Stepping source prostate brachytherapy: From target definition to dose delivery

Dinkla, A.M.

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Chapter 5
Novel tools for stepping source brachytherapy treatment planning: Enhanced Geometrical Optimization and Interactive Inverse Planning

Anna M. Dinkla, Rob van der Laarse, Kees Koedooder, Petra Kok, Niek van Wieringen, Bradley R. Pieters and Arjan Bel

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5.1 Abstract

Background: Dose optimization for stepping source brachytherapy can nowadays be performed using automated inverse algorithms. Although much quicker than graphical optimization, an experienced treatment planner is required for both methods. With automated inverse algorithms the procedure to achieve the desired dose distribution is often based on trial-and-error.

Methods: A new approach for stepping source prostate brachytherapy treatment planning was developed as a quick and user-friendly alternative. This approach consists of the combined use of two novel tools: Enhanced Geometrical Optimization (EGO) and Interactive Inverse Planning (IIP). EGO is an extended version of the common geometrical optimization method (GO), and is applied to create a dose distribution as homogeneous as possible. With the second tool, Interactive Inverse Planning (IIP), this dose distribution is tailored to a specific patient anatomy by interactively changing the highest and lowest dose on the contours.

Results: The combined use of EGO-IIP was evaluated on 24 prostate cancer patients, by having an inexperienced user create treatment plans, compliant to clinical dose objectives. This user was able to create dose plans of 24 patients in an average time of 4.4 minutes per patient. An experienced treatment planner without extensive training in EGO-IIP also created 24 plans. The resulting DVH parameters were comparable to the clinical plans and showed high conformance to clinical standards.

Conclusions: Even for an inexperienced user, treatment planning with EGO-IIP for stepping source prostate brachytherapy is feasible as an alternative to current optimization algorithms, offering speed, simplicity for the user and local control of the dose levels.

Keywords: Interstitial Brachytherapy, Prostate neoplasms, computer assisted radiotherapy planning, optimization, EGO-IIP
5.2 Background

Stepping source brachytherapy is an effective way to treat intermediate and high risk prostate cancer [1]. It is often applied as a boost treatment, after external beam radiotherapy (EBRT). Radiation is delivered by a radioactive stepping source for pulsed-dose or high-dose rate (PDR or HDR) brachytherapy, which is directed through catheters temporarily implanted in the prostate. Dose optimization takes place in the treatment planning software, based on transrectal ultrasound, CT, or MR images, acquired after transperineal implantation of the catheters. The dose distribution can be optimized by modifying the positions where the source is (dwell positions) and the duration of its stay (dwell times).

Treatment planning is a multi-objective optimization problem. Current commercially available automatic optimization algorithms apply a heuristic minimization of a single linear penalty function in which the different weighted objectives are combined [2-4]. The objectives are set by the user choosing the desired dose range for all organs. Doses outside these ranges attribute to the weighted sum of the penalty: the penalty increases linearly with doses further from the desired range.

In clinical practice, planning objectives are usually expressed as dose-volume parameters, extracted from cumulative dose-volume histograms (DVHs). As clinical demands can only be indirectly incorporated in the objective function, steering the solution towards the clinical objectives is difficult. A weak relation has been reported between the penalty value and the resulting DVH parameters as well as the relation to the expert opinion in the literature [5,6]. To acquire the most appropriate clinical solution for each individual patient is therefore often a trial-and-error procedure [6-8].

Graphical optimization is a manual method to shape the dose distribution by drag-and-drop of the isodose lines. The benefit of a graphical approach is that the user is in full control by changing the dose distribution locally while evaluating the dose distribution and the DVH parameters in real-time. However, it is time consuming and requires an experienced user [9]. A novel method is desired that combines the time efficiency of automatic inverse optimization with the local control of graphical optimization. Furthermore, such a new approach should be easy and intuitive to use.

