirmed by the elasticities in the modeling parameters for the resulting solutions, see Table 8. The elasticities for the modeling parameters referring to target and risk structure decrease within their above mentioned magnitudes for decreasing angles. For example, q_{EUD} has almost no influence in the case of 45°, since the shape of the dose distribution in the risk structure is almost fully characterized by the large target structure. The almost perfect inelasticity of the parameters $q_{\text{under,T}}$, $q_{\text{over,T}}$, $s_{\text{under,T}}$ and $s_{\text{over,T}}$ also shows that there is practically no possibility to shift dose

Angle	45°	90°	135°	180°	225°
$E^{s^*}(q_{\mathrm{EUD,R}})$	0.022	0.106	0.190	0.258	0.268
$E^{s^*}(d_{\mathrm{under,T}})$	4.75	5.88	7.94	12.5	11.7
$E^{s^*}(q_{\mathrm{under,T}})$	0.089	0.132	0.283	0.382	0.275
$E^{s^*}(s_{\mathrm{under,T}})$	-0.087	-0.116	-0.200	-0.301	-0.246
$E^{s^*}(d_{\mathrm{over,T}})$	-2.25	-3.64	-6.57	-10.8	-10.2
$E^{s^*}(q_{\mathrm{over,T}})$	0.089	0.123	0.210	0.296	0.220
$E^{s^*}(s_{\mathrm{over,T}})$	-0.061	- 0.89	-0.152	-0.234	-0.196
$E^{s^*}(d_{\mathrm{over,U}})$	-1.28	-0.976	-0.023	-0.077	-0.075
$E^{s^*}(q_{\mathrm{over,U}})$	0.112	0.097	0.003	0.010	0.011
$E^{s^*}(s_{\mathrm{over,U}})$	-0.074	-0.060	-0.002	-0.006	-0.006

Table 8. The elasticities for different spared angle segments

deposits inside the target structure to allow for an improved sparing of the risk structure. The only sensible way to do so is a relaxation of the homogeneity requirements on the target structure by lowering $d_{\mathrm{under,T}}$ or increasing $d_{\mathrm{over,T}}$, which is confirmed by their comparably high elasticities. For bigger angles and thus smaller target structures, all these elasticities increase, in particular for the latter two parameters, since then there are many more degrees of freedom to obtain a well-shaped dose distribution, which better spares the risk structure.
The requirement of sufficiently high dose deposits in a target structure obviously implies high dose deposits in some adjacent parts of the unclassified tissue. The smaller the target structure is, the smaller are these volume parts and the less important are these high doses for the plan optimization. The decreasing relevance of the overdose in the unclassified tissue is also reflected by the almost perfect inelasticity of the corresponding parameters $d_{\mathrm{over,U}}$, $q_{\mathrm{over,U}}$ and $s_{\mathrm{over,U}}$ for higher angles.

4. Conclusions

The appropriate choice of modeling parameters in IMRT plan optimization is a major topic of ongoing research. The influence of the different parameters on the resulting plan is still not fully understood and even more difficult to quantify. This publication discusses the approaches of sensitivity and elasticity as a mathematical means to profoundly answer to these questions.

4.1. Sensitivity: predicting the possible changes of a plan

The sequential computation of IMRT plans typically involves a trial and error search for the appropriate changes of the modeling parameters in order to steer the current plan in the desired direction. The concept of sensitivity is a sound approach to estimate and analyze the consequences of possible parameter changes in a cheap way, which does not require costly plan computations. The desired modification of the current treatment

plan can thus be realized by first simulating the various outcomes of a plan computation online, then generating a new fitting parameter configuration and finally conducting the real plan optimization. This avoids many unneeded computation runs and thus allows for an accelerated search for the desired treatment plan.

4.2. Elasticity: quantifying the influence of parameters

The concept of elasticity as being discussed here provides an approach to analyze the connection between parameter values and resulting plan quality. It allows for a profound classification of parameters according to their influence on the optimal value. Small or even perfect inelasticity for a parameter can easily compensate for moderate inaccuracies in the chosen value, a helpful aspect regarding its mostly statistical origin. High elasticity shows, that the value choice is highly important in view of the resulting plan. This deeper understanding may for example be used to incorporate appropriate error thresholds into the statistical fitting of parameter values. High elasticity also indicates, that modification of this parameter is a very effective means to influence the shape of the corresponding dose distribution.

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