Robust optimization of dose-volume metrics for prostate HDR-brachytherapy incorporating target volume delineation uncertainties

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Abstract

In radiation therapy planning, uncertainties in target volume definition yield a risk of underdosing the tumor. The classical way to prevent this in the context of external beam radiotherapy (EBRT) has been to expand the clinical target volume (CTV) with an isotropic margin to obtain the planning target volume (PTV). However, the EBRT-based PTV concept is not directly applicable to brachytherapy (BT) since it can lead to dose escalation (Tanderup et al., 2010). This work presents a treatment plan optimization model that uses worst-case robust optimization to account for delineation uncertainties in interstitial high-dose-rate BT. A scenario-based method was developed that handles uncertainties in index sets. Heuristics were included to reduce the calculation times to acceptable proportions. The method was applied on data from prostate cancer patients, and evaluated in terms of commonly used dosimetric performance criteria for the CTV and relevant organs at risk. The robust optimization approach was compared against the classical PTV margin concept and against a scenario-based CTV margin approach. The results show that both the scenario-based margin and the robust optimization method are well capable of reducing the risk of underdosage to the tumor. As expected, the scenario-based CTV margin approach leads to dose escalation within the target, whereas this could be prevented with the robust model.

1 Introduction

Cancer can be treated by surgery, chemotherapy, radiotherapy, or a combination of these modalities. For deep-seated solid tumors, radiotherapy is an adequate treatment option as ionising radiation can penetrate through healthy tissues to reach the tumor. Radiation therapy can either be delivered by external beam radiotherapy (EBRT) or by brachytherapy (BT). With EBRT, radiation coming from an external source is pointed at the tumor, while with BT a radio-active source is placed inside or close to the tumor.

For prostate cancer, which is the most common type of cancer among men, interstitial high-dose rate brachytherapy (HDR-BT) with a temporary implant has been shown to be an adequate treatment (Yamada et al., 2012). Typically, a template containing a large number of evenly spaced holes is placed in front of the patient’s perineum while he is under anesthesia in dorsal position. Depending on the dimensions of the prostate, around 15 up to 20 of these holes are selected for implanting a hollow catheter into the prostate. After implantation of all needles, a remote afterloader device advances a \(^{192}\)Ir source through the needles in a successive way. In each catheter, the source stops at predetermined locations (dwell positions) inside the target volume for a predetermined amount of time (dwell time) in order to deposit a sufficiently high dose to the tumor. Directly after irradiation, the source is removed from the patient and stored in the afterloader device for future use.

Radiotherapy inevitably results in exposure of healthy tissues surrounding the tumor. The spatial distribution of catheters and dwell positions together with the dwell time distribution determine the shape and magnitude of the dose distribution. The goal of treatment planning is to determine the number and locations of catheters together with the dwell times such that the tumor receives a sufficiently high dose to sterilize the tumorous cells while limiting the dose exposure to surrounding organs at risk (OARs) as much as possible to minimize the risk of side-effects. The problem of designing a treatment plan for HDR-BT lends itself to be formulated as a mathematical optimization problem (De Boeck et al., 2014).
Prior to treatment planning a scan of the patient’s anatomy is made on which the target volume and the OARs are delineated as structure sets. These delineations are subject to intra- and inter-observer variability, i.e., the same observer does not draw identical contours for the same individual case, and different observers produce different delineations for an identical case, respectively. This implies uncertainty in the location and shape of the delineated structures, and thus uncertainty in the volumes to be irradiated and the volumes to be spared. In order to numerically optimize and evaluate a dose distribution, these structures are discretized into finite sets of small volume elements, that are considered as dose calculation points. The dose deposited in each calculation point is the superposition of the dose rate contributions from all the dwell positions weighted by their respective dwell times. Uncertainties in the delineations hence translate into uncertainty in whether or not a calculation point belongs to a certain structure (Figure 1). This implies that there is uncertainty in the index sets of the optimization model. So far, optimization methods have not dealt with this type of uncertainty. Therefore, the aim of the current work is to develop an optimization method that is robust against uncertainty in index sets, and consequently can be applied for robust optimization of HDR-BT dose distributions incorporating delineation uncertainties.

Figure 1: Two delineations of a prostatic target volume based on a transversal ultrasound imaging scan. Both delineations yield a different set of calculation points residing in the structure: the blue points reside in both structures, the yellow and red points only in the yellow and red delineation, respectively.

1.1 Review of methods accounting for delineation uncertainties

The classical way to deal with uncertainties in EBRT planning is to apply a margin around the tumor volume such that a sufficiently large volume receives the therapeutic dose that was prescribed. A more recent approach is to use computational methods to numerically account for uncertainties during the treatment planning optimization process. Methods like stochastic programming (e.g. Unkelbach and Ulfke, 2004; Bohoslavsky et al., 2013) and worst-case robust optimization (e.g. Chan et al., 2006; Bortfeld et al., 2008; Fredriksson, 2013) have been suggested for this task.

1.1.1 Margin approach

According to international consensus guidelines published in the ICRU 62 report (International Commission on Radiation Units and Measurements, 1999), uncertainties in EBRT are accounted for by applying a margin around the tumor volume. Treatment preparation starts by delineating the gross palpable, visible or clinically demonstrable location of the tumor on a scan, yielding the gross tumor volume (GTV). Since microscopic disease spread surrounding the GTV is invisible on the scan, the GTV is expanded with a certain margin, resulting in the clinical target volume (CTV). An additional margin is applied to account for geometrical uncertainties in treatment planning (e.g., errors due to organ filling and movement) and delivery (e.g., set-up errors due to patient and beam positioning), which results in the planning target volume (PTV).

