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**Investigations into the Optimization of Multi-Source Strength Brachytherapy
Treatment Procedures**

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I. Executive Summary

The goal of this project is to investigate the use of multi-strength and multi-specie radioactive sources in permanent prostate implant brachytherapy. In order to fulfill the requirement for an optimal dose distribution, the prescribed dose should be delivered to the target in a nearly uniform dose distribution while simultaneously sparing sensitive structures. The treatment plan should use a small number of needles and sources while satisfying the treatment requirements. The hypothesis for the use of multi-strength and/or multi-specie sources is that a better treatment plan using fewer sources and needles could be obtained than by treatment plans using single-strength sources. Use of low-strength sources could reduce the dose to sensitive tissues and the use of higher-strength sources could reduce the overall number of sources used for treatment. We employ a recently developed greedy algorithm based on the adjoint concept as the optimization search engine. The algorithm utilizes an “adjoint ratio,” which provides a means of ranking source positions, as the pseudo-objective function. It has been shown that the greedy algorithm can solve the optimization problem efficiently and arrives at a clinically acceptable solution in less than 10 seconds. Our study was inclusive, that is, there was no combination of sources that clearly stood out from the others and could therefore be considered the preferred set of sources for treatment planning. Source strengths of 0.2 mCi (low), 0.4 mCi (medium), and 0.6 mCi (high) of ^{125}I in four different combinations were used for the multi-strength source study. The combination of high- and medium-strength sources achieved a more uniform target dose distribution due to few source implants, whereas the combination of low- and medium-strength sources achieved better sparing of sensitive tissues including that of the single-strength 0.4 mCi base case. ^{125}I at 0.4 mCi and ^{192}Ir at 0.12 mCi and 0.25 mCi source strengths were used for the multi-specie source study. This study also proved inconclusive. Treatment plans using a combination of two 0.12 mCi ^{192}Ir sources and ^{125}I sources or a combination of two 0.25 mCi ^{192}Ir sources and ^{125}I sources did not have better target and sensitive structures DVHs than that of the single specie ^{125}I 0.4 mCi base case. However, because of the high dose delivered by a ^{192}Ir source, the multi-specie treatment plan required fewer sources and needles and hence is less invasive than the treatment plan for the 0.4 mCi ^{125}I base case.

This report summarizes the work that has taken place over the course of the grant.

II. Introduction

Interstitial brachytherapy is a type of radiation therapy in which radioactive sources are implanted directly into diseased tissue. The prostate permanent implant brachytherapy in combination with the transrectal ultrasound (TRUS) imaging technique is fast becoming the preferred treatment modality for prostate cancer (Holm *et al.* 1983). The advantage of source implant over external beam irradiation is the rapid dose falloff to surrounding tissue areas, which reduces exposure to sensitive tissues (Desai *et al.* 1998). The TG 64 standard states that a treatment plan should provide (1) coverage of the target by the prescribed dose while the dose to rectum and urethra (sensitive structures) are within acceptable tolerances, (2) dose homogeneity, and (3) a simple implant plan. Hence, an optimized treatment plan is one where the dose to the rectum and urethra is minimized while simultaneously delivering the prescribed dose to diseased tissue (Yu *et al.* 1999).

The traditional methods for determining source configurations for a prostate treatment plan are based on spacing rules or on a manual trial-and-error process using single-strength radionuclides in which only a limited number of configurations can be evaluated from a large number of possible source configurations (Goodwin *et al.* 1970, Anderson *et al.* 1976, and 1993). Over the past ten years, several studies involving automated prostate implant treatment-planning algorithms using computerized optimization techniques have been performed. Four methods that frequently appear in investigations are simulated annealing (SA) (Poulit *et al.* 1996), genetic algorithm (GA) (Ezzell *et al.* 1996, Ye *et al.* 1996, Lee *et al.* 1999, Yang 1998), a simple random strategy (Chen *et al.* 1997, and 2000) and branch-and-bound (BB) method (Lee *et al.* 1999, D'Souza *et al.* 2001). Recently, a greedy algorithm optimization method based on the adjoint concept was developed. The algorithm utilizes an "adjoint ratio," which provides a means of ranking source positions, as the pseudo-objective function. It has been shown that the greedy algorithm can solve the optimization problem efficiently and arrives at a clinically acceptable solution in less than 10 seconds. For comparison, a branch-and-bound method using the basic mixed-integer programming model took more than 50 minutes to arrive at an optimal solution.

Permanent implant prostate optimization studies have shown that even though an optimal source configuration can be determined, there are a few remaining issues. First, sensitive structures still receive a relatively high dose because they are surrounded by or adjacent to the prostate. Second, though the target receives the prescribed dose, it is difficult to achieve dose uniformity in the target. And third, a large number of sources are required to deliver the prescribed dose to the target. Low-strength sources implanted around the sensitive structures would reduce the dose received by them; however, the total number of sources would increase to deliver the prescribed dose to the target. If high-strength sources are used to reduce the number of implanted sources, the sensitive structures would likely receive a higher dose than the tolerance level; however, the target dose uniformity would be improved. In this paper we investigate the use of multi-strength and multi-specie radioactive sources in permanent prostate implant brachytherapy. The hypothesis for the use of multi-strength and/or multi-specie sources is that a better treatment plan using fewer sources and needles could be obtained than for treatment plans using single-strength sources. The investigation will use the recently developed greedy algorithm as the optimization engine. Treatment plans using different combinations of multi-strength sources and multi-specie sources are compared to the basic single-strength source model.

III. Background Material and Calculational Methods

III.1 Case Set Up: Ultrasound Image

A TransRectal UltraSound (TRUS) probe is inserted through the rectum for image acquisition of the prostate. The probe takes a series of prostate images in transverse axis at 5 mm intervals. Fig. 1 displays the prostate image on the TRUS monitor screen with the four regions of interest manually contoured by an oncologist. The four anatomical regions of interest are: the prostate (gray contour), the urethra (white contour), the rectum (black contour) and normal surrounding tissue (external from the rectum and prostate volumes). From a treatment planning point of view, the whole prostate is treated as the tumor.

