We consider intensity-modulated photon and proton therapy in the presence of setup uncertainty. The uncertainty is accounted for by worst case optimization, in which the planning criteria are constrained to be satisfied under all setup errors from a specified set. To handle that the set may contain errors under which the planning criteria cannot be satisfied, a method is introduced that includes the magnitudes of the setup errors within the set as variables in the optimization, which is aimed at making these magnitudes as large as possible (within specified bounds) while satisfying all planning criteria under the errors. This is equivalent to maximizing the probability of satisfying the planning criteria.

The method is studied with respect to photon and proton therapy applied to a prostate case and a lung case, and compared to worst case optimization with respect to an a priori determined set of errors. For both modalities, slight reductions of the magnitudes of the considered setup errors resulted in plans that satisfied a substantially larger number of planning criteria under the retracted errors, and also a larger number of criteria under the a priori errors: for the prostate case, the plans accounting for retracted errors satisfied 1.5 (photons) and 1.2 (protons) times as many planning criteria as the method accounting for a priori errors, and for the lung case, the numbers were 2.7 (photons) and 1.6 (protons).

1. Introduction

Misalignment of the patient relative to the beams can lead to large differences between the planned and the delivered dose distributions in external beam radiation therapy. The conventional approach to account for such errors is to apply margins during treatment planning [12,13]. Planning is then performed towards delivery of high doses to an enlarged target volume, called the planning target volume (PTV), and low doses to enlarged organ at risk (OAR) volumes. The margins are generally specified in accordance with the magnitudes of previously measured errors in order to ensure a high probability of meeting the planning goals [24]. However, in cases...
for which the conflicting criteria between PTV coverage and OAR sparing cannot be simultaneously fulfilled, the margins are sometimes retracted in the directions that correspond to the problematic conflicts \[27\]: Prostate tumors are often given less margin towards the rectum than in the other directions, not because the prostate is less likely to move posteriorly, but because the rectum sparing is considered more important. Consequently, the resulting plan is not robust against the target moving posteriorly, but on the other hand satisfies the goal of rectum sparing. Determining how large margins that can be used in different directions while satisfying the planning criteria for the enlarged volumes is a nontrivial issue; the weighting of beams from different directions, among other parameters, changes the dose distribution in ways that make adequate margins difficult to determine by simple geometric considerations.

In the present paper, we devise a method that determines how large setup errors treatment plans can be robust against, or, equivalently, under how large errors all planning criteria can be satisfied. If larger errors than these are accounted for, then some criteria cannot be satisfied. By finding these magnitudes, the proposed method maximizes the probability of satisfying the planning criteria.

For cases of heterogeneous density, and especially cases subject to ion treatments, conventional margins do not always provide the intended robustness against uncertainties \[2, 16\]. Methods that explicitly incorporate information about the uncertainties into the optimization appear to lead to more robust plans in general \[5, 7, 14, 23\]. To be able to use the method proposed in the present paper for intensity-modulated proton therapy (IMPT) as well as photon-mediated intensity-modulated radiation therapy (IMRT), we do not use margins, but base our method on worst case (or “minimax”) optimization \[5–7\]. In worst case optimization, the objective function is evaluated for a number of setup shifts (or other errors), and the worst objective function value over these shifts is optimized. The optimization thereby determines where to deposit dose in order to yield robustness against the included setup shifts. Thus, worst case optimization can be considered a form of inverse planning of margins.

In order to determine how large errors that can be protected against while satisfying the planning criteria, our method includes the magnitudes of the considered setup shifts as variables in the optimization. The optimization then tries to make these magnitudes as large as possible (within specified bounds) to protect against as large setup errors as possible, while enforcing the planning criteria to be satisfied under these errors. This is similar to maximizing the sizes of the region of interest (ROI) margins (within specified bounds) while ensuring that all planning criteria for these enlarged structures are satisfied.

Changing the magnitudes of the errors against which the plan should be robust has similarities to previous methods: Gordon and Siebers \[10\] iteratively updated the sizes of the PTVs and reoptimized the treatment plans until a coverage probability was met. Gordon et al. \[9\] and Moore et al. \[17\] used probabilistic planning methods in which they considered multiple setup error scenarios and tried to meet the planning criteria for a fraction of the errors and thereby reach a specified probability of satisfying the criteria. The method proposed in the present paper differs
from these methods in that it optimizes the probability of satisfying the planning criteria directly rather than trying to reach a predetermined probability. It can thereby reach the highest probability for which the treatment goals can be fulfilled.

Methods with the same goal as ours have been considered by Yang et al. [26] and Sobotta et al. [19]. Instead of optimizing functions penalizing deviations from prescribed dosimetric criteria, they optimize the probability of satisfying the dosimetric criteria. Their methods essentially consider a number of predetermined error scenarios (e.g., a number of possible setup shifts) and try to satisfy the planning criteria under as many of these scenarios as possible. By taking into consideration the probability of the scenarios occurring, they can maximize the probability of satisfying the planning criteria. The method proposed in the present paper also maximizes this probability, but differs from the previous methods in that it does not use predetermined error scenarios. Instead, it considers a set of errors, the magnitudes of which can be modified. This makes it feasible to consider a smaller number of error scenarios than previous methods require, which reduces the number of dose computations and thereby the planning time.