The PTV concept as described in the ICRU 62 report has been developed for EBRT, where the aim is to expand the dose distribution into a homogeneous plateau reaching beyond the CTV. For BT however, Tanderup et al. (2010) noted that: “a homogeneous dose cannot be obtained in and around a brachytherapy CTV”, since adding PTV margins would lead to an undesirable dose escalation within the target. Applying a margin around the CTV to account for delineation uncertainties is thus not applicable for BT.
1.1.2 Robust optimization

So far, robust optimization and stochastic programming have only been applied to treatment planning models for EBRT. Stochastic programming considers the probability distribution of an uncertain parameter, for example through optimizing the expectation of the objective function or by restricting the probability of constraint violations (e.g. Chu et al., 2005; Olsson and Wright, 2006; Unkelbach and Ulfke, 2004; Bohoslavsky et al., 2013; Fredriksson, 2013). This inherently requires knowledge or assumptions regarding the probability distribution of the uncertain parameter. However, such information is often not available, as is the case in our application. Worst-case robust optimization on the other hand assumes an uncertainty region or a scenario-set in which the uncertain parameter resides. A worst-case robust optimization model only considers solutions that are robust feasible, i.e., solutions that are feasible for all possible realizations of the parameters. Among these solutions, a worst-case robust minimization (maximization) problem selects the solution that minimizes (maximizes) the maximum (minimum) over all possible parameter values or scenarios of the objective function (Ben-Tal et al., 2009). As a result, worst-case robust optimization yields treatment plans that are more robust than plans obtained with a stochastic programming approach, i.e., they perform better in the worst case scenario (Fredriksson, 2012). Robust optimization for EBRT has been considered by various groups and can be applied to treatment planning models at three different levels: one can require robustness per calculation point (e.g. Chan et al., 2006; Bortfeld et al., 2008; Liu et al., 2012), per objective and constraint (Chen et al., 2011) or for the complete model (Fredriksson et al., 2011, e.g.). For a detailed comparison of these three approaches, we refer to Fredriksson and Bokrantz (2014). We believe that each constraint should be satisfied in all of the scenarios, and that the robustness of each objective should be considered separately (as opposed to an aggregate of the objectives), hence we apply robustness per objective.

The methods described above have been applied to EBRT planning models for various types of uncertainties (e.g. organ motion or setup uncertainties), but none have considered delineation uncertainties. However, uncertainties in target volume delineation are known to be among the major causes of geometrical uncertainties (Weiss and Hess, 2003) in EBRT and BT. So far, methods for robust treatment planning only considered uncertainties that yield uncertainty in the location of the calculation point relative to the source (e.g. through organ motion or a setup uncertainties), while the structure the calculation point belongs to is fixed. This implies uncertainty in the dose rate (i.e., the dose per unit time), which is an important input parameter in treatment planning optimization models. On the other hand, delineation uncertainties do not change the location of a calculation point, so the dose rate remains fixed. Instead, they yield uncertainty in the structure a calculation point belongs to. The literature on robust optimization only considers uncertainty in input parameters. As our problem concerns uncertainty in index sets, we cannot use previously developed models, and a new approach is required.

1.2 Aim and contribution of the paper

The goal of this work is to take delineation uncertainties into account in the treatment planning optimization process for prostate HDR-BT using a worst-case robust optimization approach. For this we need to develop a worst-case robust optimization method to incorporate delineation uncertainties in index sets. We aim to reduce the risk of underdosing the CTV while still respecting the pre-defined OAR constraints. We compare our method to the classical margin approach.

The contributions of this work are (1) using computational methods to incorporate delineation uncertainties in the treatment plan optimization, (2) extending the robust optimization approach to account for uncertainties in index sets, (3) using robust optimization to deal with uncertainties in BT and (4) providing a speed-up for the nominal treatment planning model for BT that optimizes clinical objectives (Gorissen et al., 2013).

This paper is organized as follows. In Section 2, HDR-BT plan optimization is further clarified (Section 2.1) and the nominal model for HDR-BT of prostate cancer is introduced (Section 2.2). Next, an alternative margin approach is proposed in Section 2.3 and the robust model is developed in Section 2.4. Methods for reducing the calculation times are presented in Section 2.5. The computational experiments and their results are presented in Section 3. A discussion and conclusion are provided in Sections 4 and 5, respectively.

2 Treatment plan optimization model

2.1 Dose prescription and plan evaluation

The dosimetric quality of a treatment plan is usually evaluated using dose-volume histogram (DVH) metrics. These metrics are denoted by \( D_{x\%}(S) \) and \( D_{vcc}(S) \), which reflect the minimum dose received by the hottest \( x\% \) and \( vcc \) of the structure volume \( S \), respectively, or by \( V_{y\%}(S) \), which denotes the fraction of the structure volume \( S \) receiving at least \( y\% \) of the prescribed tumor dose. A treatment plan should satisfy pre-set constraints on the DVH metrics. An example of a dose prescription protocol for prostate HDR-BT, for which the rectum...
and urethra are the most relevant OARs, is presented in Table 1. Here, $D_{90\%}(PTV)$ is given as a percentage of the prescribed tumor dose.

**Table 1: Dose-volume criteria based on the protocol by Hoskin et al. (2007).**

<table>
<thead>
<tr>
<th></th>
<th>PTV</th>
<th>Rectum</th>
<th>Urethra</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_{90%}$</td>
<td>$\geq 100%$</td>
<td>$D_{10%} \leq 7.2$ Gy</td>
<td>$D_{10%} \leq 10$ Gy</td>
</tr>
<tr>
<td>$V_{100%}$</td>
<td>$\geq 95%$</td>
<td>$D_{2cc} \leq 6.7$ Gy</td>
<td>$D_{0.1cc} \leq 10$ Gy</td>
</tr>
<tr>
<td>$V_{150%}$</td>
<td>$\leq 55%$</td>
<td>$V_{150%} \leq 20%$</td>
<td></td>
</tr>
<tr>
<td>$V_{200%}$</td>
<td>$\leq 20%$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The optimization models that are currently exploited by treatment planning systems assign a penalty to each calculation point based on the difference between the planned and the prescribed dose, and minimize the total penalty (e.g., Lessard and Pouliot, 2001). Since such penalties are a surrogate for the actual planning goals, which is to satisfy the pre-set DVH criteria, recently developed methods directly optimize the DVH metrics (Siauw et al., 2011; Gorissen et al., 2013; Holm et al., 2013). As a DVH-based optimization model uses clinically relevant objectives, we use the model from Gorissen et al. (2013).