The white dots overlaid on the prostate image in Figure 1 indicate potential needle insertion positions on the source implant template needle guide for the preloaded treatment needles. The actual needle positions used for treatment are determined from the treatment plan. The white dots are 5 mm apart in the vertical and horizontal directions. The slice thickness is 5 mm and the field size of one 2-D image is 66 mm by 50 mm. The prostate is an ellipsoidal-shaped organ with a volume of approximately 30 to 40 cm³. The prostate of this patient spans about 10 slices of ultrasound images and the target volume is 33.06 cm³.

Figure 1. TransRectal Ultrasound image of the prostate with the regions of interest contoured. The gray contour indicates the prostate, the white the urethra, and the black the rectum.

The dose calculation is performed with a voxel resolution of 1 mm by 1 mm by 5 mm (x,y,z). For the multi-strength analysis, we used ¹²⁵I sources (model 6711) with source strengths of 0.2 mCi (0.254 U) as the low-strength source, 0.4 mCi as the medium-strength source, and 0.6 mCi as the high-strength source. For the multi-specie analysis, we used a ¹²⁵I source at 0.4 mCi and ¹⁹²Ir sources at 0.12 mCi and 0.25 mCi. For all sources the dose was computed by used the TG43 dose formalism (Nath *et al.* 1995) and the National Institute of Standard and Technology (NIST) 1999 source strength standard for dose computation. A treatment dose of 145 Gy was prescribed to the target (prostate).

III.2 The Adjoint Concept

The greedy algorithm-based optimization method used in this study for the permanent prostate implant treatment planning optimization engine is based on the adjoint concept of particle transport. The adjoint particle transport method is the opposite of the conventionally used forward particle transport method. In the forward transport method, one begins the calculation with well-defined source parameters, that is, the position, energy and emission direction of the source are known. The quantity of interest in a forward calculation is the forward flux distribution from which the reaction rate (detector response, the dose rate) at a position r is computed. Note that source photons travel through a medium and interact with electrons in the medium via the photoelectric effect, the Compton effect, or the pair production effect. Depending on the specific interaction, photons are either absorbed, depositing energy, scattered, losing energy (down scattered) or create two 0.511 MeV photons; overall, a net energy loss relative to the original photon. In the adjoint transport method one begins the calculation with well-defined detector response parameters, that is, the position, the energy dependence, and the preferred direction of interaction of the detector response are known. The quantity of interest in an adjoint calculation is the adjoint flux distribution from which one can once again compute a reaction rate. Note that in contrast to the forward case, photons travel through the medium in the “backward direction,” back towards source locations. The photons undergo absorption and scattering interactions as in the forward case; however, the photons gain energy in a scattering interaction. The question comes to mind, why one would choose to use the adjoint method to compute a dose response when, for most applications, the forward method is more appealing and yields the same result? The answer lies in the additional information one can gain from an adjoint calculation that is not as readily available from a forward calculation. What is appealing is that one begins the calculation with the response of the medium (region) and computes a sensitivity field for source placement in the source space. For example, if one were interested in evaluating the response of a region on the placement of a source at two or more locations, a single adjoint transport calculation would readily produce a sensitivity distribution (adjoint flux) from which one could easily evaluate the individual responses for the various source locations.

In mathematical terms, the dose using the forward method is computed from the inner product of the forward flux and the adjoint source, S^+ , over time and energy, where the adjoint source is the detector (tissue) response function, which, for our investigation, is the mass energy absorption coefficient, multiplied by the energy. The dose computed using the adjoint method is the inner product of the adjoint flux, ϕ^+ , and the source over time and energy: (Nuclear Reactor theory 1970)

$$D = \langle \phi \cdot S^+ \rangle = \langle \phi^+ \cdot S \rangle \quad \text{Eqn. (1)}$$

Appendix A provides a detailed mathematical statement for the equivalence of the forward and adjoint dose calculation.

During the course of our investigation, it was found that if one were to construct a forward dose matrix D relating each detector voxel to each source location and if one were to construct an adjoint dose matrix D^+ relating each source location to each detector voxel, the adjoint dose matrix would be equivalent to the transpose of the forward dose matrix. For a uniform spatial grid, the equivalence is expressed as $D^+_{j,i} \equiv D_{i,j}$. Because of difficulties computing the adjoint flux distribution in three dimensions, this equivalence was used to construct the three-dimensional adjoint dose matrix from the forward dose matrix. As was noted in the previous section, for all sources the forward dose matrix was computed using the TG43 dose formalism (Nath *et al.* 1995) and the NIST 1999 source strength standard for dose computation.

As noted above, the adjoint dose matrix, $D^+_{j,i}$, relates each source position to each source location. The greedy algorithm search engine, however, requires whole region of interest (ROI) adjoint information, not individual adjoint voxel dose information. The ROI adjoint distribution matrix can be computed from the

individual adjoint voxel dose matrix by an integration of the individual adjoint voxel-dose over all voxels in the ROI; $D_{j,ROI}^+ = \frac{1}{N_{ROI}} \cdot \sum_{i \in ROI} D_{j,i}^+$, where N_{ROI} is the number of voxels in the ROI. Hence, we have constructed a dose sensitivity matrix, that is, this matrix relates the dose deposited in the region as a function of source position. For example, a high target-ROI-adjoint value corresponds to a source location for which the dose deposited in the target would be high. Hence, if one's optimization strategy is based on high dose deposition, a position that has a high target-adjoint value indicates a preferred source position for dose deposition. If the doses to sensitive structures are to be minimized, then, a source position with a low sensitive structure adjoint value is a preferred location for sparing these tissues. This concept is used in the greedy algorithm to select preferred source positions. We also note that the integrated dose (average dose) to the ROI for a given source position can be computed from the whole ROI adjoint distribution.