This paper describes two tools for stepping source brachytherapy treatment planning, combining 1) a forward method, Enhanced Geometrical Optimization (EGO), to obtain a dose distribution that is as homogeneous as possible and 2) interactive inverse planning (IIP), an inverse optimization tool to interactively shape the dose distribution locally according to the target and organs at risk (OARs) by entering dose limits that are used clinically. IIP can be used on its own or used to fine-tune any other optimization. The method was tested by one experienced and one inexperienced user who both created
prostate brachytherapy treatment plans with the combined use of EGO-IIP. The aim was to show a proof of concept of our novel optimization method, which enables both experienced and inexperienced users to create treatment plans that are compliant to clinical standards, in a short time span.

5.3 Methods

Planning procedure: EGO-IIP
Two tools were developed for the new approach: Enhanced Geometrical Optimization (EGO) and Interactive Inverse Planning (IIP). The general workflow in this study is that EGO is applied to generate a starting dose distribution with maximized homogeneity. Next, the user applies IIP to shape the dose according to the specific patient anatomy and to find the most desirable compromise between conflicting DVH parameters. This is done by interactively changing the dose limits to each organ, thereby fine-tuning the dose distribution.

EGO
Enhanced Geometrical Optimization (EGO) is an extended version of the common geometrical optimization method (GO). With traditional GO, the distances between the dwell positions themselves are used to determine dwell weights [10,11]. The dwell weights are initially set to 1, after which the dwell weight \( w_i \) of a dwell position \( i \) is set inversely proportional to the sum of the dose contribution from all other dwell positions \( j \) to that dwell position \( i \), so

\[
    w_i \propto \left( \sum_{j=1}^{M} D_{i,j} \right)^{-1}
\]

where \( M \) is the total number of (activated) dwell positions within the implant and \( D_{i,j} \) is the dose contribution from dwell position \( j \) to dwell position \( i \). Before the introduction of anatomy- or image-based optimization, GO was commonly used in dwell-time optimization to obtain an optimized dose distribution from a fixed catheter configuration [11-13].

The homogeneity of a dose distribution obtained by traditional GO is not always optimal, especially when catheters are diverging [11]. For this reason EGO was developed. EGO modifies the dwell weight \( w_i \) obtained by GO, by increasing its difference from weight 1. The strength of enhancement is a user-defined factor, the volume strength \( s_{EGO} \), ranging between 0-1: \( w'_i = w_i - s_{EGO} \cdot (1- w_i) \), with additional constraint \( w'_i \geq 0 \). Here \( w_i \) is the current dwell weight as calculated by GO and \( w' \) the ‘enhanced’ dwell weight. When GO is applied on a volume (“GO on volume” method), usually the dose contributions from all dwell positions in the same catheter are excluded to increase the influence of catheter configuration inside the implanted volume, thereby ‘filling in’ cold spots
between the catheters [10]. In EGO, the flexibility is increased by a second parameter, the Volume Range $r_{EGO}$, which can be chosen to set the “radius of exclusion”. Dwell positions in the same catheter within range $r_{EGO}$ of the current dwell position are excluded. When $r_{EGO}$ is zero, no dwell positions are excluded.

Finding optimal settings for the two parameters $s_{EGO}$ and $r_{EGO}$ is not straightforward. Changing $r_{EGO}$ requires the re-evaluation of the full range of $s_{EGO}$ values. Therefore, the option Auto-EGO was developed, which uses a binary search algorithm to find the values of the parameters that give the highest value for the dose homogeneity as defined by the Quality Index QI [12]. The quality index QI, is derived from the Natural DVH (NDVH) [14,15]. A more homogeneous dose distribution over the implant results in a larger QI.

**IIP**

After applying an implant-based method like EGO there will usually be the need for corrective (interactive) optimization [16,17]. Interactive Inverse Planning (IIP) is a tool to steer the distribution of dwell weights by changing the upper and lower dose limits on the surface of a region of interest (ROI). IIP can be used on its own, after applying EGO, or after any other (automated) optimization method. With IIP, the current lowest or highest doses on the surface of a ROI can be changed to adapt the dose distribution (Figure 1), which is done in an interactive manner. This way the user can shape the dose distribution locally and optimize the treatment plan to clinical needs. Because the interaction with the dose distribution is real-time, the possibilities and trade-offs for each patient are explored and evaluated efficiently. To restrict IIP to a specific region, the control of the dose distribution is further increased by the possibility to select individual transversal planes. An angle interval can be specified within these planes by setting the Start and Stop angle. Then the dose limits can be set in only the selected (parts of the) contours. Every ROI surface is approximated by placing points on the contours, delineated in the different slices of the image data set. Points are placed on the contours, by default 4 mm apart, in which the dose is calculated.