### 2.2 Nominal model with isotropic PTV margin

In Gorissen et al. (2013), both catheter locations and dwell time distributions are optimized, where active dwell locations were given for each possible catheter location with a 3 mm separation. The goal is to maximize the fraction of the PTV receiving at least the prescribed dose, denoted by $V_{100\%}(PTV)$:

\[
(LDV) \quad \max \frac{1}{|I_P|} \sum_{i \in I_P} v_i \\
s.t. \quad d^T_i t \geq v_i D_{pres} \quad \forall i \in I_P \\
\quad t \geq 0 \\
\quad v_i \in \{0, 1\} \quad \forall i \in I_P \\
\text{[see Appendix for additional constraints (4) up to (8)]}
\]

Here, $d_i \in \mathbb{R}_{+}^{J}$ denotes the vector with dose rates from each dwell position to calculation point $i$, $I_P$ denotes the set of dose calculation points in the PTV, and $J$ denotes the set of dwell positions. The optimization variable $t \in \mathbb{R}_{+}^{J}$ contains the (nonnegative) dwell times of all dwell positions. As a result, $d^T_i t$ gives the total dose planned to be delivered to calculation point $i$. $D_{pres}$ denotes the prescribed dose to the PTV, and $v_i$ is an auxiliary variable that is equal to one if calculation point $i$ receives at least the prescribed dose, and zero otherwise. This is enforced by the first constraint and the objective. The latter maximizes the fraction of calculation points receiving at least the prescribed dose.

Additional constraints are included to restrict the dose to the rectum and the urethra and to choose the number of catheters and their locations (see Appendix). These constraints are not provided in detail here, as they remain the same in the robust model.

### 2.3 Nominal model with scenario-based margin

Given a nominal delineation of the CTV and using Smith et al. (2007), we generate scenarios for delineations and the corresponding sets of CTV calculation points. Since the CTV-to-PTV margin is smaller than the delineation uncertainty reported in the literature, the PTV does not fully contain all the CTV scenarios, and $I_P$ does not contain all of the calculation points that are in the CTV according to at least one scenario. Therefore, we also test the nominal model using a scenario-based margin. The union of all CTV scenarios is considered as the PTV, and the set of all calculation points that may be in the CTV according to our scenario set, denoted by $\tilde{I}_C$, is used instead of the set $I_P$. In the remainder of this article, we refer to this approach as the “margin model”.

### 2.4 Robust treatment plan optimization model

We use a scenario-based approach for our robust optimization model. For each scenario in the set $S$, we know the set of calculation points within the CTV. This information is stored in matrix $C$, an $|S| \times |I|$ matrix where
each row corresponds to a scenario and each column corresponds to a calculation point. The entry on the $s^{th}$ row in the $i^{th}$ column equals 1 if calculation point $i$ resides in the CTV for scenario $s$, and zero otherwise. This matrix is used to calculate CTV coverage for each scenario $s$ as $V_{100\%}^{(CTV)} = (C_s v)/(C_s e)$, where $C_s$ denotes row $s$ of matrix $C$, $e$ is the all-ones vector and $v$ is as before. The numerator counts the number of calculation points that receive at least the prescribed dose and are in the CTV according to scenario $s$, while the denominator counts the number of calculation points in the CTV according to scenario $s$.

The robust counterpart of the $(LDV)$ model is formulated as:

$$(RC) \quad \max \quad V$$

s.t. 

$$V \leq \frac{C_s v}{C_s e} \quad \forall s \in S$$

$$\bar{d}_i^T t \geq D_{pres} v_i \quad \forall i \in \tilde{I}_C$$

$$t \geq 0$$

$$v_i \in \{0,1\} \quad \forall i \in \tilde{I}_C$$

[additional constraints (4) up to (8) in Appendix A].

Initial tests show that $(RC)$ yields a risk of overdosage, reflected by a too high $V_{200\%}^{(CTV)}$. Therefore, we added the following constraints to $(RC)$ in order to limit $V_{200\%}$ for each scenario:

$$\bar{d}_i^T t \leq 2D_{pres} + Mu_i \quad \forall i \in \tilde{I}_C$$

$$\frac{C_s u}{C_s e} \leq 0.2 \quad \forall s \in S$$

$$u_i \in \{0,1\} \quad \forall i \in \tilde{I}_C,$$

where $u_i$ is a binary variable that is 0 only if calculation point $i$ receives at most twice the prescription dose and 1 otherwise, and $M$ is an arbitrary large number. For scenario $s$, we have $V_{200\%} = C_s u/C_s e$, which is restricted to be at most 0.2 according to the protocol by Hoskin et al. (2007), see Table 1.

The size of $(LDV)$ and $(RC)$ can be found in Table 2, where we only consider the constraints and variables presented here, and skip the constraints and variables corresponding to OAR sparing, maximum dwell times and catheter choice as these are identical for both models. This table clearly shows the major advantage of our approach: the number of binary variables does not increase with the number of scenarios $|S|$, but only with the number of calculation points in the uncertainty region $|\tilde{I}_C|$. The number of constraints increases polynomially with $|S|$.

<table>
<thead>
<tr>
<th>Table 2: Problem sizes for $(LDV)$ and $(RC)$.</th>
<th>(LDV)</th>
<th>(RC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of binary variables</td>
<td>$</td>
<td>I_P</td>
</tr>
<tr>
<td>Number of continuous variables</td>
<td>$</td>
<td>J</td>
</tr>
<tr>
<td>Number of constraints</td>
<td>$</td>
<td>I_P</td>
</tr>
</tbody>
</table>

2.5 Reduction of solution times

Even though the number of binary variables increases only with the size of the uncertainty region, the solution time becomes more than several days, which is too long for the model to be used in clinical practice, or may not be solved at all due to memory issues. Therefore, we propose several heuristics that are combined in one algorithm to speed up the optimization, which is summarized in Algorithm 1.