Other methods for robustness generally account for errors of magnitudes specified prior to the optimization. Some previous such methods optimize the expected value of the functions penalizing deviations from prescribed dose levels [21, 23], or optimize the dose deviation penalties of the worst case dose distributions, in which each voxel considered independently receives its highest or lowest dose from a number of different scenarios [14, 18, 22]. Minimax optimization has also been considered [5–7].

2. Method

We introduce a method that maximizes the probability of satisfying the planning criteria for treatment plans subject to setup uncertainty. It does so by determining the largest setup errors that can be accounted for while all criteria are satisfied under all considered errors.

2.1. Uncertainties and scenarios

Systematic setup errors are considered. A shift of the patient setup corresponds to a translation of the beam isocenters. For computational reasons, only a finite number of setup shifts can be considered. The possible setup shifts are therefore discretized into a number of representative scenarios, each corresponding to an isocenter shift. The planning scenario, corresponding to no setup shift, is called the “nominal scenario.”

The method proposed in this paper is based on worst case scenario optimization [5–7], which tries to make the dose distribution as good as possible in the worst of the considered scenarios. Similar to how margins are specified to achieve high probability of target coverage or OAR sparing, the scenarios are selected to represent the, e.g., 95 % most probable errors. Random errors can be incorporated into the model by a van Herk-type method [25]: by including setup shifts up to $2.5\Sigma + 0.7\sigma$ from the nominal position, where $\Sigma$ is the standard deviation of the systematic errors and $\sigma$ that of the random errors.
Because the magnitudes of the considered errors can be ROI specific (in the same way as the margins need not be of equal size for all ROIs), each ROI may require dose distributions from an individual set of scenarios. Each scenario corresponds to a shift of the isocenters, so the scenarios in which a given ROI is considered is denoted by the name of the ROI and the direction of the isocenter shift. The scenario in which the rectum is considered, and in which the beam isocenters have been shifted in the anterior direction, is thus referred to as “the anterior isocenter shift scenario for the rectum.”

2.2. Mathematical formulation

The ROIs are enumerated by the set $\mathcal{R}$ and the criteria to be satisfied for each ROI $r$ in $\mathcal{R}$ is measured by a function of dose $f_r$. For a target, this function usually measures how well the target dose matches the prescribed dose level, and for an OAR, how well the OAR dose falls below its desired maximum levels. It is assumed that the criteria for ROI $r$ are satisfied whenever $f_r$ evaluates to 0 or less. The random variable representing the systematic setup error is denoted by $S$, which is thus a random variable vector in $\mathbb{R}^3$ determining a shift of the isocenters. The dose distribution is a function of the optimization variables $x$, which may be machine parameters or spot weights. The set of feasible variables, which are within hardware limitations, is denoted by $\mathcal{X}$. The dose distribution is also a function of the setup shift $s$ in $\mathbb{R}^3$, and is therefore denoted by $d(x, s)$.

Our aim is to find plans that are as robust as possible while satisfying the planning criteria. This corresponds to maximizing the probability of satisfying the planning criteria. The objective function to be maximized is thus given by

$$\mathbb{P} (\text{the criteria of all ROIs are satisfied}) ,$$

which can be mathematically formulated as

$$\mathbb{P} (f_r(d(x, S)) \leq 0 \text{ for all } r \in \mathcal{R}) , \quad (2.1)$$

where $\mathbb{P}(A)$ denotes the probability of the event $A$ occurring.

Under scenarios where only a subset of the criteria can be satisfied, it may still be beneficial to satisfy this subset of criteria as long as it does not reduce the probability of satisfying all criteria simultaneously. A term that encourages maximizing the probability of satisfying the criteria for each ROI individually may to this end be weighted into the objective by a factor $\rho$ such that $0 < \rho \ll 1$. This term is given by

$$\sum_{r \in \mathcal{R}} \mathbb{P} (\text{the criteria of ROI } r \text{ are satisfied})$$

or, mathematically,

$$\sum_{r \in \mathcal{R}} \mathbb{P} (f_r(d(x, S)) \leq 0) . \quad (2.2)$$

To pursue the objectives (2.1) and (2.2), we enforce the criteria of all ROIs whenever the setup error $S$ falls within some region $U$, and optimize the size of $U$. 
simultaneously with the variables $x$. To allow for optimization of the size of the regions for individual ROIs, let the vector $\alpha_r$ in $\mathbb{R}^n_+$ parameterize the size of the region for which the criteria of ROI $r$ must be satisfied. This region is denoted by $U(\alpha_r)$. The size of $U(\alpha_r)$ in some directions $p_i$ in $\mathbb{R}^3$ is determined by the scalar elements $\alpha_{r,i}$ of $\alpha_r$ for $i = 1, \ldots, n$. The a priori, maximally desired, magnitude of errors that are accounted for in the direction $p_i$ for ROI $r$ is denoted by $\bar{\alpha}_{r,i}$. Hence, $\alpha_{r,i}$ must be less than $\bar{\alpha}_{r,i}$. An illustration of a region $U(\alpha_r)$ is given in Figure 1.