Figure 2. One image slice of whole ROI adjoint distributions; (a) target, (b) urethra, (c) rectum and (d) normal tissue. Figure 2-(d) has ROIs contoured on x-y plane.

Figure 2 shows the four ROI-adjoint distributions: target, urethra, rectum and normal tissue. The z-axis indicates the amount of average dose-rate that would be delivered to a ROI due to a unit source (0.4 mCi ^{125}I) placed at an arbitrary location. The adjoint distribution provides source-to-dose-rate sensitivity distributions for each ROI.

III.3 Greedy Algorithm

The optimization engine used in this study is based on a class of algorithms known as heuristic algorithms. The heuristic problem-solving technique is one in which the most appropriate solution of several alternatives is selected at each successive stage of the problem. As the name implies, in the greedy algorithm, the element chosen is the one that gives the greatest immediate benefit to the objective function. Once an element is chosen, it is kept throughout the remaining stages of the solution search. Hence, it is known as one of the more efficient algorithms because of its strategy of selecting a solution

and retaining it throughout the remainder of the problem solution. For some classes of problems, the algorithm yields an optimum solution; however, usually the resulting combination of selected elements yields a good solution, not necessarily the optimum solution. Its strength is in the efficient manner in which it reaches a good acceptable solution. This method has been used in aligning DNA sequences and diagnosing genetic abnormalities, etc. (Zhang *et al.* 2000, Kosaraju *et al.* 1998)

It is very important to design a proper objective function for the greedy algorithm because the elements chosen at each stage of the search contribute directly to the final solution; no chosen element is modified. The objective function developed in this study is based on the whole ROI adjoint values, which are computed prior to the optimization search. Because ideally one must simultaneously maximize the dose to the target while minimizing the dose to the sensitive structures, a source position with a high target adjoint value that also has low sensitive structure adjoint values is a preferred position. To capture this feature in an objective function, we define a quantity called the adjoint ratio, which is the sum of the weighted sensitive structure adjoint values divided by the weighted target adjoint value for a source position:

$$z_{\phi^+}(j) = \frac{w_{urethra} \cdot D_{j,urethra}^+ + w_{rectum} \cdot D_{j,rectum}^+ + w_{normal} \cdot D_{j,normal}^+}{w_{target} \cdot D_{j,target}^+} \quad \text{Eqn. (2)}$$

where the w 's are weighting factors that indicate the importance of each ROI relative to other ROIs. This ratio is computed for all potential source positions and it provides a means of ranking source positions according to their preference or impact on the target and other structures. We have termed this ratio a "pseudo-objective function" because the ratios constitute a pre-computed dataset whose values are not changed by source placement during the optimization search. Figure 3 displays one 2-D image slice of the adjoint ratio in arbitrary units. The regions of interests are contoured. For our study, all weighting factors in Equation 2 have been set to one.

Figure 3. 2-D image slice of the adjoint ratio with ROIs contoured: target, urethra, rectum, and normal tissue. The ratio is in arbitrary units.

Equation 3 presents a flow chart of the iterative greedy algorithm. The optimization begins by searching for a source position j that has a low value for the pseudo-objective function value (minimum adjoint ratio value). If j belongs to the search space X , a source is placed at j ; otherwise, the algorithm searches for another source position that gives the next minimum pseudo-objective function value. After a source position is selected, it is added to the source configuration Q , and the dose distribution D_i is computed over all voxels i . After the dose is computed, the terminate criterion is checked. If the final solution criterion has been achieved, the iterative procedure terminates and the current source configuration Q becomes the greedy solution.

Otherwise, the process continues with the selection of another source. This iterative procedure continues until the final termination criterion is achieved. The final criterion in our study is set such that the dose to each voxel in the target receives greater than 96% of the prescribed dose D_p . (Nemhauser *et al.* 1998 and 1989)

Initialization. $Q^0 = 0$, $D_{\forall i, Q^0}^0 = 0$, $t = 1$

Iteration t . Let j_t minimize $z_{\phi^*}(j_t)$, where $j \in X$ such that $D_{X, Q^{t-1}}^{t-1} \leq \eta \cdot (t-1)$.

$$Q^t = Q^{t-1} \cup \{j_t\} \text{ and } D_{i, Q^t}^t = D_{i, Q^{t-1}}^{t-1} + D_{i, j_t}^t. \quad \text{Eqn. (3)}$$

If $D_{\forall i \in \text{target}, Q^t}^t \geq \alpha$, stop. Solution is Q^t . Otherwise, let $t \leftarrow t + 1$.

Figure 4. 3-D Isodose surface constraint with 0.4mCi sources for the (a) 2nd, (b) 3rd, (c) 4th, and (d) 58th iteration. 3-D prostate image; red is prostate, green is rectum, and blue is the isodose surface constraint. The search space X is inside of the red area and excludes the volume bounded by the blue region.

In addition to the use of a pseudo objective function, the greedy algorithm employs a search space constraint. The search space, X , is determined by an isodose surface constraint $\eta^*(t-1)$, where t is the number of iterations and is equivalent to the number of sources, and η is the estimated average dose delivered to the target by one source. For this study, a couple of assumptions have been made: 1) η is a constant which is set to 1.8% of the prescribed dose, and 2) the average dose to the target increases linearly with the number of the sources. If a region inside of the target receives a dose less than the constraint, $\eta^*(t-1)$, the region belongs to the search space, X . Conversely, if a region inside of the target receives a dose greater than the constraint, it is excluded

from the search space, X . Hence, for each greedy algorithm iteration, the search space for the next source placement is limited to a region (volume) where the delivered dose is smaller than the constraint.