First of all, for the CTV we relax the requirement $v_i \in \{0,1\}$ to $v_i \in [0,1]$. Besides strongly reducing the number of binary variables and thus the calculation times, this relaxation has an appealing interpretation. Both for the binary and the continuous case, we have that $v_i = 1$ when calculation point $i$ receives at least the prescribed dose. When $i$ receives a dose below the prescription dose, the binary $v_i$ equals 0, whereas the continuous variable $\hat{v}_i$ equals the delivered dose as a fraction of the prescribed dose. Thus, when using continuous variables, the dose to calculation point $i$ is still pushed upwards to $\hat{D}_{pres}$, even when calculation point $i$ does not receive the prescribed dose.

Secondly, optimization speed is improved by exploiting the fact that calculation points in close proximity to the catheters are likely to receive a high dose, while calculation points at a larger distance are likely to receive a low dose. This is due to the inverse quadratic relation between the dose rate from a dwell position to a calculation point and the distance between the two points. It may thus not be necessary to optimize for all calculation points in $\tilde{I}_C$. Therefore, we initially assume that the calculation points near the catheters,
denoted by the set $\tilde{I}_n^C$, receive at least the prescribed dose (i.e., $v_i = 1$ $\forall i \in \tilde{I}_n^C$), and that calculation points far from the catheters, denoted by $\tilde{I}_f^C$, do not receive more than $2D_{pres}$ (i.e., $u_i = 1$ $\forall i \in \tilde{I}_f^C$). An example of such sets is illustrated in Figure 2. One could think of many ways to define these sets. We base our choice on the outcome of the nominal optimization model: all calculation points that receive a dose above $D_{pres}$ or below $2D_{pres}$ when applying the nominal treatment plan are included in $\tilde{I}_n^C$ and $\tilde{I}_f^C$, respectively. Note that for the calculation points outside $I^C$ and $I^F$ no assumptions on the received dose levels are made. $(RC)$ is optimized where constraints (1) and (2) only apply to calculation points in $I_C \setminus I_n^C$ and $I_C \setminus I_f^C$, respectively. After optimization, we check for each of the calculation points in $\tilde{I}_n^C$ and $\tilde{I}_f^C$ whether they indeed receive a sufficiently high and low dose as respectively was assumed. If not, we exclude a predetermined number of the coldest and hottest calculation points from the sets $\tilde{I}_n^C$ and $\tilde{I}_f^C$, respectively, and re-optimize using the previous optimal treatment plan as a starting solution. This process is continued until the number of calculation points for which we made an incorrect assumption is sufficiently low (inner while loop in Step 1 of Algorithm 1).

Thirdly, we implement the adversarial approach (Bienstock and Özbay, 2008). The robust model is solved using the scenario set $S_{100\%} \subset S$ for the $V_{100\%}$ objective and $S_{200\%} \subset S$ for the constraint on $V_{200\%}$ of the CTV. Initially, $S_{100\%}$ only contains the nominal scenario and $S_{200\%}$ is empty. Using the optimal treatment plan, the scenario with the lowest $V_{100\%}(CTV)$ is added to $S_{100\%}$, unless it is in the set already. Furthermore, if the highest $V_{200\%}$ over all scenarios is larger than 0.2, the corresponding scenario is added to $S_{200\%}$. The model is re-optimized and the scenario sets are updated until no more scenarios are added to either of the sets (outer while loop in Step 1 of Algorithm 1).

The final iterations in the optimization are often spent on improving the optimality bound while the objective value is hardly or not at all reduced. Furthermore, improving the objective a little bit may in practice have little effect on the dose to the tumor or OARs. It is thus not necessary to solve the model to optimality. This particularly holds for optimization of the catheter configuration: the minor improvements in the final iterations are likely to result from a change in dwell times, not from a change in catheter configuration. Therefore, we optimize the robust model up to a pre-determined optimality gap (Step 1 of Algorithm 1), fix the catheter configuration, and continue optimizing the beam-on times up to a second, smaller optimality gap (Step 2 of Algorithm 1).

### 3 Computational experiments

#### 3.1 Patient and source data

Data from three prostate cancer patients were used to test our robust optimization method. Delineations of the CTV, rectum and urethra as well as catheter- and dwell locations were obtained from the treatment planning system (HDRplus, version 3.0, Eckert and Ziegler BEBIG GmbH, Berlin, Germany), see Table 3 for the structure volumes. For the nominal plan, the PTV was obtained by expanding the CTV with an isotropic margin of 2 mm. This is the same dataset as was used in Gorissen et al. (2013) and in Balvert et al. (2015). Calculation points were hexagonally distributed over the structures using MATLAB Release 2012b (The Mathworks, Inc., Natick, USA), of which details can be found in Table 4. We used the same number of dose calculation points for optimization as the treatment planning system did, and used a larger set for the dosimetric evaluation of the treatment plan in order to obtain more accurate DVH measures. Dose rates were calculated according to the TG-43 formalism (Nath et al., 1995) for which $^{192}$Ir source-specific parameters were obtained from Granero et al. (2006).
Algorithm 1

Step 0. Initialize

Solve \((RC)\) for nominal scenario, yielding optimal \(t^*\) and \(V^*\).
Initialize \(\tilde{I}_C^a := \{i \in I_C | d_i^a t^* \geq L\}\) and \(\tilde{I}_C^f := \{i \in I_C | d_i^f t^* \leq 2L\}\).
Initialize the fraction of calculation points to be removed from \(\tilde{I}_C^a\) and \(\tilde{I}_C^f\) in each iteration, denoted by \(\eta \in [0, 1]\).
Initialize optimality gaps \(g_1\) and \(g_2\) \(\in [0, 1]\), \(g_1 > g_2\).
Initialize the sets of scenarios included in optimization for constraints (1) and (2), denoted by \(S_{100\%} := \{\text{nominal scenario}\}\) and \(S_{200\%} := \emptyset\), respectively.
Initialize the accepted gap between the true objective value and the value obtained when using fewer calculation points, denoted by \(\Delta V \in [0, 1]\).
Set the stopping parameter for the adversarial approach \(\text{stopAdv} := 0\).
if \(\bar{s} := \arg \min_{s \in S} \{V_s^{100\%}(t^*)\}\) is not the nominal scenario then set \(S_{100\%} := S_{100\%} \cup \bar{s}\).
end if
if \(\max_{s \in S} \{V_s^{200\%}(t^*)\} > 0.2\) then set \(S_{200\%} := \arg \max_{s \in S} \{V_s^{200\%}(t^*)\}\).
end if