Here, the directions $p_i$ for $i = 1, \ldots, 4$ are the positive and negative axis directions, so that the parameters $\alpha_r$ determine how large errors the plan must be robust against for ROI $r$ in the axis directions, much like a margin would be specified. The parameters $\alpha$ for all ROIs are included as variables in the optimization and constraints are introduced to enforce the criteria of all ROIs $r$ in $\mathcal{R}$ for all setup errors within their respective regions $U(\alpha_r)$. An optimization problem corresponding to optimizing (2.1) can now be formulated as

$$\begin{align*}
\text{maximize} & \quad \mathbb{P}(S \in U(\alpha_r) \text{ for all } r \in \mathcal{R}) \\
\text{subject to} & \quad f_r(d(x, s)) \leq 0, \quad r \in \mathcal{R}, \quad s \in U(\alpha_r), \\
& \quad 0 \leq \alpha_{r,i} \leq \bar{\alpha}_{r,i}, \quad r \in \mathcal{R}, \quad i = 1, \ldots, n, \\
& \quad x \in \mathcal{X},
\end{align*}$$

The objective function measures the probability that the setup error $S$ falls within the region $\cap_{r \in \mathcal{R}} U(\alpha_r)$ and the constraints ensure that the criteria for all ROIs are satisfied within this region. Objective (2.2) may be added to the objective of problem (2.3) by the introduction of terms $\mathbb{P}(S \in U(\alpha_r))$ for $r$ in $\mathcal{R}$, weighted by a factor $\rho$ such that $0 < \rho \ll 1$. Computational details of the objective functions are given in Appendix A.

Note that the constraints of this optimization problem should represent the minimally acceptable criteria, i.e., the criteria such that there is little meaning in
treating the patient unless they are satisfied. These criteria are not intended to fine-tune the tradeoffs between conflicting goals, and should be contrasted to the conventional optimization goals constituting the objective function, which reflect the goals that are desirable, but not necessary, to satisfy.

2.3. Scenario position optimization problem

Because $U(\alpha_r)$ contains infinitely many points (unless $\alpha_r = 0$), the formulation (2.3) has infinitely many constraints. The constraints are moreover changing with the variables $\alpha$. Therefore, the formulation (2.3) cannot be easily optimized. To make the problem better suited for optimization, we propose an approximation of (2.3) that constrains only the nominal scenario and scenarios corresponding to a few points on the boundary of $U(\alpha_r)$. These points are selected as the points $\alpha_{r,i}p_i$ determined by the scalar elements $\alpha_{r,i}$ of the vector $\alpha_r$ and the directions $p_i$, for $i = 1, \ldots, n$ and $r$ in $\mathcal{R}$, as illustrated in Figure 1. Because each setup shift scenario corresponds to a position in $\mathbb{R}^3$, the point $\alpha_{r,i}p_i$ is referred to as the “scenario position” of the scenario. A larger number of scenarios could be used to increase the quality of the approximation. We let $\alpha_{r,0}p_0$ be fixed and correspond to the nominal scenario by setting $\alpha_{r,0} = 0$ and $\bar{\alpha}_{r,0} = 0$. The optimization problem approximating (2.3) can now be formulated as the scenario position optimization problem

$$
\begin{align*}
\text{maximize} \quad & \mathbb{P}(S \in U(\alpha_r) \text{ for all } r \in \mathcal{R}) \\
\text{subject to} \quad & f_r(d(x, \alpha_{r,i}p_i)) \leq 0, \quad r \in \mathcal{R}, \quad i = 0, \ldots, n, \\
& 0 \leq \alpha_{r,i} \leq \bar{\alpha}_{r,i}, \quad r \in \mathcal{R}, \quad i = 0, \ldots, n, \\
& x \in \mathcal{X}.
\end{align*}
$$

(2.4)

Because the dose is generally nonconvex in the scenario positions (and, for IMRT, also in machine parameters such as the multileaf collimator leaf positions), problem (2.4) is a nonconvex optimization problem. Therefore, the scenario positions resulting after optimization of this problem cannot be guaranteed to be globally optimal. While the problem is nonconvex, it is likely that the partial derivatives of the constraints with respect to the scenario positions are positive for conformal dose distributions, since the target coverage and OAR sparing often deteriorates as the distance of a scenario from the nominal position is increased.

When going from problem (2.3) to the approximation (2.4), it is assumed that if the criteria for ROI $r$ in $\mathcal{R}$ are satisfied in the nominal scenario and for a few points on the boundary of $U(\alpha_r)$, they will be satisfied in the full region $U(\alpha_r)$. This approximation was empirically found to be adequate for a number of cases in a previous study of ours [7]. Casiraghi et al. [4] found the approximation to accurately predict bounds on the DVHs, but not always on the point doses. Since we use dose-volume criteria in the optimization, it can be assumed that correctly bounded DVHs suffice. However, when the magnitudes of the errors are larger than the target, the approximation will not hold, and additional constraints for other points in $U(\alpha_r)$ ought to be included in the optimization.
Previous methods for maximizing the probability of satisfying the planning criteria evaluate the optimization functions under a large number of error scenarios. Using probabilistic models of the optimization function values, they approximate the probability of satisfying the planning criteria [19, 26]. An accurate model requires a large number of scenarios. Yang et al. [26] used 5 scenarios for errors in one dimension. Sobotta et al. [19] used 1000 scenarios for a two-dimensional case; a larger number would be required for a three-dimensional case. Since our method only requires scenarios at the boundaries of the regions $U(\alpha_r)$, it reduces the dimension of the problem by 1 and thus makes it more computationally attractive.

2.4. Optimizing margins

The formulation (2.4) that optimizes the scenario positions is intended to be as general as possible, and is not restricted to a specific modality or patient geometry. The requirement of computing doses under multiple scenarios amounts to an increased computational cost compared to conventional problems. Margins are commonly used to account for uncertainties in photon therapy treatments [12, 20]. For cases when margins can be assumed to be sufficient, the parameters $\alpha_r$ in $\mathbb{R}^n_+$ for a given ROI $r$ in $\mathbb{R}$ could be used to parameterize the margin of the ROI, so that the margins would be optimized instead of the scenario positions. Since this approach would not require multiple constraints for each structure nor dose computations in multiple scenarios, it would potentially be faster than the scenario position optimization.