Figure 4 displays the 3-D isodose surface constraints computed using 0.4 mCi sources for the 2nd, 3rd, 4th and 58th iteration. The prostate is in red, the rectum is in green, and the blue is the isodose surface constraint. After the 1st source is placed at the position with the highest ratio value (lowest objective value), the voxel dose is computed to form the isodose surface (blue surface). The search space X is constrained to the target volume (red area), but excludes the volume bounded by the blue region.

IV. Results and Discussion

As mentioned previously, the goal of this project is to investigate the use of multi-strength and multi-specie radioactive sources in permanent prostate implant brachytherapy. The hypothesis for the use of multi-strength and/or multi-specie sources is that a better treatment plan using fewer sources and needles could be obtained than by treatment plans using single-strength sources. Use of low-strength sources could reduce the dose to sensitive tissues and the use of higher-strength sources could reduce the overall number of sources used for treatment. Treatment plans using different combinations of multi-strength sources and multi-specie sources are compared to the basic ^{125}I single-strength source model.

IV.1. Multi-Strength Sources

Four different source scenarios were investigated using three different strength sources (0.2 mCi, 0.4 mCi and 0.6 mCi) of ^{125}I . There are a total of 259 possible source positions within the prostate being treated. Using the pseudo-objective function, each source position is ranked according to its adjoint ratio value. The first ranked position in the data set is the most preferred position for a source placement. It delivers a high dose to the target and simultaneously spares the sensitive structures. For multiple source strengths, it is explicit that a high-strength source should be placed at a high-ranked source position to have the most effect on the target and that a low-strength source should be placed at a low-ranked source position to spare the sensitive structures. We define a parameter “rank-cut” in the greedy algorithm to assure that high-strength sources are placed only at high ranked positions and low-strength sources are placed only at low-ranked positions. This parameter, rank-cut, was determined after some numerical experiments with the algorithm.

The isodose constraint required some modification for use with multi-strength sources. The isodose surface constraint value, $\eta^*(t - 1)$, should be small enough to prevent direct adjacent source placement but also large enough to allow a region for the next source placement. The value of η is different for the various source strengths. This is in order to account for the fact that the area under a certain isodose surface increases more when high-strength sources are added as opposed to low-strength sources. Hence, the isodose surface constraint was set at a value, which allowed for a greater range in possible source positions for a next iteration. For each scenario, this parameter was determined after some numerical experimentation. Table 1 shows the values of the parameters for each scenario.

Case	Strength			η	Rank-cut	
	0.2 mCi	0.4 mCi	0.6 mCi			
M	---	X	---	1.8%	NA	
LM	X	X	---	1.6%	< 200	
MH	---	X	X	2.0%	< 160	
LMH	X	X	X	1.8%	< 140	< 180

Table1. Parameter setup: M is the case with medium-strength sources only, LM with low- and medium-strength sources, MH with medium- and high-strength sources, and LMH with low-, medium- and high-strengths sources all together. “Rank-cut” refers to the rank-cut limit for the use of different strength sources according to rank of source positions, i.e., in the case of LMH, <140 means that the high-strength sources (0.6 mCi) are used at source positions ranked from 1 to 139, <180 means that the medium-strength sources (0.4 mCi) are used at source positions from 140 to 179, and the low-strength sources are placed at the rest of the source positions.

As indicated in Table 1, the four cases examined are the M, LM, MH and LMH, corresponding to source strengths of 0.4 mCi only, 0.2 mCi and 0.4 mCi sources, 0.4 mCi and 0.6 mCi sources, and all three sources respectively. Figure 5 compares the source configuration and isodose lines for four of the 10 image slices: the first slice, the two middle slices (5th and 6th) and the last slice (10th) for the four cases. The source positions are marked as ‘L’ for the low-strength 0.2 mCi, ‘M’ for the medium-strength 0.4 mCi, and ‘H’ for the high-strength 0.6 mCi sources. The first column (from the left to right) is the result of the case with the medium-strength sources only, the second column is the result of the case with the low- and medium-strength sources, the third column is the result of the case with the medium- and high-strength sources and the fourth column is the result of the case with all sources. Recall that this is a 3-dimensional optimization and that sources placed in neighboring slices have an influence on the slice displayed. Note that the lowest strength sources available are placed in both end slices (first and last

Figure 5. Source configurations and isodose lines of four cases in 2-D image slices; The 1st column from the left is with the medium-strength sources only; the 2nd is with the low- and medium-strength sources; the 3rd is with the medium- and high-strength sources; and the last column is with all sources. The ROIs are drawn in dotted lines; target (prostate), urethra, and rectum. ‘L’ is for a low-strength source, ‘M’ for a medium-, and ‘H’ for a high-strength source. The isodose lines of 200%, 150%, and 80% of the prescribed dose are drawn in solid lines with a thicker line for the prescribed dose line.

slices). This is because the adjoint ratio value for the end slices are quite low due to the larger volume of the sensitive structures relative to the target volume on the 2-D plane. The high-strength sources appear mostly in the central slices except when very close to the sensitive structures (urethra and rectum), where low- or medium-strength sources are placed. For the case without the high-strength sources, the medium-strength sources are used throughout the bulk of the prostate except near sensitive structures. However, even if the source configurations are different, the prescribed dose line (thick solid lines) well covers the target, avoiding the rectum in all cases.

The dose volume histograms (DVHs) for the four anatomical regions of interest for the four cases are compared in Figure 6. The target DVH indicates more than 96% of the prescribed dose is delivered to the target in all four cases, but the dose falls off more rapidly in the case of the medium- and high-strength sources, indicating that a more uniform dose distribution is achieved in the target. This is because the treatment using high-strength sources requires fewer sources. The urethra DVH displays the expected result that its dose is reduced (improved sparing) with the use of low-strength sources. This can be seen

Figure 6. Comparison of four cases in dose volume histograms (DVHs) for each ROI: the dotted vertical line is at D_p (145 Gy) for the target and normal tissue, at 360 Gy for the urethra, and at 90 Gy for the rectum.

in Table 2 where the integrated dose to the urethra is given. The case with the medium- and high-strength sources delivers the most dose to the urethra among all four cases. The case with all three types of sources achieves the best urethra sparing. Concerning the rectum, it is hard to distinguish which case spares the rectum region the best. All four cases have very similar rectum DVHs, but of the four, the case with the medium- and high- (MH) strength sources has the highest integrated dose to the rectum and the case with the low- and medium- (LM) strength sources has the lowest integrated dose (see Table 2).