Step 1.
Set \(g_1\) as optimality tolerance.
while \(\text{stopAdv} = 0\) do
while \(\text{stopCalc} = 0\) do
Solve \((RC)\) with \(\tilde{I}_C^a\) and \(S_{100\%}\) replaced by \(\tilde{I}_C^f\) and \(S_{200\%}\) in constraint (1) and \(\tilde{I}_C^a\) and \(S_{200\%}\) in constraint (2).
Update \(t^*\) and \(V^*\), calculate the true worst case objective value \(V_{\text{true}}\) and \(V_{200\%}\).
if \(V_{\text{true}} - V^* \leq \Delta V\) and \(V_{200\%} \leq 0.2\) then Set \(\text{stopCalc} := 1\).
else
if \(V_{\text{true}} - V^* > \Delta V\) then Remove the \(\eta|\tilde{I}_{CTV}|\) calculation points with the lowest dose from \(\tilde{I}_C^f\).
end if
if \(V_{200\%} > 0.2\) then Remove the \(\eta|\tilde{I}_{CTV}|\) calculation points with the highest dose from \(\tilde{I}_C^f\).
end if
end if
end while
if \(\bar{s} := \arg \min_{s \in S} \{V_s^{100\%}(t^*)\}\) \(\in S_{100\%}\) and \(\max_{s \in S} \{V_s^{200\%}(t^*)\} \leq 0.2\) then \(\text{stopAdv} = 1\).
else
if \(\bar{s} \notin S_{100\%}\) then \(S_{100\%} := S_{100\%} \cup \bar{s}\).
end if
if \(\max_{s \in S} \{V_s^{200\%}\} > 0.2\) then \(S_{200\%} := S_{200\%} \cup \arg \max_{s \in S} \{V_s^{200\%}\}\).
end if
end if
end while
Step 2. Set \(\text{stopAdv} = 0\) and \(g_2\) as optimality tolerance, fix the catheter configuration as found in \(t^*\).
Repeat the process described in Step 1.

Table 3: Tissue structure volumes (cc).

<table>
<thead>
<tr>
<th>Structure</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTV</td>
<td>31.7</td>
<td>55.2</td>
<td>47.6</td>
</tr>
<tr>
<td>PTV</td>
<td>39.6</td>
<td>62.8</td>
<td>63.2</td>
</tr>
<tr>
<td>Rectum</td>
<td>6.8</td>
<td>7.5</td>
<td>9.4</td>
</tr>
<tr>
<td>Urethra</td>
<td>2.1</td>
<td>2.6</td>
<td>2.3</td>
</tr>
</tbody>
</table>
### Table 4: Number of dose calculation points.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Optimization Patient 1</th>
<th>Optimization Patient 2</th>
<th>Optimization Patient 3</th>
<th>Evaluation Patient 1</th>
<th>Evaluation Patient 2</th>
<th>Evaluation Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTV (nominal)</td>
<td>1750</td>
<td>1759</td>
<td>1743</td>
<td>8108</td>
<td>8112</td>
<td>8247</td>
</tr>
<tr>
<td>CTV (total)</td>
<td>2959</td>
<td>2766</td>
<td>2729</td>
<td>20232</td>
<td>22218</td>
<td>24009</td>
</tr>
<tr>
<td>PTV</td>
<td>1750</td>
<td>1754</td>
<td>1757</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Rectum</td>
<td>253</td>
<td>258</td>
<td>264</td>
<td>2427</td>
<td>2707</td>
<td>2533</td>
</tr>
<tr>
<td>Urethra</td>
<td>465</td>
<td>489</td>
<td>488</td>
<td>2049</td>
<td>2164</td>
<td>1922</td>
</tr>
</tbody>
</table>

#### 3.2 Experiment setup

To define the uncertainty region, we used scenarios obtained from the original contours by stretching or shrinking the delineated CTV in the left, right, anterior, posterior, superior and inferior direction. The centroid-to-surface distances in each direction were varied independently of each other. Distances were assumed to vary at most two standard deviations from the mean (delineated) distance. Standard deviations were obtained from Smith et al. (2007) and were fixed at 2.2 mm for the superior and inferior directions, and at 1.15 mm for the remaining directions. For patient 2, the original, smallest and largest possible CTV shapes are depicted in Figure 3.

This method of scenario generation is rather straightforward as it neglects the fact that delineations of an observer may deviate from those delineated by others in a consistent manner, for example one observer may always draw larger shapes than his/her colleague. The assumption of independent deviations in each direction may be invalid. However, to the best of our knowledge, there is no data available on this dependency. Our method can be easily adapted if such data would become available.

![Figure 3: Vectorized figure of minimal (light gray), delineated (medium gray) and maximum (dark gray) CTV shape.](image)

In order to limit the number of scenarios taken into account in the optimization process, we considered only the minimum, nominal and maximum distance for each direction, which gives $3^6 = 729$ possible shapes. Note that the assumption of independent deviations for each direction may result in unrealistically large or small shapes, e.g., when we fully stretch the shape in each direction, the volume becomes clinically unrealistically large. Therefore, all scenarios with a clinically unrealistic CTV volume (smaller than 20 cc or larger than 65 cc) were excluded before optimization. This results in 596, 534 and 602 scenarios for patients 1, 2 and 3, respectively. In order to evaluate the plan quality, 10,000 scenarios were generated for each patient by randomly drawing centroid-to-surface distances for each direction. Again, extremely small and large scenarios were excluded.