2.5. Computational study

2.5.1. Patient cases

The scenario position optimization (2.4) was applied to a prostate case and a lung case. For the two cases, IMRT plans as well as IMPT plans were optimized. For the prostate case, a five-field IMRT treatment with equispaced beams beginning at $0^\circ$, and a two-field IMPT treatment with beams at $90^\circ$ and $270^\circ$ were optimized. For the lung case, a seven-field IMRT treatment with equispaced beams beginning at $0^\circ$, and a two-field IMPT treatment with beams at $35^\circ$ and $250^\circ$ were optimized. For both cases, the dose grid resolutions were $2.5 \times 2.5 \times 2.5$ mm$^3$ and the covariance matrices $\Sigma$ of the systematic setup errors were assumed to be given by $\Sigma = \sigma^2 I$ where $\sigma = 5$ mm. It was assumed that it was desired to account for errors of at most $2\sigma = 1$ cm. Transversal slices of the patients are shown in Figure 2.

2.5.2. Optimization

Scenario position optimization was implemented in the RayStation 2.8 treatment planning system (RaySearch Laboratories, Stockholm, Sweden). The optimization in RayStation is performed by a sequential quadratic programming algorithm using quasi-Newton updates of an approximation of the Hessian of the Lagrangian. A similar method is described by Gill et al. [8].

The scenario position optimization was initialized from plans reached by optimization with fixed scenario positions for seven iterations. For IMRT, these seven
Maximizing the probability of satisfying the planning criteria

(a) Prostate case

(b) Lung case

Figure 2. Transversal slice of the patient cases. Contours indicate the targets (white) and the main OARs (gray).

iterations were fluence map optimization iterations, and the resulting plan was segmented before the scenario positions were optimized in combination with direct step-and-shoot optimization [11].

When the problem (2.4) has been solved, $\alpha$ determines the scenario positions corresponding to the largest errors that can be accounted for while satisfying the planning criteria. After the scenario position optimizations that determined such values of $\alpha$, we optimized plans using worst case optimization [7] with the scenario positions fixed at the locations determined by $\alpha$. These plans were compared to plans optimized with the scenarios fixed at the a priori scenario positions of distance $2\sigma = 1$ cm from the nominal scenario. Given the scenario positions $\alpha_{r,i} p_i$ for $i = 0, \ldots, n$ and $r$ in $\mathcal{R}$, the worst case optimization problem is thus formulated as

$$
\begin{align*}
\min_{x \in \mathcal{X}} & \quad \sum_{r \in \mathcal{R}} \max_{i=0,\ldots,n} f_r(d(x, \alpha_{r,i} p_i)) \\
\text{subject to} & \quad g_r(d(x, \alpha_{r,i} p_i)) \leq 0, \quad r \in \mathcal{R}, \quad i = 0, \ldots, n,
\end{align*}
$$

(2.5)

where $f_r$ is the weighted sum of penalties for ROI $r$ and $g_r$ represents the constraints of ROI $r$. The optimization functions constituting the objectives and constraints used in this paper are defined mathematically in Appendix B.

2.5.3. Scenario dose calculation

During the optimizations, the doses under the different scenarios were calculated using the nominal mapping from fluence to dose for both IMRT and IMPT, but with the fluence maps shifted (and bilinearly interpolated) according to the displacements of the scenarios. An error along a beam direction was assumed to affect the resulting beam dose only according to the inverse-square law, so that when the patient moves away from the treatment unit, the beam dose is scaled downwards. Derivatives with respect to the scenario positions were approximated by finite differences.

In the robustness evaluation, the doses under the different scenarios were calculated with the beam isocenters shifted. There was thus a difference in the scenario
dose calculation used during the optimization and that used in the evaluation, since the shifted fluence used during the optimization results in slight inaccuracies due to the different divergence. The discrepancy implies that constraints that are satisfied with respect to the doses used during optimization are not necessarily satisfied with respect to the evaluation doses.

The scenario position optimization for IMRT was performed using a fast dose calculation algorithm based on singular value decomposition of pencil beam kernels [3]. For the optimizations with fixed scenario positions, the same algorithm was primarily used, but accurate dose was computed by a collapsed cone dose calculation algorithm [1] at intermediate iterations, and the subsequent optimization was performed on the dose of the fast algorithm incremental from the accurate dose.

For IMPT, the dose was computed using the pencil beam dose calculation algorithm of RayStation, which takes heterogeneities into account, also within the cross-section of each spot. The line spacing and the energy layer separation (in water equivalent media) were both set to 5 mm, but to improve upon the approximate dose calculation with shifted fluences used during the optimization, auxiliary spots were computed for 2.5 mm line spacing. The weights of the auxiliary spots were not included as variables in the optimization. In Unkelbach et al. [21], auxiliary spots were used in a similar way, but they applied nearest neighbor interpolation to the shifted spots instead of bilinear interpolation, which is used in the present paper.

3. Results

3.1. Prostate case

The prostate case was simplified to only include setup shifts in the anterior and posterior directions.