**IIP: Decreasing the maximum dose or increasing the minimum dose on a ROI**

The flowchart in Figure 2a shows how the highest dose on a ROI surface is decreased using IIP. The user enters a value in the corresponding Upper limit box. IIP iteratively searches for the contour point currently receiving the highest dose and then decreases the weight of the dwell position nearest to that point with 5% of its value. This is repeated in the next iteration. The iteration stops when the highest dose found on the contours is equal to or lower than the user-defined upper limit. A similar iteration is performed when the user wants to increase the lowest dose on a ROI contour.

**IIP: Increasing the maximum dose or decreasing the minimum dose on a ROI**

To increase the highest dose, or decrease the lowest dose on a ROI surface, the iterative approach as described above would not give the desired effect. With that approach only
one dwell position per iteration is affected, the one nearest to the current maximum or minimum dose found on the contour. In this case the same principle as used in graphical optimization is applied, which is commonly used in brachytherapy treatment planning systems to drag-and-drop an isodose line. A flowchart shows this principle for use in IIP (Figure 2b). When the users enters a lower minimum dose (or higher maximum dose), IIP will first search for the lowest (or highest) dose currently on the contour points. First all dwell weights within a sphere around this contour point containing the lowest (or highest) dose are slightly changed; the closer the dwell position the larger the change. Then the dose value in this dose limit point is recalculated using all dwell positions. Finally, the difference between the new limit value and the old one is used to determine the factor with which the changed dwell weights must be multiplied in order to get the required dose limit. The pseudo-code of this procedure is described in the appendix.

Numerical evaluation
An inexperienced user (User 1) created treatment plans of 24 prostate patients, based on the set of clinical dose objectives in use (Table 1). User 1 was a bachelor student in biomedical engineering with no previous experience in radiotherapy or brachytherapy.
Figure 2: IIP flow diagram to reduce the highest dose on the surface of a ROI. The same principle is used to increase the lowest dose (a). IIP flow diagram to increase the highest dose on a ROI surface. The same principle is applied to decrease the lowest dose (b).

After a four weeks general introduction into radiotherapy, brachytherapy and the concepts of EGO-IIP, he was asked to create plans with the software containing EGO-IIP. A second user was an experienced treatment planner (User 2). After receiving a short demonstration, User 2 also created plans using EGO-IIP.

The PTV was defined as the prostate without margin. All plans were created by applying Auto-EGO on all dwell positions inside the prostate plus a margin of 2.5 mm. In the cranial direction, this dwell positions activation margin was set to 5 mm. After Auto-EGO, IIP was applied to shape the dose to achieve clinical standards. In general, the lower limit of the PTV was increased first, in order to increase the coverage of the prescribed
dose (PD) on the PTV, after which the dose to the outside PTV contour was reduced by lowering the upper limit. After this, the upper limits of the OARs were adjusted in order to meet the objectives. Finally, the PTV dose was increased by increasing the lower limit and a compromise between target coverage and OAR dose was found. In general, to explore the trade-offs, all ROIs were adjusted at least once.

Relevant DVH parameters as well as planning time were recorded. Objective values for these parameters are displayed in Table 1. We also evaluated the conformity, by calculating the conformation number CN [18], which is defined as the product of the coverage index (CI) and ‘coverage outside’-index (CO). The formulas are defined in Table 1.

To evaluate the quality of the plans created by User 1 and User 2, they were compared to each other and to the clinical benchmark, which were the plans as used in the clinic. These had been created by different planners using graphical optimization. No other planning algorithms were considered in this proof of concept. We recorded multiple DVH parameters of the prostate ($V_{100\%}$, $V_{150\%}$, $V_{200\%}$ and $D_{90\%}$), the urethra D1.0cm$^3$, rectum D2cm$^3$, bladder D2cm$^3$, CI, CO and CN. The D1.0cm$^3$ and D2cm$^3$ represent the minimum dose to the highest exposed 1 and 2 cm$^3$ of an organ. The $V_{100\%}$, $V_{150\%}$ and $V_{200\%}$ represent the percentage of target volume receiving at least 100%, 150% and 200% of the PD, respectively. The $D_{90\%}$ is the lowest percentage of the PD that is at least achieved in the highest exposed 90% of the target volume.

These DVH parameters were compared using a Student’s t-test. A p value <0.02 was considered statistically significant. To correct for performing three comparisons simultaneously, the commonly used value of 0.05 was lowered using a Bonferroni correction (0.05/3).

### 5.4 Results and discussion

The resulting DVH parameters of the EGO-IIP plans were comparable to the clinical plans (Table 1). The average target coverage ($V_{100\%}$) was well above 95%. Compared to the clinical plans, the $V_{100\%}$ and $D_{90\%}$ were slightly higher with EGO-IIP, although not statistically significant (p > 0.02). This did lead to relatively large $V_{150\%}$ and $V_{200\%}$. Although the $V_{150\%}$ of User 1 was higher than the $V_{150\%}$ of the clinical plans (p < 0.02), in the majority of patients the $V_{150\%}$ (58%) and $V_{200\%}$ (75%) were still lower than the objective value. The mean values for the D1cm$^3$ and D2cm$^3$ of the OARs were also lower than the dose objectives. The largest compromise between target dose and OAR dose was visible at the urethral dose. Although the urethral D1cm$^3$ was on average lower than the objective value, this dose objective was achieved by User 1 and 2 only for 11 and 13 patients respectively. In the plans used clinically, this value was also difficult to achieve (N=11). User 2 achieved a better balance between a high target dose ($V_{100\%}$ and $D_{90\%}$) and high dose volumes.
(lower $V_{150\%}$ and $V_{200\%}$) than User 1. This also resulted in lower urethral dose. However, it appears that it is at the cost of a slightly higher bladder and rectum dose ($p < 0.02$). Furthermore, the conformity was lowest for User 2. User 1 created EGO-IIP plans with the highest conformity. No planning objective has been established for the conform-

Table 1. DVH parameters of the clinical plans and plans created with EGO-IIP, expressed as mean value ± 1 standard deviation (SD) in % of the total prescribed dose. $N$ describes how often the dose objective was met (out of 24 plans).

<table>
<thead>
<tr>
<th>Objective Value</th>
<th>Clinical Mean ± 1 SD (%)</th>
<th>EGO-IIP User 1 Mean ± 1 SD (%)</th>
<th>EGO-IIP User 2 Mean ± 1 SD (%)</th>
<th>Post-hoc analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{100%}$</td>
<td>&gt;95%</td>
<td>94.9 ± 4.8 15</td>
<td>96.4 ± 1.1 22</td>
<td>96.9 ± 1.4 20</td>
</tr>
<tr>
<td>$V_{150%}$</td>
<td>&lt;50%</td>
<td>43.6 ± 7.8 18</td>
<td>49.3 ± 5.2 14</td>
<td>47.0 ± 5.7 19</td>
</tr>
<tr>
<td>$V_{200%}$</td>
<td>&lt;20%</td>
<td>16.5 ± 3.6 20</td>
<td>19.0 ± 4.3 18</td>
<td>16.9 ± 3.6 20</td>
</tr>
<tr>
<td>$D_{90%}$</td>
<td>&gt;110%</td>
<td>110.7 ± 9.8 17</td>
<td>113.1 ± 2.3 21</td>
<td>115.1 ± 3.6 22</td>
</tr>
<tr>
<td>OARs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urethra $D_{1cm^3}$</td>
<td>&lt;120%</td>
<td>112.3 ± 18.2 11</td>
<td>111.3 ± 19.6 11</td>
<td>111.0 ± 17.4 13</td>
</tr>
<tr>
<td>Rectum $D_{2cm^3}$</td>
<td>&lt;81%</td>
<td>61.35 ± 14.61 22</td>
<td>60.3 ± 13.4 23</td>
<td>64.8 ± 12.1 22</td>
</tr>
<tr>
<td>Bladder $D_{2cm^3}$</td>
<td>&lt;121%</td>
<td>72.5 ± 12.3 24</td>
<td>71.8 ± 11.0 24</td>
<td>80.0 ± 12.7 24</td>
</tr>
<tr>
<td>Conformity index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI</td>
<td>$V_{100%,i}/PTV$</td>
<td>0.95 ± 0.05</td>
<td>0.96 ± 0.01</td>
<td>0.97 ± 0.01</td>
</tr>
<tr>
<td>CO</td>
<td>$V_{100%,i}/V_{100%,i}$</td>
<td>0.61 ± 0.07</td>
<td>0.65 ± 0.05</td>
<td>0.57 ± 0.06</td>
</tr>
<tr>
<td>CN</td>
<td>CI * CO</td>
<td>0.58 ± 0.07</td>
<td>0.63 ± 0.05</td>
<td>0.56 ± 0.06</td>
</tr>
</tbody>
</table>

*A statistically significant difference ($p < 0.02$), according to the Student’s t-test, between the following pairs: Clinical - User 1 (1); Clinical - User 2 (2); User 1 - User 2 (3)
city, which could explain these differences. The conformity values presented here were comparable or lower than those found in other publications [9,19]. This could be a consequence of the high target dose ($D_{90\%}$), but it could also be related to the peripheral geometry of our implanted catheters as well as the number of catheters [20], which is relatively low at our institution.

EGO-IIP did not result in a dosimetric benefit, as compared to the clinical plans created with graphical optimization. The clinical plans were already of high quality, making it difficult to improve the DVH parameters. Improving plan quality was not the main goal, however, but improving the ease and time needed for planning, without compromising on dosimetry.

Mean planning time with EGO-IIP was 4.4 minutes ±1.1 min standard deviation (SD) for User 1. User 2, who had been given less time to get acquainted with the program, needed more time: 9.0 minutes ±3.6 min SD. Planning times of our clinical plans had not been recorded, so no direct comparison could be made, but we estimate it to be around 30-45 minutes. In the literature, planning times for graphical optimization of up to two hours have been reported [9]. So while maintaining the benefit of the full control that is available in graphical optimization, treatment planning is more time efficient with EGO-IIP, with planning times similar to automated inverse methods.

The resemblance of EGO-IIP plans to graphically optimized plans is also reflected by the dwell time distribution. Peak heights and number of active dwell positions (with nonzero dwell time) are comparable between the two methods. Dwell time gradients (mean difference between all neighbouring dwell positions per patient) were not significantly different between the graphically optimized plans and EGO-IIP plans of User 2 ($p = 0.4$).

With the feature Auto-EGO one can easily reach a good starting position for optimization. To run Auto-EGO usually takes about one minute. In this study, this starting point was used for optimization with IIP. Applying EGO is not mandatory; one can choose to set all activated dwell weights equal and immediately start shaping the dose with IIP. Like graphical optimization, IIP can be used to fine-tune the dose distribution from any other inverse planning algorithm. For instance, IIP can be applied after running a standard class solution of an automated inverse algorithm that might need some adjusting to the physician’s wishes. Within IIP, increasing the maximum dose or decreasing the minimum dose on a ROI, will be done less often than increasing the minimum dose and decreasing the maximum dose, but can be applied to lower the minimum dose on the urethra to the prescription dose level, or to lower the minimum dose to the PTV boundary. Although the dose can also be lowered by decreasing the maximum dose, lowering dose to the PTV via the minimum dose, could prove a more effective way to improve target conformity than lowering the maximum dose to the target.
The differences in DVH parameters found between the experienced and inexperienced user can be reduced by making clear agreements or by creating a fixed protocol. IIP is suited for protocolled treatment planning, meaning that all steps during treatment planning can be executed according to a protocol, or even executed automatically. This is currently under development to improve the efficiency of steering towards the right dose distribution and to potentially reduce user-dependence.

With IIP we do not offer an automatic optimization method, but an interactive way to shape the dose distribution. Automated algorithms may be even faster and easier in their first attempt. However, they often require trial-and-error by adaptation of the penalty function to obtain optimal DVH parameters. IIP does not optimize directly on DVH parameters either, but on dose limits that are related to the volume receiving at least a given dose. Nevertheless, the relationship between these volumes and the minimum and maximum doses on the organ’s surface is clear to interpret. In the latest version of IIP, one can enter a volume that should receive at least a certain dose, so direct optimization based on DVH parameters. IIP then iterates on its own, until this volume is reached. This feature was not yet available during this study. IIP has no mechanism to optimize conflicting dose objectives simultaneously. Interacting with the dose distribution is essential to explore the trade-offs for a specific patient. Since all IIP actions are real-time, the user can efficiently visualize and understand the possibilities.

A comparison with other optimization methods was beyond the scope of this report. Another study comparing EGO-IIP to three other methods showed that all of them could reach the same level of compliance to clinical dose objectives [21]. User preference and expert opinion of the physician play a determinant role in the choice of optimization method.

Lastly, IIP can change the dose locally, without degrading the overall dose distribution, whereas the automated methods are global methods, i.e. they optimize the entire dose distribution at once. With an automated inverse algorithm, changing the penalty function will result in a different overall dose distribution. Therefore, an attempt to modify the local dose, e.g. to spare an OAR, often yields undesired and unpredictable side-effects on the dose distribution in other regions. The local interaction and control within IIP makes it a straightforward, easy method that is suitable for less experienced users. Yet, some treatment planning experience is desirable for efficient and reasonable navigation through possible dose distributions.

### 5.5 Conclusions

This proof of concept showed that with the combined use of EGO-IIP, stepping source prostate brachytherapy treatment plans can be created easily and in a short amount of
time. Optimized plans were created by an inexperienced user within 5 minutes with the combined use of EGO-IIP, with comparable plan quality to the clinical benchmark. As an easy and intuitive method, plans can be created even without long experience with manual treatment planning.

Conflicts of interest: Nucletron has filed a patent application for EGO and IIP. Dr. Pieters is a non-salary consultant for Elekta Brachytherapy.

Acknowledgements: This project was sponsored in part by Elekta Brachytherapy.

5.6 Appendix

Pseudo-code of IIP (Increasing the maximum dose or decreasing the minimum dose on a ROI)

This is based on the implementation of graphical optimization in Oncentra Brachy (Nucletron, Veenendaal, the Netherlands). In the case of decreasing the lower limit, the nearest dwell positions around this contour point with the lowest dose, $P_{\text{min}}$, are searched. The nearest dwell position is at distance $d_{\text{min}}$ from point $P_{\text{min}}$. Next all dwell positions within distance $f_{\text{width}} * d_{\text{min}}$ are determined, where the default value of $f_{\text{width}}$ is 10. All dwell weights $w_i$ of dwell positions $i$ within this distance from $P_{\text{min}}$ are increased by adding a factor: $w'_i = w_i + (d_{\text{min}}/d)^p$, with $d$ the distance between the dwell position $i$ and $P_{\text{min}}$. The exponent $p$ is also set to 10. The values for $f_{\text{width}}$ and $p$ have been determined empirically but can be adapted to the users’ preferences. Then the updated dose contribution from all sources in point $P_{\text{min}}$, $D_{\text{Pmin}}$, is calculated. From that contribution, the factor $f$ is calculated for the weights within distance $d_{\text{min}}$ to obtain the desired dose in $P_{\text{min}}$: $f = (L_{\text{new}} - L_{\text{old}}/D_{\text{Pmin}} - L_{\text{old}})$, where $L_{\text{old}}$ is the current minimum dose on the organ and $L_{\text{new}}$ is the dose set by the user as the desired minimum dose. Finally the correct weight factor to each dwell weight $i$ within distance $f_{\text{width}} * d_{\text{min}}$ from $P_{\text{min}}$ is applied: $w'_i = w_i + (d_{\text{min}}/d)^p (f - 1)$. If one wants to increase the maximum dose, the formula to calculate $f$ changes to: $f = (L_{\text{old}} - L_{\text{new}}/D_{\text{Pmax}} - L_{\text{new}})$, in order to keep the factor $f$ positive.

5.7 References


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