Models were compared based on DVH evaluation criteria for all scenarios as well as solution times. The models were solved using the Gurobi 5.5 optimizer (Gurobi Optimization, Inc., Houston, USA) interfaced with MATLAB Release 2012b on a computer with an Intel i7-2670 QM processor.

The dwell positions that correspond to each catheter location are predefined. In our test cases, only the dwell positions that are in the CTV were activated and thus included in the optimization process. As the union of the scenarios is larger than the original target volume, there are dwell positions that were not included in the optimization process whereas they may be inside the target volume. It may thus be necessary to include additional dwell positions for each catheter. This is illustrated in Figure 4, where the PTV is delineated in green. The red dwell positions are included in the original dataset, which can be extended by including the green dwell positions as well. The robust and margin models are therefore solved using both the original and the extended set of dwell positions.
3.3 Numerical results

3.3.1 Comparison of nominal, margin and robust approach

Treatment plans were generated for each patient using the nominal, the margin and the robust model, where the solution times of the margin and the robust models were reduced using Algorithm 1. The nominal model was solved to optimality. Additional treatment plans were generated by solving the margin and robust models with additional dwell positions. For each treatment plan and scenario, DVH parameters were calculated. The distributions of the values for $V_{100\%}(CTV)$, $D_{90\%}(CTV)$ and $V_{200\%}(CTV)$ over all scenarios are presented in histograms (Figures 5, 6 and 7 for each of the three patients). The DVH parameters for the rectum and the urethra are summarized in Table 5.

For all three patients, the distribution of $V_{100\%}(CTV)$ shows a clear shift towards the higher values when using the margin or the robust model instead of the nominal PTV plan. For patients 1 and 2, a similar shift is visible for $D_{90\%}(CTV)$, whereas for patient 3 the use of the margin and robust model only results in less variation among the scenarios. Adding dwell positions does not change this distribution.

The margin approach showed an increased risk of target overdosage for patient 1 (Figure 5c): the number of scenarios with a too high $V_{200\%}(PTV)$ has become larger. An increased $V_{200\%}(CTV)$ was also observed for patient 2, though this did not result in undesirably high values as it was rather low for the nominal case already. The DVH metrics of the organs at risk did not differ among the models, which is a result of the model constraints.

Table 5: Summary of DVH statistics for the OARs for each scenario, obtained with five different planning models. All values are given in Gy. dps = dwell positions.

<table>
<thead>
<tr>
<th>Patient</th>
<th>DVH parameter</th>
<th>Treatment planning model</th>
<th>Nominal</th>
<th>Margin</th>
<th>Robust</th>
<th>Margin extra dps</th>
<th>Robust extra dps</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$D_{10%}(Rectum)$</td>
<td>5.0</td>
<td>5.6</td>
<td>5.4</td>
<td>6.4</td>
<td>6.0</td>
<td></td>
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<tr>
<td></td>
<td>$D_{2cc}(Rectum)$</td>
<td>4.4</td>
<td>5.0</td>
<td>4.7</td>
<td>5.6</td>
<td>5.1</td>
<td></td>
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<tr>
<td></td>
<td>$D_{10%}(Urethra)$</td>
<td>7.8</td>
<td>8.2</td>
<td>8.2</td>
<td>8.7</td>
<td>8.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$D_{0.1cc}(Urethra)$</td>
<td>8.1</td>
<td>8.4</td>
<td>8.6</td>
<td>8.9</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>$D_{10%}(Rectum)$</td>
<td>7.0</td>
<td>7.4</td>
<td>7.4</td>
<td>7.4</td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$D_{2cc}(Rectum)$</td>
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<td>6.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$D_{10%}(Urethra)$</td>
<td>9.6</td>
<td>10.0</td>
<td>9.9</td>
<td>10.0</td>
<td>9.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$D_{0.1cc}(Urethra)$</td>
<td>10.0</td>
<td>10.2</td>
<td>10.0</td>
<td>10.2</td>
<td>9.9</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>$D_{10%}(Rectum)$</td>
<td>6.8</td>
<td>7.3</td>
<td>7.3</td>
<td>7.3</td>
<td>7.3</td>
<td></td>
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<tr>
<td></td>
<td>$D_{2cc}(Rectum)$</td>
<td>6.2</td>
<td>6.8</td>
<td>6.8</td>
<td>6.8</td>
<td>6.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$D_{10%}(Urethra)$</td>
<td>9.7</td>
<td>9.9</td>
<td>9.9</td>
<td>9.9</td>
<td>9.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$D_{0.1cc}(Urethra)$</td>
<td>9.8</td>
<td>10.1</td>
<td>10.2</td>
<td>10.0</td>
<td>9.7</td>
<td></td>
</tr>
</tbody>
</table>