3.1.1. Optimization problem

The criteria for the target and the rectum of the prostate case were assumed to require robustness. Other criteria were included for the nominal scenario only. Five scenarios were included: the nominal scenario, and posterior and anterior isocenter shifts for the target and for the rectum. The optimization problem was formulated similar to (2.4). Its minimum robust requirements, as well as its nominal requirements, are presented in Table 1. The objective was to maximize the probability that the setup error will be smaller than the considered posterior and anterior isocenter shifts for the target and for the rectum.

3.1.2. Optimized scenarios

The posterior and anterior isocenter shifts for the prostate and the rectum were included as variables in the IMRT and IMPT optimizations. The optimizations did not result in changes to the posterior isocenter shift scenario for the target or the anterior isocenter shift scenario for the rectum, but kept these at their maximum positions of 1 cm. The two other shifts were modified for both modalities. Figure 3
Maximizing the probability of satisfying the planning criteria

**Table 1.** Robust and nominal constraints for the prostate case.

<table>
<thead>
<tr>
<th>Robust constraints</th>
<th>Nominal constraints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>Function</td>
</tr>
<tr>
<td>Target</td>
<td>Min dose</td>
</tr>
<tr>
<td>Target</td>
<td>Min 98% DVH</td>
</tr>
<tr>
<td>Rectum</td>
<td>Max 45% DVH</td>
</tr>
<tr>
<td>Rectum</td>
<td>Max 20% DVH</td>
</tr>
<tr>
<td>Rectum</td>
<td>Max 5% DVH</td>
</tr>
<tr>
<td>Target</td>
<td>Max 20% DVH</td>
</tr>
<tr>
<td>Bladder</td>
<td>Max dose</td>
</tr>
<tr>
<td>L. femoral head</td>
<td>Max dose</td>
</tr>
<tr>
<td>R. femoral head</td>
<td>Max dose</td>
</tr>
<tr>
<td>External</td>
<td>Max dose</td>
</tr>
</tbody>
</table>

displays the progress of the modified scenario positions and the maximum constraint violation during the optimizations.

![Scenario positions for IMRT](a) ![Maximum constraint violation for IMRT](b)

![Scenario positions for IMPT](c) ![Maximum constraint violation for IMPT](d)

**Figure 3.** Progress of the scenario positions and maximum constraint violation during the prostate case optimizations.

The optimizations first retract the scenario positions rapidly to improve upon the feasibility. For both IMRT and IMPT, the maximum constraint violation drops below $10^{-6}$ shortly after iteration 25. At the same time, the scenario positions are
being slowly pushed outwards, which improves upon the objective value. For IMRT, the scenario position optimization resulted in the positions 0.67 cm and 0.68 cm for respectively the target anterior and the rectum posterior isocenter shift scenarios. For IMPT, it resulted in the positions 0.72 cm and 0.74 cm.

### 3.1.3. Feasible scenario positions

In order to determine what could best be expected from a scenario position optimization, optimizations with fixed scenario positions were performed for an enumeration of possible scenario positions for the two ROIs. The posterior isocenter shift scenario for the target and the anterior isocenter shift scenario for the rectum were always set to 1 cm, while the anterior shift for the target and the posterior shift for the rectum were considered fixed for each point on an $8 \times 8$ point regular discretization of the $[0.5,0.85] \times [0.5,0.85]$ cm$^2$ box. For each point on the grid, an optimization with fixed scenario positions was performed for 100 iterations. The combinations of scenarios that resulted in feasible solutions are shown in Figure 4. The nonlinear constraints were considered satisfied when they evaluated to less than $10^{-6}$. Bilinear interpolation was used to approximate the cutoff when it occurred between points.

![Figure 4](image.png)

**Figure 4.** Feasible region (white) for the prostate case after optimization for 100 iterations. The crosses (x) denote the positions found by the scenario position optimization.

For IMRT, the optimized scenario positions came very close to what was deemed feasible for optimization with fixed scenario positions. For IMPT, the difference was a few tenth of a millimeter.

### 3.1.4. Robust plans with optimized scenarios

The optimized scenario positions were used as fixed positions in standard robust optimizations according to the formulation (2.5). The constraints from Section 3.1.1 were kept, but mean dose objectives of unity weight were introduced to reduce the doses to all healthy ROIs.
Robust optimizations with the scenario positions fixed at the a priori locations (1 cm in the posterior as well as the anterior direction) were also performed. Since with the a priori scenarios the constraints could not be satisfied, the target and rectum goals were relaxed into objective constituents with weights 100 for that optimization.

The DVHs resulting under the optimized and a priori scenarios for these plans are shown in Figure 5. For IMRT as well as IMPT, the plans with optimized scenarios neglect the 1 cm shift for the target but are in return able to perform better under the other scenarios than the plans optimized with a priori scenarios. The same is true of the −1 cm shift for the OAR.

![Prostate case DVHs for the plans optimized with respect to optimized scenario positions](image_a)

![Prostate case DVHs for the plans optimized with respect to a priori scenario positions](image_b)

**Figure 5.** Prostate case DVHs for the plans optimized with respect to optimized scenario positions and the plans optimized with respect to a priori scenario positions. The setup shifts in the anterior direction are annotated. Black curves correspond to the optimized scenario positions and gray curves correspond to the a priori scenario positions (setup shifts of ±1 cm in the anterior direction).