Each treatment plan can be evaluated against several criteria to assess the plan's effectiveness. Table 2 summarizes the evaluation parameters for a comparison of the four cases. The percentage volume of a ROI that is enclosed by 100% of the D_p (the prescribed dose) is denoted as V100, and the dose that covers 100% of the volume of a ROI is denoted as D100 in the table. All four cases have 96% of the target volume enclosed by the prescribed dose, but the case with the MH strength sources has a 10% smaller V150 value (23.82%) than the others. This indicates that this plan has good dose uniformity as noted by the Dose Non-uniformity Ratio: $DNR = 0.25$. The DNR is one parameter among several proposed parameters to measure dose uniformity and it is expressed as: (Saw *et al.* 1998)

$$DNR = \frac{V_{high\ dose}}{V_{D_p}} \quad (4)$$

where $V_{high\ dose}$ is the target volume covered by the high dose (150% of D_p), and V_{D_p} is the target volume

	Target						Urethra		
	V100 [%]	V150 [%]	D50 [Gy]	D100 [Gy]	DNR	CN	V360 _{Gy} [%]	D10 [Gy]	D90 [Gy]
M	96.69	35.80	203.22	113.56	0.37	0.75	0	192.23	156.03
LM	96.17	34.35	201.78	106.83	0.36	0.75	0	184.89	140.87
MH	95.92	23.82	191.63	124.98	0.25	0.76	1.27	195.32	156.26
LMH	96.10	35.38	202.30	101.15	0.37	0.73	0	171.68	131.52

	Rectum			Num. of Sources				Num. of Needles
	V90 _{Gy} [%]	D10 [Gy]	D90 [Gy]	Num. Low	Num. Med	Num. High	Total	
M	43.38	130.01	50.38	.	58	.	58	41
LM	41.43	130.17	47.62	18	48	.	66	38
MH	45.06	145.20	55.85	.	22	23	45	31
LMH	43.05	137.76	51.26	24	11	24	59	38

Table 2. Evaluation: the notation V100 is the percent volume of a ROI that is enclosed by 100 % of the D_p , and D100 is the dose that covers 100 % of the volume of a ROI. DNR is the Dose Non-uniformity Ratio, CN is Conformation Number, V360_{Gy} is the percent urethra volume that receives the dose greater than 360 Gy, V90_{Gy} is the percent rectum volume that receives the dose greater than 90 Gy. The number of sources implanted is indicated for each strength source configuration, as is the total number of needles used.

enclosed by D_p . The DNR ranges from 0 to 1. A high DNR value indicates that a large fraction of the target volume is covered by the high dose, leading to dose inhomogeneity in the target; on the contrary, a low value means there is a more uniform target dose distribution. This is also indicated by the D50 and D100 parameters. The MH case has a smaller D50 (191.63 Gy), but larger D100 (124.98 Gy), than those of other cases.

All four cases have similar levels of dose conformity in the target ($CN \approx 0.7$). The conformation number (CN) is used to assess the quantitative degree of dose conformality in the target, that is, how well the target is covered by the prescribed dose. It is defined as (Riet *et al.* 1997):

$$CN = \frac{V_{target, D_p}}{V_{target}} \times \frac{V_{target, D_p}}{V_{D_p}} \quad (5)$$

where V_{target, D_p} is the volume of the target enclosed by the prescribed dose D_p , V_{target} is the target volume, and V_{D_p} is the volume enclosed by D_p . The conformation number ranges between 0 and 1. A CN value of 1 implies a complete coverage of the target with the prescribed dose without irradiation of any healthy tissue, that is, optimal dose conformality. A value of 0 means no part of the target receives the prescribed dose, that is, no conformation at all. Thus, the higher the CN value, the better the treatment plan. According to the TG64 prostate treatment standard, the average value of CN for prostate source implants is 0.72. For all cases examined, the CN is greater than 0.72, with the MH case having the highest value.

V_{360Gy} is the percent urethra volume enclosed by the 360Gy isodose line and is indicated in the urethra DVH. A maximum urethral dose above this value is significantly correlated with grade 2 – 3 urinary morbidity. (Wallner *et al.* 1995) Hence, a good plan keeps the dose to the urethra below this value. The case with the MH strength sources has 1.27% of the urethra volume irradiated to the sensitive dose of 360 Gy. The D10 is 195.32 Gy and the D90 is 156.26 Gy. Both values are greater than those of other cases. Hence, the MH source strength case does a poor job sparing the urethra.

Wallner *et al.* also suggests a useful parameter to analyze dissymmetric planning for the rectum; the V_{90Gy} parameter, which is the percent rectal volume that receives more than 90 Gy. Rectal wall bleeding or ulceration correlates significantly with the rectal wall receiving a dose greater than 90 Gy. (Wallner *et al.* 1995) As with the urethra dose, the MH case delivers the highest dose to the rectum. The V_{90Gy} is 45.06 %, which is about 2 – 4 % greater, D10 is 145.20 Gy, which is up to 15 Gy greater, and D90 is 55.85 Gy, which is up to 8 Gy greater than those of other cases. Hence, the MH case does not spare the rectum well. As was noted from the rectum DVH, the LM case spares the rectum the most among all cases.

For the results presented, we note that no case stood out clearly as giving the preferred treatment configuration. Each case delivered the prescribed dose to the target but there was a broad variation on the effect of the sensitive structures (urethra and rectum). The MH case had the better coverage for the target region but overexposed the sensitive structures. The LM case did a better job sparing the sensitive structures and did a decent job in the target region. The LMH case spared the urethra well and did a decent job with the target and rectum. The single-source strength case did a respectable job with all three regions of interest.

IV.2. Multi-Specie Sources

Figure 7. Dose distribution of 0.12 mCi ^{192}Ir permanent implant vs. dose distribution of 0.4 mCi ^{125}I permanent implant.

mCi) combined with a 0.4 mCi ^{125}I source. Two ^{192}Ir sources were placed at pre-selected positions within the prostate for all cases. These positions were selected after examining the source positions selected in the greedy algorithm. For cases I and II, the pre-selected positions are (50, 35, 5) and (15, 35, 5) which are the first two selected source positions using the 0.4 mCi ^{125}I source ranking. Cases III through VI have the two ^{192}Ir sources in the 4th and 7th slices but at the same (x, y) coordinates as cases I and II. The difference between Cases III and V and Cases IV and VI is that the z coordinates have been interchanged. Table 3 summarizes the ^{192}Ir source location within the prostate. With the two ^{192}Ir sources in place, the greedy algorithm searches a ^{125}I source placement that gives the minimum pseudo-objective value while satisfying the isodose surface constraint until the final criteria is achieved. The isodose surface constraint value η is set to 3.35% for all six cases.

	Positions for two ^{192}Ir sources (x, y, z)		^{192}Ir strength
Case I	(50, 35, 5)	(15, 35, 5)	0.25 mCi
Case II	(50, 35, 5)	(15, 35, 5)	0.12 mCi
Case III	(50, 35, 4)	(15, 35, 7)	0.25 mCi
Case IV	(50, 35, 4)	(15, 35, 7)	0.12 mCi
Case V	(50, 35, 7)	(15, 35, 4)	0.25 mCi
Case VI	(50, 35, 7)	(15, 35, 4)	0.12 mCi

Table3. Cases I – VI for multi-specie sources. Two ^{192}Ir sources are placed at the pre-selected positions and ^{125}I sources are used to complete the rest of treatment plan.

The average energy of the emitted photons from ^{192}Ir is 370 keV whereas the average energy of the emitted photons from ^{125}I is about 30 keV. Because of their high energy, photons from ^{192}Ir have a longer mean free distance in tissue than ^{125}I photons, resulting in a higher dose being deposited further from the source location than for ^{125}I . This is clearly seen in the dose profiles depicted in Figure 7. A higher dose can be deposited in distance tissue for ^{192}Ir sources than for ^{125}I sources. Hence, it is stipulated that we can reduce the total number of implanted sources using ^{192}Ir and ^{125}I sources versus only ^{125}I sources.

Six different source scenarios were investigated using two different ^{192}Ir strength sources (0.25 mCi, and 0.12

Figure 8. Source configurations and isodose lines of three cases in 2-D image slices; The left column is the Case I with the two 0.25 mCi ^{192}Ir sources at the 5th slice; the middle column is Case III with one 0.25 mCi ^{192}Ir source at the 4th slice and the other at the 7th slice; the right column is Case V with one 0.25 mCi ^{192}Ir source at the 4th slice and the other at the 7th slice but with positions switched from the Case III. The ROIs are drawn in dotted lines: target (prostate), urethra, and rectum. 'o' is for a 0.25 mCi ^{192}Ir source, 'x' for a 0.4 mCi ^{125}I source. The isodose lines of 200%, 150%, and 80% of the prescribed dose are drawn in solid lines with a thicker line for the prescribed dose line.

Figure 8 compares the isodose lines of the three middle slices (4th through 7th slice) for the three cases (Cases I, III, and V). The mark 'o' indicates a 0.25 mCi ^{192}Ir source and the mark 'x' is a 0.4 mCi ^{125}I source. For all cases, the prescribed dose line (thick solid lines) encompasses the target. One may note that there are not as many sources in the central slices as there were for the multi-strength source cases. This is due to the high dose delivered by the ^{192}Ir sources. Figures 9 and 10 compare the DVH results of all six cases against the basic case that uses only the single specie ^{125}I sources with strength of 0.4 mCi.

Figure 9. Comparison of four cases in dose volume histograms (DVHs) for each ROI. The dotted vertical line is at D_p (145 Gy) for the target and normal tissue, at 360 Gy for the urethra, and at 90 Gy for the rectum. ‘Basic’ refers to the single specie ^{125}I 0.4 mCi source case. Two 0.25 mCi ^{192}Ir sources together with ^{125}I sources are used in Cases III, V, and I.

Figure 9 displays the DVHs of three cases with two 0.25 mCi ^{192}Ir sources that are placed at different positions. The target DVHs in all cases indicate that more than 95% of the prescribed dose is delivered to the target. However, one notes that there is less sparing of the sensitive structures, in particular for the urethra for which a small region receives more than 360 Gy (note table 4). The basic ^{125}I case delivers a more uniform dose to the target and spares the sensitive structures better.

Figure 10. Comparison of four cases in dose volume histograms (DVHs) for each ROI. The dotted vertical line is at D_p (145 Gy) for the target and normal tissue; at 360Gy for the urethra, and at 90Gy for the rectum. ‘Basic’ refers to the single specie ^{125}I 0.4 mCi source case. Two 0.12mCi ^{192}Ir sources together with ^{125}I sources are used in Cases II, IV, and VI.

We noted in Figure 9 that the sensitive tissue DVH curves were fairly high compared to the basic ^{125}I cases. This was due to the high ^{192}Ir source strength. For the next three cases, the ^{192}Ir source strength was reduced by half. Figure 10 depicts the DVH results. Overall, there is improvement for most cases, particularly for the sensitive structures. The 360 Gy overdose of the urethra has been reduced and the curves have a steeper drop, indicating a more uniform exposure of the urethra. The target DVHs for all cases indicates that more than 95% of the prescribed dose is delivered to the target. These results indicate that one needs to reduce the ^{192}Ir source strength further in order to improve the sparing of the sensitive structures. As with the higher ^{192}Ir source strength, the basic ^{125}I case delivers a more uniform dose to the target and spares the sensitive structures to a greater degree.

Table 4 summarizes the evaluation parameters of all the multi-specie cases. As noted above, all cases have 96% of the target volume enclosed by the prescribed dose. The cases with 0.25 mCi ^{192}Ir sources yield smaller V150 as well as good dose uniformity, which is slightly better than the basic case result. All cases deliver a greater dose to the sensitive structures than does the basic case. The only parameters that show significant improvement are the number of sources and needles used for the treatment. There are substantially fewer sources and needles used in the multi-specie case than for the multi-strength source

cases. This is directly related to the flatter radial dose profile for ^{192}Ir at extended distances from the source location.

	Target						Num. of Sources	Num. of Needles
	V100	V150	D50	D100	DNR	CN		
	[%]	[%]	[Gy]	[Gy]				
Basic	96.69	35.80	203.22	113.56	0.37	0.75	58	41
Case I	96.42	32.74	214.60	122.63	0.34	0.65	26	23
Case II	99.14	45.04	228.10	134.18	0.45	0.65	28	27
Case III	96.84	22.30	214.06	122.32	0.33	0.69	25	22
Case IV	98.70	46.48	229.95	135.26	0.47	0.66	28	22
Case V	96.23	32.83	214.14	137.66	0.35	0.65	26	24
Case VI	98.11	45.45	226.60	121.02	0.46	0.67	27	27
	Urethra			Rectum				
	V360 _{Gy}	D10	D90	V90 _{Gy}	D10	D90		
	[%]	[Gy]	[Gy]	[%]	[Gy]	[Gy]		
Basic	0	192.23	156.03	43.38	130.01	50.38		
Case I	3.82	276.05	170.89	66.10	170.51	65.58		
Case II	0.96	224.70	175.01	69.61	198.22	79.29		
Case III	0.32	209.48	152.86	63.83	157.42	65.59		
Case IV	0.32	235.90	173.27	59.42	157.45	62.98		
Case V	4.14	277.24	171.62	65.52	170.77	65.68		
Case VI	0.32	223.81	138.29	61.17	184.73	65.98		

Table 4. Evaluation: the notation V100 is the percent volume of a ROI that is enclosed by 100 % of the D_p , and D100 is the dose that covers 100 % of the volume of a ROI. DNR is the dose non-uniformity ratio, CN is conformation number, V360_{Gy} is the percent urethra volume that receives the dose greater than 360 Gy, V90_{Gy} is the percent rectum volume that receives the dose greater than 90 Gy. The number of sources implanted (Num. of source) and the number of needles used are indicated for each strength source.

V. Conclusion

The goal of this project was to investigate the use of multi-strength and multi-specie radioactive sources in permanent prostate implant brachytherapy. The hypothesis for the use of multi-strength and/or multi-specie sources is that a better treatment plan using fewer sources and needles could be obtained than for treatment plans using single-strength sources. The recently developed greedy algorithm based on the adjoint concept was used as the optimization engine in this study. Our findings were that there was no combination of sources that clearly stood out from the others and could therefore be considered the preferred set of sources for treatment planning. For the ^{125}I multi-strength sources, the combination of high- (0.6 mCi) and medium- (0.4 mCi) sources tended to deliver a more uniform dose to the target whereas using a combination of low- (0.2 mCi) and medium-strength sources tended to achieve better sparing of sensitive structures than using solely medium-strength sources. Except for over-exposure of the urethra for the medium- and high-source case, all source configurations had comparable DVHs. The multi-specie source study used two ^{192}Ir source strengths (0.12 mCi and 0.25 mCi) in combination with

0.4 mCi of ^{125}I . For all cases, the prescribed dose was delivered to the target; however, sensitive tissue sparing, in particular that of the urethra, was worst than for the base ^{125}I case (single-source strength). This was largely due to the enhanced radial dose profile of the ^{192}Ir sources as compared to the ^{125}I dose profile. Indications are that a lower strength ^{192}Ir source might improve sparing of the sensitive structures. However, one of the positive features of the ^{192}Ir treatment plans was the use of fewer sources and needles than for the base ^{125}I case. These plans would be less invasive than those of the base case.

For permanent prostate implant, it is essential that the treatment procedure remain simple and as noninvasive as possible. The smaller the number of needles, the less invasive the procedure and the lower the probability of side effects. In the investigations above, no needle or source constraints were applied in the optimization. This resulted in an unacceptable number of needles being used for the multi-strength source cases and the ^{125}I base case. The multi-specie source cases performed better in this regard though other aspects of the plans were less positive. Though no definitive conclusions can be drawn from our study, we believe that further investigations are warranted before a concrete conclusion can be drawn as to the use of multi-strength and multi-specie sources in brachytherapy treatment procedures.

VI. References

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VII. Appendices

Appendix A

Dose Computation in Forward and Adjoint Transport

The “forward” form of the Boltzmann transport equation is a balance equation for photons due to a photon source within a medium (Bell and Glasstone):

$$\hat{\Omega} \cdot \vec{\nabla} \Phi(\vec{r}, \hat{\Omega}, E) + \mu_t(\vec{r}, E) \Phi(\vec{r}, \hat{\Omega}, E) = \int_{E'} \int_{\Omega'} \mu_s(\vec{r}, \hat{\Omega}' \rightarrow \hat{\Omega}, E' \rightarrow E) \Phi(\vec{r}, \hat{\Omega}', E') d\hat{\Omega}' dE' + S(\vec{r}, \hat{\Omega}, E) \quad (\text{A.1})$$

where $\Phi(\vec{r}, \hat{\Omega}, E)$ is the solution of the transport equation known as the forward (angular) flux in position, direction and energy. The two terms on the left-hand side are referred to as the streaming and collision terms, respectively, and represent loss of particles from the phase space. On the right-hand side, the scattering and external source terms represent particle gains in the phase space. We can compute dose to a detector voxel i from a source voxel j with the forward flux distribution Φ :

$$D_{ij} = \int_0^\infty \int_{V_i} \int_{4\pi} \int_0^\infty \Phi_{i \leftarrow j}(\vec{r}, \hat{\Omega}, E) \mu_{en}(\vec{r}, E) E dt d\hat{\Omega} d\vec{r} dE \Big/ \int_{V_i} \rho(\vec{r}) d\vec{r} \quad (\text{A.2})$$

where D_{ij} indicates dose to the voxel i due to a source at j computed by using forward flux, $\Phi_{i \leftarrow j}$, which is forward flux to i from j , μ_{en} is an energy absorption coefficient of the voxel i , and ρ is the density of the voxel i . Evaluating the angular integration in eq. (A.2) gives:

$$D_{ij} = \int_0^\infty \int_{V_i} \int_0^\infty \Phi_{i \leftarrow j}(\vec{r}, E) \mu_{en}(\vec{r}, E) E dt d\vec{r} dE \Big/ \int_{V_i} \rho(\vec{r}) d\vec{r} \quad (\text{A.3})$$

With the assumptions of homogeneous medium and spatially uniform flux in the voxel i , we can solve the spatial integral obtaining:

$$D_{ij} = \int_0^\infty \int_0^\infty \Phi_{i \leftarrow j}(E) \mu_{en}(E) E dt dE \Big/ \rho_i. \quad (\text{A.4})$$

The mass energy absorption coefficient times energy ($\mu_{en}(E)E/\rho$) is defined as the flux-to-dose-rate conversion factor CF, which is also referred to as the detector response function. For the adjoint calculation, CF is used as the adjoint source S^+ :

$$D_{ij} = \int_0^\infty \int_0^\infty \Phi_{i \leftarrow j}(E) CF(E) dt dE \quad (\text{A.5})$$

Thus, the dose can be expressed by the inner product of the forward flux and the adjoint source over time and energy:

$$D = \langle \Phi, CF \rangle = \langle \Phi, S^+ \rangle \quad (\text{A.6})$$

The “adjoint” form of the Boltzmann equation is a balance equation for adjoint “particles” resulting from an adjoint source in the medium (Bell and Glasstone):

$$-\hat{\Omega} \cdot \vec{\nabla} \Phi^+(\vec{r}, \hat{\Omega}, E) + \mu_t(\vec{r}, E) \Phi^+(\vec{r}, \hat{\Omega}, E) = \int_E \int_{\Omega'} \mu_s(\vec{r}, \hat{\Omega}' \rightarrow \hat{\Omega}, E' \rightarrow E) \Phi^+(\vec{r}, \hat{\Omega}', E') d\hat{\Omega}' dE' + S^+(\vec{r}, \hat{\Omega}, E) \quad (\text{A.7})$$

where $\Phi^+(\vec{r}, \hat{\Omega}, E)$ is the solution of the adjoint equation known as the adjoint (angular) flux in position, direction and energy. We can also compute dose to a detector voxel i from a source voxel j with the adjoint flux (or function) Φ^+ . With the assumption of homogeneous medium containing an adjoint source S^+ in the voxel i, the dose is

$$D_{ji}^+ = \int_0^\infty \int_{V_j} \int_{4\pi} \int_0^\infty \Phi_{j \leftarrow i}^+(\vec{r}, \hat{\Omega}, E) S_j(\vec{r}, \hat{\Omega}, E) dt d\hat{\Omega} d\vec{r} dE \Big/ \int_{V_i} d\vec{r} \quad (\text{A.8})$$

where the notation D_{ji}^+ is used instead of D_{ij} to indicate the dose being calculated using the adjoint function. Evaluating the angular integration and assuming an isotropic source, the dose is

$$D_{ji}^+ = \int_0^\infty \int_{V_j} \int_0^\infty \Phi_{j \leftarrow i}^+(\vec{r}, E) S_j(\vec{r}, E) dt d\vec{r} dE \Big/ \int_{V_i} d\vec{r} \quad (\text{A.9})$$

With the assumption of a spatially uniform adjoint flux over the voxel i and also uniform source over the voxel j, and with the homogeneous medium, the dose is

$$D_{ji}^+ = \int_0^\infty \int_0^\infty \Phi_{j \leftarrow i}^+(E) S_j(E) V_j dt dE \Big/ V_i \quad (\text{A.10})$$

If the detector voxel i and the source voxel j have the same volume, the dose by using the adjoint function is

$$D_{ji}^+ = \int_0^\infty \int_0^\infty \Phi_{j \leftarrow i}^+(E) S_j(E) dt dE \quad (\text{A.11})$$

Thus, the dose can be expressed by the inner product of the adjoint flux and the source over time and energy:

$$D = \langle \Phi^+, S \rangle \quad (\text{A.12})$$

which is equivalent to equation A.6.

Reference:

Bell G.I., Glasstone S., *Nuclear Reactor Therapy* (Van Nostrand, Princeton 1970), Chap. 1. & 6.

Appendix B

Conference Presentations and Publications

[1] S. Yoo¹, D. L. Henderson², and B. R. Thomadsen¹, "A Greedy Algorithm for the Optimization of Prostate Implant using the Adjoint Concept," 44rd Annual AAPM (American Association of Physicists in Medicine) Meeting, July 14-18, 2002, Montreal, Canada.

[2] S. Yoo¹, D. L. Henderson², and B. R. Thomadsen¹, "A Greedy (Heuristic) Algorithm for Prostate Implant Treatment Planning Optimization using the Adjoint Concept," in preparation for submission to the Journal of Medical Physics, November 2002.

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Patent Disclosure

A patent disclosure was submitted to the Wisconsin Alumni Research Foundation on work developed as part of this investigation.