3.3.2 Solution times

In order to see the effects of using binary instead of continuous variables, we first consider the $(LDV)$ model evaluated in the nominal scenario only. The relaxation of the $(LDV)$ model for the nominal case results in a large
Figure 5: Histogram of (a) $V_{100\%}(\text{CTV})$ as a percentage of the total CTV volume, (b) $D_{90\%}(\text{CTV})$ as a percentage of the prescribed dose and (c) $V_{100\%}(\text{CTV})$ and $V_{200\%}(\text{CTV})$ as a percentage of the total CTV volume for patient 1, measured over all scenarios for the nominal (black), margin model (white), robust model (gray), margin model with extra dwell positions (white striped) and robust model with extra dwell positions (gray striped). The vertical dashed line indicates the desired minimum level for $V_{100\%}(\text{CTV})$ and $D_{90\%}(\text{CTV})$ and the desired maximum level for $V_{200\%}(\text{CTV})$. 
Figure 6: Histogram of (a) $V_{100\%}(\text{CTV})$ as a percentage of the total CTV volume, (b) $D_{90\%}(\text{CTV})$ as a percentage of the prescribed dose and (c) $V_{100\%}(\text{CTV})$ and $V_{200\%}(\text{CTV})$ as a percentage of the total CTV volume for patient 2, measured over all scenarios for the nominal (black), margin model, (white), robust model (gray), margin model with extra dwell positions (white striped) and robust model with extra dwell positions (gray striped). The vertical dashed line indicates the desired minimum level for $V_{100\%}(\text{CTV})$ and $D_{90\%}(\text{CTV})$ and the desired maximum level for $V_{200\%}(\text{CTV})$. 
Figure 7: Histogram of (a) $V_{100\%}(\text{CTV})$ as a percentage of the total CTV volume, (b) $D_{90\%}(\text{CTV})$ as a percentage of the prescribed dose and (c) $V_{100\%}(\text{CTV})$ and $V_{200\%}(\text{CTV})$ as a percentage of the total CTV volume for patient 3, measured over all scenarios for the nominal (black), margin model, (white), robust model (gray), margin model with extra dwell positions (white striped) and robust model with extra dwell positions (gray striped). The vertical dashed line indicates the desired minimum level for $V_{100\%}(\text{CTV})$ and $D_{90\%}(\text{CTV})$ and the desired maximum level for $V_{200\%}(\text{CTV})$. 
reduction of solution times, without a significant compromise in plan quality (Table 6). Note that for patient 1 the dose requirement $D_{0.1cc}$ is slightly violated, though the violation is very small and thus not important. The solution times of the robust model without the relaxation of $v_i$ and Algorithm 1 are unacceptable: after 5 hours, the optimality gap is still approximately 5%, 15% and 10% for patients 1, 2 and 3, respectively. This makes the model with binary variables unusable and the relaxation necessary.

Table 6: Comparison of treatment plans generated with (LDV) and plans generated with a relaxation of (LDV).

<table>
<thead>
<tr>
<th>DVH parameter</th>
<th>unit</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_{90%}(PTV)$</td>
<td>%</td>
<td>109.4</td>
<td>108.6</td>
<td>102.3</td>
</tr>
<tr>
<td>$V_{100%}(PTV)$</td>
<td>%</td>
<td>99.9</td>
<td>99.8</td>
<td>100.0</td>
</tr>
<tr>
<td>$V_{150%}(PTV)$</td>
<td>%</td>
<td>41.0</td>
<td>41.3</td>
<td>22.9</td>
</tr>
<tr>
<td>$V_{200%}(PTV)$</td>
<td>%</td>
<td>18.3</td>
<td>19.0</td>
<td>8.9</td>
</tr>
<tr>
<td>$D_{10%}(Rectum)$</td>
<td>Gy</td>
<td>6.8</td>
<td>6.8</td>
<td>7.2</td>
</tr>
<tr>
<td>$D_{2cc%}(Rectum)$</td>
<td>Gy</td>
<td>6.2</td>
<td>6.2</td>
<td>6.7</td>
</tr>
<tr>
<td>$D_{10%}(Urethra)$</td>
<td>Gy</td>
<td>9.9</td>
<td>9.9</td>
<td>9.4</td>
</tr>
<tr>
<td>$D_{0.1cc%}(Urethra)$</td>
<td>Gy</td>
<td>10.2</td>
<td>10.1</td>
<td>9.6</td>
</tr>
<tr>
<td>Solution time s</td>
<td></td>
<td>92</td>
<td>5</td>
<td>219</td>
</tr>
</tbody>
</table>

The solution times of all methods for all patients are reported in Table 7. The robust approach clearly needs the most time, though the solution times are still clinically acceptable.

As noted in the previous section, it is not necessary to solve the models to optimality, so the algorithm optimizes the model up to a predetermined optimality gap. However, from initial tests it appeared that an optimality gap that finds a balance between solution time and plan quality is different for each of the patients. The accepted optimality gaps in Algorithm 1 were set to 0.5%, 0.15% and 0.05% for patients 1, 2 and 3, respectively. Using one of these gaps for all patients did not yield good results: for patient 1 the model cannot be solved up to an optimality gap of 0.05%, whereas using a gap of 0.5% for patient 3 yielded plans that perform worse than the nominal plan.

4 Discussion

Robust optimization methods published in literature have neither been applied to treatment planning models for BT nor have they been used to account for delineation uncertainties. This article presents a treatment plan optimization method for prostate HDR-BT that uses worst-case robust optimization to handle uncertainty in target volume delineations. Delineation uncertainties translate into uncertainties in index sets. Since current robust optimization methods cannot handle uncertainties in index sets, we have developed a new method in this work.

The importance of accounting for any type of uncertainty in BT planning models has been emphasized by Kirisits et al. (2014). In particular, they note that intra- and inter-observer delineation variabilities, together with intra- and inter-fraction set-up uncertainties, contribute most to dosimetric uncertainty.

In EBRT it is common practice to account for setup- and delineation uncertainties by applying a PTV margin around the CTV (International Commission on Radiation Units and Measurements, 1999). However, a PTV margin approach is questionable for brachytherapy. First of all, often an isotropic margin is used, whereas the delineation uncertainties vary non-isotropically (Smith et al., 2007). Furthermore, Tanderup et al. (2010) argue that margins cannot be applied to brachytherapy, since delivering a homogeneous target dose that reaches beyond the CTV would require a dose escalation in the interior of the target volume. These two observations

Table 7: Solution times (s) for all solution approaches and three patients, dps = dwell positions.
were the motivation to develop our robust treatment planning method, and to compare it against the classical margin approach and against a margin approach that is based on scenarios of target volume delineations.

Our results indicate that target coverage is improved by using the scenario-based margin model instead of the isotropic 2 mm margin, which implies that the 2 mm margin used in the clinic may be insufficient. This particularly holds for the anterior and posterior directions, where the delineation uncertainty is larger than in other directions (Smith et al., 2007). We conclude that an isotropic margin is indeed not adequate. A downside of the scenario-based margin model is an increased $V_{200\%}^{\text{CTV}}$, which is in agreement with the findings from Tanderup et al. (2010). The robust treatment planning model results in an improvement in target coverage similar to the scenario-based margin approach. Additionally, in this model an overdose, reflected in excessively high values for $V_{200\%}^{\text{CTV}}$, can be prevented by adding a constraint that requires $V_{200\%}^{\text{CTV}}$ to be below a preset level for each of the scenarios. This constraint does not work well for the margin approach, since there it applies to an extended CTV only, which is a rather large volume. As a result, individual scenarios were not protected from overdosage. The dose escalation in the interior of the CTV may be caused by the absence of dwell positions in the volume. Therefore, we re-optimized the model with the scenario-based margin approach using additional dwell positions located in the margin. This did not improve the treatment plan quality, and we can conclude that dose escalation inherent to the margin approach cannot be prevented by including more dwell positions.