Each robust constraint of Table 1 (with volume level relaxed by 0.5 %) was eval-
uated under each of the optimized scenarios as well as under the a priori scenarios. For each of these two scenario groups and each method, the number of satisfied robust constraints was summed over the scenarios. The total numbers of satisfied constraints are shown in Table 2. The IMRT and IMPT plans optimized with respect to scenarios determined by the scenario position optimization satisfied respectively 5 and 3 constraints more under the optimized scenarios than the plans optimized with respect to the a priori scenarios. They also satisfied respectively 3 and 1 constraints more under the a priori scenarios. Totally, the number of satisfied robust constraints increased by a factor of respectively 1.5 and 1.2 when optimization was performed with respect to the retracted scenario positions.

**Table 2.** The number of satisfied robust constraints for the prostate case under the three optimized scenarios and under the three a priori scenarios. Five constraints and three scenarios make the maximum 15.

<table>
<thead>
<tr>
<th>Method</th>
<th>Under optimized scenarios</th>
<th>Under a priori scenarios</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMRT w.r.t. optimized scenarios</td>
<td>13</td>
<td>11</td>
<td>24</td>
</tr>
<tr>
<td>IMRT w.r.t. a priori scenarios</td>
<td>8</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>IMPT w.r.t. optimized scenarios</td>
<td>12</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>IMPT w.r.t. a priori scenarios</td>
<td>9</td>
<td>9</td>
<td>18</td>
</tr>
</tbody>
</table>

3.2. Lung case

For the lung case, not only the anterior and posterior, but also the left, right, superior, and inferior isocenter shift scenarios were included in the scenario position optimization.

3.2.1. Optimization problem

The target and the heart were considered to be the only goals of the lung case requiring robustness. Other goals were included for the nominal scenario only. There were 13 scenarios included: the nominal scenario, and left, right, posterior, anterior, superior, and inferior isocenter shift scenarios for the target and for the heart. The optimization problem was formulated similar to (2.4). Its minimum robust requirements, as well as its nominal requirements, are presented in Table 3. The objective was to maximize the probability that the setup error will be smaller than the errors considered for the target and for the heart.

3.2.2. Optimized scenarios

The left, right, posterior, anterior, superior, and inferior isocenter shift scenarios for the target and the heart were included as variables in the IMRT and IMPT optimizations. Figure 6 displays the progress of the modified scenario positions and the maximum constraint violation during the optimizations.
Maximizing the probability of satisfying the planning criteria

Table 3. Robust and nominal constraints for the lung case.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Function</th>
<th>Dose level [Gy]</th>
<th>Structure</th>
<th>Function</th>
<th>Dose level [Gy]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Min dose</td>
<td>68</td>
<td>Lung</td>
<td>Max 37 % DVH</td>
<td>20</td>
</tr>
<tr>
<td>Target</td>
<td>Min 98 % DVH</td>
<td>70</td>
<td>External</td>
<td>Max dose</td>
<td>77</td>
</tr>
<tr>
<td>Target</td>
<td>Max dose</td>
<td>77</td>
<td>Heart</td>
<td>Max 1 % DVH</td>
<td>40</td>
</tr>
</tbody>
</table>

Figure 6. Progress of the scenario positions and maximum constraint violation during the lung case optimizations.
As for the prostate case, the optimizations first retract the scenario positions rapidly to improve upon the feasibility. For both IMRT and IMPT, the maximum constraint violation drops below $10^{-6}$ before iteration 75. At the same time, the scenario positions are being slowly pushed outwards, which improves upon the objective function value. The resulting scenario positions are shown in Table 4.

### Table 4. Optimized scenario positions for the lung case.

<table>
<thead>
<tr>
<th>Direction</th>
<th>IMRT Target scenario [cm]</th>
<th>IMRT Heart scenario [cm]</th>
<th>IMPT Target scenario [cm]</th>
<th>IMPT Heart scenario [cm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>1.0</td>
<td>0.35</td>
<td>0.94</td>
<td>0.65</td>
</tr>
<tr>
<td>Right</td>
<td>0.5</td>
<td>1.0</td>
<td>0.81</td>
<td>1.0</td>
</tr>
<tr>
<td>Posterior</td>
<td>1.0</td>
<td>1.0</td>
<td>0.87</td>
<td>1.0</td>
</tr>
<tr>
<td>Anterior</td>
<td>1.0</td>
<td>1.0</td>
<td>0.73</td>
<td>1.0</td>
</tr>
<tr>
<td>Superior</td>
<td>1.0</td>
<td>1.0</td>
<td>0.70</td>
<td>1.0</td>
</tr>
<tr>
<td>Inferior</td>
<td>0.92</td>
<td>1.0</td>
<td>1.0</td>
<td>0.75</td>
</tr>
</tbody>
</table>

#### 3.2.3. Feasible scenario positions

Due to its multidimensionality, the feasible region of the scenario positions for the lung case optimization problem cannot be as easily determined as that of the prostate case problem. To determine whether the scenario position optimizations resulted in unnecessarily retracted scenario positions, plans with fixed scenario positions were optimized. First, the scenario positions as determined by the scenario position optimizations, shown in Table 4, were used. Second, these scenario positions were pushed 0.1 mm outwards, but to a maximum of 1 cm, and these extended positions were used. In the first case, the IMRT as well as the IMPT optimization resulted in feasible plans, with maximum constraint violation less than $10^{-6}$. With the scenarios pushed outwards, neither the IMRT nor the IMPT optimization resulted in a feasible solution. This indicates that the scenario positions found could not be much improved upon.

#### 3.2.4. Robust plans with optimized scenarios

The optimized scenario positions were used as fixed positions in robust optimizations with standard robust goals according to the formulation (2.5). The constraints from Section 3.2.1 were kept, but mean dose objectives of unity weight were introduced to reduce the doses to all healthy ROIs.

Robust optimizations with the scenario positions fixed at the a priori locations (1 cm in the positive and negative axis directions) were also performed. Since with the a priori scenarios the constraints could not be satisfied, the target and heart goals were relaxed into objective constituents with weights 100 for that optimization.

The DVHs resulting under the optimized and a priori scenarios for these plans are shown in Figure 7. The 1 cm right shift for IMRT and the 1 cm superior shift for IMPT resulted in the worst target coverage for the plans with optimized scenario positions. While the plans with optimized scenario positions neglect some shifts,
they are in return able to improve upon the target coverage and OAR sparing in other shifts compared to the optimizations with a priori scenarios.

![Graphs showing DVHs for IMRT and IMPT plans optimized with respect to optimized and a priori scenario positions.](image)

**Figure 7.** Lung case DVHs for the plans optimized with respect to optimized scenario positions and the plans optimized with respect to a priori scenario positions. Black curves correspond to the optimized scenario positions and gray curves correspond to the a priori scenario positions (±1 cm in all axis directions).

Each robust constraint of Table 3 (with volume level relaxed by 0.5 %) was evaluated under each of the optimized scenarios as well as under the a priori scenarios. Since no method satisfied the target min 98 % DVH constraint in any scenario, its dose level was relaxed from 70 Gy to 69.5 Gy in the evaluation. For each of these two scenario groups and each method, the number of satisfied robust constraints was summed over the scenarios. The total numbers of satisfied constraints are shown in Table 5. The IMRT and IMPT plans optimized with respect to scenarios determined by the scenario position optimization satisfied respectively 13 and 10 constraints more under the optimized scenarios than the plans optimized with a
4. Discussion

Worst case optimization aims at plans that are robust against all scenarios within some bounds. When the bounds are too loose, there is a risk that not all scenarios can be satisfied. In such cases, the plan quality in scenarios corresponding to smaller errors may suffer as well. After a slight tightening of the bounds within which the optimization is required to be robust, it may be possible to achieve better plan quality with respect to the scenarios within the tighter bounds. The results of this paper shows that such tightening can enable better plan quality with respect to the majority of the scenarios within the loose a priori bounds as well: By disregarding one or a few of the a priori scenarios, the method proposed in the present paper yielded better quality with respect to all other scenarios. It thereby resulted in higher probability of satisfying the planning criteria.

For the simplified goals of the prostate case, the proposed method resulted in the intuitively correct solution: The posterior isocenter shift scenario for the target and the anterior isocenter shift scenario for the rectum did not move from their maximum positions, as could be expected since these scenarios were not in conflict with other scenarios. The other two shifts moved to become compatible. By retracting these scenarios, the scenario position optimization enabled better solutions with respect to all other shifts and thereby achieved higher probability of satisfying the planning criteria than optimization with the scenario positions fixed at the a priori locations. This shows that asking for a little less in the optimization may sometimes lead to better overall plan quality.

For the lung case, the intuitively correct solution would move the target right scenario and the heart left scenario. The scenario position optimization did so, but moved other scenarios as well. As for the prostate case, neglecting the worst scenario positions in some directions enabled better solutions with respect to the other positions and thus higher probability of satisfying the planning criteria. That multiple scenarios were retracted shows that it is hard to determine before the

priori constraints. They also satisfied respectively 12 and 2 constraints more under the a priori scenarios. Totally, the number of satisfied robust constraints increased by a factor of respectively 2.7 and 1.6 when optimization was performed with respect to the retracted scenario positions.

Table 5. The number of satisfied robust constraints for the lung case under the seven optimized scenarios and under the seven a priori scenarios. Four constraints and seven scenarios make the maximum 28.

<table>
<thead>
<tr>
<th>Method</th>
<th>No. of satisfied constraints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Under optimized scenarios</td>
</tr>
<tr>
<td>IMRT w.r.t. optimized scenarios</td>
<td>21</td>
</tr>
<tr>
<td>IMRT w.r.t. a priori scenarios</td>
<td>8</td>
</tr>
<tr>
<td>IMPT w.r.t. optimized scenarios</td>
<td>20</td>
</tr>
<tr>
<td>IMPT w.r.t. a priori scenarios</td>
<td>10</td>
</tr>
</tbody>
</table>

4. Discussion
optimization which scenarios to retract; that they were retracted differently shows that it is hard to determine how much they should be retracted.

The differences between the robust plans accounting for optimized scenarios and the robust plans accounting for a priori scenarios were larger for IMRT than for IMPT. The IMRT plans accounting for optimized scenarios satisfied a much larger number of constraints than the plans accounting for a priori scenarios, also when evaluated under the a priori scenarios. This shows that for IMRT, one sometimes gets more than one asks for, which was also the rationale behind the iterative updates of margins performed by Gordon and Siebers [10]. For IMPT, the plans accounting for optimized scenarios and those accounting for a priori scenarios were more alike when evaluated under the a priori scenarios, but the plans accounting for optimized scenarios still satisfied a larger number of constraints. A reason for the smaller difference could be that IMPT has more degrees of freedom than does IMRT, so that it has more possibilities to yield solutions that closely comply with what is requested.

For the prostate case, the enumeration of the scenario positions showed that the positions determined by the scenario position optimization could not be much improved upon while maintaining feasibility. For the lung case, no feasible solution was found when the scenario positions were simultaneously extended by 0.1 mm. This shows that although the scenario position optimization problem is nonconvex, it resulted in solutions close to what could be best achieved for the considered cases.

In the present paper, only setup errors were considered. For IMPT, range uncertainty is another influential error source [15]. If interpolation between the energy layers in the spot grid can be used to approximate the effects of range errors, doing so would provide a parameterization of range uncertainty scenarios that could be used in a scenario position optimization like the one used for setup errors in this paper.

5. Conclusion

A method was introduced that maximizes the probability of satisfying the planning criteria in the presence of setup uncertainty. The method enforces the planning criteria under all errors within a specified region. The parameters that determine the size of this region are included as variables in the optimization, and the probability that the error will fall within this region is maximized. The method was applied to a prostate and a lung case and the resulting plans were compared to plans optimized with respect to errors within a priori determined regions. For the prostate case, the plans of the proposed method fulfilled $1.5$ (IMRT) and $1.2$ (IMPT) times as many planning criteria as the method with a priori determined region. For the lung case, the numbers were $2.7$ (IMRT) and $1.6$ (IMPT).

Acknowledgment

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A. Probability computation

The setup errors are assumed to be normally distributed with zero mean and covariance matrix $\Sigma = \sigma^2 I$. If there were only a single direction along which to move (i.e., $n = 2$, $p_1, p_2 \in \mathbb{R}$, and $p_1 = -\beta p_2$ for some $\beta > 0$), the probability density function would be $(\sigma \sqrt{2\pi})^{-1} e^{-t^2/2\sigma^2}$, so the probability that the criteria of ROI $r$ in $\mathcal{R}$ were satisfied given $\alpha_r$ would be

$$P(S \in [-\alpha_r,1|p_1|, \alpha_r,2|p_2|]) = \frac{1}{\sigma \sqrt{2\pi}} \int_{-\alpha_r,1|p_1|}^{\alpha_r,2|p_2|} e^{-t^2/2\sigma^2} dt = \frac{1}{2} \sum_{i=1}^{2} \text{erf} \left( \frac{\alpha_{r,i}|p_i|}{\sigma \sqrt{2}} \right),$$

where the error function erf$(x)$ is defined by

$$\text{erf}(x) = \frac{2}{\sqrt{\pi}} \int_{0}^{x} e^{-t^2} dt.$$

For simplicity, the probability that the criteria of $r$ in $\mathcal{R}$ are satisfied, corresponding to the constituents of objective (2.2), when there are multiple directions is assumed to be the sum of such single direction probabilities, viz.,

$$P(S \in U(\alpha_r)) = \frac{1}{n} \sum_{i=1}^{n} \text{erf} \left( \frac{\alpha_{r,i}||p_i||_2}{\sigma \sqrt{2}} \right),$$

where the length of $p_i$ is measured by the norm instead of the absolute value, since $p_i$ is now in $\mathbb{R}^3$. This assumption says that the different directions contribute independently to the probability. The probability that the criteria of all ROIs in $\mathcal{R}$ are satisfied, corresponding to objective (2.1), is then given by

$$P(S \in U(\alpha_r) \text{ for all } r \in \mathcal{R}) = \frac{1}{n} \sum_{i=1}^{n} \min_{r \in \mathcal{R}} \text{erf} \left( \frac{\alpha_{r,i}||p_i||_2}{\sigma \sqrt{2}} \right).$$

The function erf$(x)$ is concave in $x \in \mathbb{R}_+$ and the min operator preserves concavity. Hence, since the objective function is maximized, the objective of problem (2.3) under this probability computation assumption does not introduce additional non-convexity to the optimization problem.

If it can be assumed that only one ROI is compromised in each scenario direction $i = 1, \ldots, n$ while each other ROI $r$ in $\mathcal{R}$ keeps its corresponding value of $\alpha_{r,i}$ at its upper bound throughout the optimization (assuming that it is initialized to its upper bound), the solutions resulting from using the objectives

$$\frac{1}{n} \sum_{i=1}^{n} \min_{r \in \mathcal{R}} \text{erf} \left( \frac{\alpha_{r,i}||p_i||_2}{\sigma \sqrt{2}} \right) \quad \text{and} \quad \sum_{r \in \mathcal{R}} \frac{1}{n} \sum_{i=1}^{n} \text{erf} \left( \frac{\alpha_{r,i}||p_i||_2}{\sigma \sqrt{2}} \right)$$

are the same. That this is the case is assumed in the present paper, and therefore only the latter term is used as objective in the scenario position optimizations.
B. Optimization functions

Given the optimization variables \( x \in \mathcal{X} \), let \( D(v; x) \) parameterize the DVH of some considered ROI as a function of the volume \( v \in (0, 1] \). A max DVH optimization function with dose level \( \hat{d} \) and volume parameter \( \hat{v} \) is given by

\[
\int_{\hat{v}}^{1} \left( D(v; x) - \hat{d} \right)^2 \, dv.
\]

Min DVH functions are defined analogously, but with the signs of \( D(v; x) \) and \( \hat{d} \) reversed and with the integration taken over \((0, \hat{v}]\). Max and min dose functions are derived from the corresponding DVH functions with \( \hat{v} \) set to respectively 0 and 1. A mean dose function is given by

\[
\left( \int_{0}^{1} D(v; x) \, dv \right)^2.
\]

References