Although our method successfully incorporates delineation uncertainties in the treatment planning optimization process, further development is mandatory before it can be applied in clinical practice. The optimality gap that is acceptable varies among the patients. This issue may be overcome through an iterative procedure, where in each iteration the model is optimized up to a predetermined optimality gap, after which either the plan is accepted by the treatment planner or the optimization is resumed and the model is solved up to a smaller optimality gap. Unfortunately, this increases the time required for treatment planning.

We observed that the solution time varies strongly among patients. Note that this is also the case for the nominal model. Furthermore, the solution time of the robust model halves for patient 1 when adding dwell positions, whereas it doubles for patient 2 and is unchanged for patient 3. These discrepancies may be caused by the iterative nature of our approach: for one case, the procedure chose the most important scenario in an early stage, whereas more iterations were needed in another case. These discrepancies need further investigation.

Our study setup also has some limitations. Firstly, we used a small dataset which comprises only three patients. This allowed us to perform an extensive study where we compared various models. Even though our dataset comprises patients with different prostate sizes, a more elaborate investigation is required to confirm our conclusions. Secondly, we have only considered uncertainties in target volume delineations, whereas the OAR contours are likely to be subject to variabilities as well. Including OAR contouring variabilities in the model raises two issues. First, when there is uncertainty in multiple structures, some calculation points may be both in some scenarios for the target volume and in some scenarios for an OAR. Second, the size of the model and hence the calculation times will increase. As there is insufficient data on delineation uncertainties for OARs available in the literature, we have not considered OAR contouring variabilities in our research.

Our approach may be applicable for other body sites as well, and would require reliable data on target volume and OAR delineation uncertainties of the particular organ(s) in question. One may also apply our method to setup uncertainties by viewing these variations as a rigid shift of the organs and hence the delineations, leaving the position of the calculation points and hence the dose rate fixed. This would allow us to combine all uncertainties into one composite uncertainty in the index set. A thorough investigation is mandatory to assess the feasibility and value of this approach.

5 Conclusion

The worst-case robust treatment plan optimization model presented in this work is well capable of accounting for target delineation uncertainties. Uncertainties in index sets can be accounted for by using a scenario-based approach. Although the treatment plan optimization model becomes too large to be solved within a clinically acceptable amount of time, our heuristic approach reduces the calculation times to acceptable proportions for both the nominal and the robust optimization models.

Acknowledgement

We thank Ulrich Wimmert† from SonoTECH GmbH (Neu-Ulm, Germany) for providing a research version of the HDRplus software that has the ability to export the dose rate kernel matrix and the coordinates of surface points, dose calculation points and dwell positions.
A Full nominal treatment plan optimization model

The full treatment plan optimization model described by Gorissen et al. (2013) is the following:

\[ \text{(LDV) } \max \sum_{i \in I_P} v_i \quad \forall i \in I_P \]
\[ \text{s.t. } d_t^iT \geq v_iL \quad \forall i \in I_P \]
\[ d_t^I t \leq L_\ast + (U_\ast - L_\ast)(1 - u_i) \quad \forall i \in I, \forall \ast \in \{R, U\} \]
\[ \sum_{i \in I} u_i \geq \tau_\ast |I_\ast| \quad \forall \ast \in \{R, U\} \]
\[ t_j \leq T_{\max}\ b_k \quad \forall j \in J_k, \forall k \in K \]
\[ b_{k_2} \leq 1 - b_{k_1} \quad \forall k_2 \in \Gamma(k_1), \forall k_1 \in K \]
\[ \sum_{k \in K} b_k \leq 20 \]
\[ t \geq 0 \]
\[ v_i \in \{0, 1\} \quad \forall i \in I_P \]
\[ u_i \in \{0, 1\} \quad \forall i \in I, \forall \ast \in \{R, U\} \]
\[ b_k \in \{0, 1\} \quad \forall k \in K. \]

The objective and constraint (3) are discussed in Section 2.2. Constraint (4) ensures that a calculation point in the rectum or urethra does not receive a dose above \( U_R \) and \( U_U \), respectively. At most a fraction \( \tau_R \) of the calculation points in the rectum and \( \tau_U \) of the calculation points in the urethra may receive a dose above \( L_R \) and \( L_U \), respectively, as is enforced by constraints (4) and (5). The variable \( b_k \) is binary, and is equal to 1 when catheter \( k \) is used. The set \( K \) is the set of possible catheter locations, and \( J_k \) is the set of dwell positions in catheter \( k \). At most 20 catheters can be used (constraint (8)). Dwell times within catheter \( k \) can only be positive if the catheter position is used, and can never exceed a predetermined maximum dwell time \( T_{\max} \) (constraint (6)). Two neighboring catheters cannot be used both, as is ensured by constraint (7), where \( \Gamma(k) \) is the set of catheter locations neighboring location \( k \). The parameter values that were used in our tests can be found in Table 8. The maximum allowed dwell time is set to 5 seconds.

<table>
<thead>
<tr>
<th></th>
<th>Rectum</th>
<th>Urethra</th>
</tr>
</thead>
<tbody>
<tr>
<td>( L_\ast )</td>
<td>7.2 Gy</td>
<td>8 Gy</td>
</tr>
<tr>
<td>( U_\ast )</td>
<td>10 Gy</td>
<td>10.6 Gy</td>
</tr>
<tr>
<td>( \tau_\ast )</td>
<td>0.9</td>
<td>0.9</td>
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</table>

The references are:


