Mixed Integer Programming Optimization Models for Brachytherapy Treatment Planning

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Mixed integer programming is proposed as an approach for generating treatment plans for brachytherapy. Two related, but distinct, mixed integer programming models are tested on data from eight prostate cancer patients. The results demonstrate that in some cases, "good" treatment plans can be obtained in less than five CPU minutes.

INTRODUCTION

Brachytherapy is a type of radiation therapy that involves the placement of radioactive sources (seeds) either in tumors (interstitial implants) or near tumors (intracavitary therapy and mold therapy). In this approach radiation is emitted outward and limited to short distances. Thus, unlike external beam radiotherapy, where radiation must traverse normal tissue in order to reach the tumor, brachytherapy is much more localized and therefore reduces radiation exposure to normal tissue while allowing an escalation in the radiation dose. However, the "optimal" placement and dosage of the radioactive seeds in brachytherapy is a difficult problem.

Prior to the wide availability of computers, strategies used to obtain reasonable dose uniformity throughout a region implanted with radioactive seeds included the Manchester Paterson-Parker system [1], the Quimby system [2], and the Paris system [3]. Although such strategies have been, and in some cases, continue to be, useful in determining brachytherapy treatment plans, the use of the computer enables much more sophisticated techniques to be employed. Computer aided planning typically consists of sequentially adjusting the position and/or the number and strengths of sources within the target in order to achieve the "best possible" fit of a desired dose distribution. Adjustments may be performed manually, guided by repeated viewing of graphical representations of isodose and target contour representations [4], or automatically by optimization algorithms [5, 6, 7, 8, 9].

In this paper mixed integer programming (MIP) optimization models are proposed for aiding in the selection of treatment plans. The models are presented in Section 2, and numerical experiments using data obtained from eight prostate cancer patients are reported in Section 3.

One potential advantage of computer-assisted treatment planning is speed. Due to the labor intensive nature of the traditional strategies mentioned above, when such strategies are used treatment plans must typically be generated at least 24 hours in advance of the actual implantation of the seeds. Unfortunately, it is often the case that the position of the diseased organ in the operating room differs from the position in the original CT scan. In such a case, there may be a need to change the plan in the operating room. One goal of an automated treatment plan system is to be able to assist physicians and radiation physicists in obtaining good treatment plans "on the fly." Hence, it is imperative that the optimization component of an automated system obtain solutions quickly. The numerical results presented in Section 3 show that, in some cases, "good" solutions can be obtained in under 300 seconds.

OPTIMIZATION MODELS

Our basic model involves using 0/1 variables to record placement or non placement of seeds in a prespecified three-dimensional grid of potential locations. The locations correspond to the intersections of the needles in the instrument used to deposit seeds with the regions where the diseased organ resides in each of a number slices (obtained via a CT scan) of the tumor site and neighboring healthy organs. If a seed is placed in a specific location, then it contributes a certain amount of radiation dosage to each of the points in the discretized representations. The dose contribution to a point is proportional to the inverse square of the

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distance from the source. Once the grid of potential seed locations is specified, the total dose level at each point can be modeled.

Let x_j be a 0/1 indicator variable for recording placement or non placement of a seed in grid position j. Then the total radiation dose at point P is given by

$$\sum_j D(\|P - X_j\|)x_j, \tag{1}$$

where X_j is a vector corresponding to the coordinates of grid point j, $\|\cdot\|$ denotes the Euclidean norm, and $D(r)$ denotes the dose contribution of a seed to a point r units away. The target lower and upper bounds, L_P and U_P, for the radiation dose at point P can be incorporated with (1) to form constraints for the MIP model:

$$\begin{aligned} \sum_j D(\|P - X_j\|)x_j &\geq L_P \\ \sum_j D(\|P - X_j\|)x_j &\leq U_P. \end{aligned} \tag{2}$$

Unfortunately, it is typically not possible to satisfy all such constraints simultaneously. Indeed, due to the inverse square factor, the dose level contribution of a seed to a point less than 0.3 units away, say, is typically larger than the target upper bound for the point.

One possible approach is to identify a *maximum feasible subsystem*. This is the essence of our first MIP model. By introducing additional 0/1 variables one can directly maximize the *number* of points satisfying the specified bounds. In this case, constraints (2) are replaced by

$$\begin{aligned} \sum_j D(\|P - X_j\|)x_j - L_P &\geq -N_P(1 - v_P) \\ \sum_j D(\|P - X_j\|)x_j - U_P &\leq M_P(1 - w_P), \end{aligned} \tag{3}$$

where v_P and w_P are 0/1 variables, and M_P and N_P are suitably chosen positive constants. If a solution is found such that $v_P = 1$, then the right hand side of the first inequality in (3) is zero; and hence, the lower bound for the dose level at point P is not violated. Similarly, if $w_P = 1$, then the right hand side of the second inequality in (3) is zero; and hence, the upper bound for the dose level at point P is not violated. In order to find a solution that satisfies as many bound constraints as possible, it suffices to maximize the sum of these additional 0/1 variables; i.e., maximize $\sum_P (v_P + w_P)$. In practice, achieving the target dose levels for certain points may be more critical than achieving the target dose levels for certain other points. In this case, one could maximize a weighted sum: $\sum_P (\alpha_P v_P + \beta_P w_P)$, where the more critical points receive a relatively larger weight. We found that using a weighted sum was important for the prostate cancer cases to be discussed in Section 3. Since there were substantially fewer urethra and rectum points compared to the number of points in the tumor, to increase the likelihood that the former points achieved the target dose levels, a large weight was placed on the associated 0/1 variables.

The role of the constants N_P and M_P in (3) is to ensure that there will be feasible solutions to the mathematical model. In particular, these constants must be chosen suitably large so that if v_P or w_P is zero, the associated constraint in (3) will not be violated.

An alternative model involves using continuous variables to capture the deviations of the dose level at a given point from its target bounds and minimizing a weighted sum of the deviations. In this case, the constraints (2) are replaced by constraints of the form

$$\begin{aligned} \sum_j D(\|P - X_j\|)x_j + y_P &\geq L_P \\ \sum_j D(\|P - X_j\|)x_j - z_P &\leq U_P, \end{aligned} \tag{4}$$

where y_P and z_P are nonnegative, continuous variables. The objective for this model takes the form: minimize $\sum_P (\alpha_P y_P + \beta_P z_P)$, where α_P and β_P are nonnegative weights selected according to the relative importance of satisfying the associated bounds. For example, weights associated with an upper bound on the radiation dose for points in a neighboring healthy organ may be given a relatively larger magnitude than weights associated with an upper bound on the dose level for points in the diseased organ.

The target bounds L_P and U_P are typically expressed as appropriate multiples of a *target prescription dose*, T_P. Thus, another natural approach is to capture the deviations from T_P directly [10]. In our model, this can be achieved by replacing constraints (2) with

$$\sum_j D(\|P - X_j\|)x_j + y_P = T_P, \tag{5}$$

where y_P is a continuous variable, unrestricted in sign. One can then minimize the q norm

of the vector y of all deviations; i.e., minimize $\|y\|_q = (\sum_P |y_P|^q)^{1/q}$. We have not yet explored this modification numerically, but mention it to demonstrate the flexibility of our basic model.

Another enhancement that we have not yet explored, but that could be incorporated into any of the above models, is the allowance of alternative seed types. There are a variety of radioactive sources that are used for brachytherapy, including cesium-137, iridium-192, iodine-125, and gold-198, each of which has its own set of exposure rate constants. Typically however, a single seed type is used in a given treatment plan. This fact is, in part, due to the difficulty of designing treatment plans with multiple seed types. The mixed integer programming approach would allow consideration of multiple seed types with little additional cost; and more importantly, the added flexibility of allowing multiple seed types may have a substantial impact on the number of points at which the target dose levels can be satisfied. To incorporate multiple seed types one can modify the total dose level expression (1) as

$$\sum_j \sum_i D_i(\|P - X_j\|)x_{ij}. \qquad (6)$$

Here, x_{ij} is the indicator variable for placement or non placement of a seed of type i in grid location j, and $D_i(r)$ denotes the dose level contribution of a seed of type i to a point r units away. In this case, a constraint restricting the number of seeds implanted at grid point j is also needed: $\sum_i x_{ij} \leq 1$.

NUMERICAL RESULTS

Data from eight prostate cancer patients were used to test our models. The data for a given patient include discretized representations of slices obtained via a CT scan of the tumor site and neighboring healthy organs (urethra and rectum), together with prespecified target bounds for the radiation dosage at each of the points in the representations. In each case, the grid of potential seed positions was specified by a radiation physicist in consult with a physician. Iodine-125 was used for the radioactive sources, with exposure rate constants for the sources provided by the manufacturer. Four separate categories of points were given. Contour points specify the boundary of the diseased organ in each of the slices. The region determined by each boundary is populated with uniformly spaced points, termed uniformity points. Finally, two points representing the positions of the urethra and rectum in each slice are specified. Table 1 summarizes the data for each patient (Pt), giving the number of rectum points, the number of urethra points, the number of contour points, and the number of uniformity points.

Table 1. Number of Data Points by Type for each Patient

Pt	Rectum	Urethra	Contour	Uniformity
1	10	10	595	1589
2	8	8	492	1237
3	7	7	399	1104
4	6	6	308	800
5	7	7	485	1416
6	7	7	479	1620
7	9	9	433	859
8	6	6	317	821

The lower and upper bounds for each of the point types were specified as multiples of the target prescription dose of 16000 rads. These are tabulated in Table 2.

Table 2. Lower and Upper Bound Specifications as Multiples of Target Prescription Dose

	Rectum	Urethra	Contour	Uniformity
Lower Bound	0	0.9	1.0	1.0
Upper Bound	0.78	1.1	1.5	1.5

Numerical tests were performed using two distinct models. Model 1 utilizes constraints (3), and Model 2 constraints (4). Various combinations of objective function weights for each of the two models were tested. Here we focus on one set of weights for each model which have provided consistent numerical results.

For Model 1 we found it necessary to place relatively large weights on the 0/1 variables associated with urethra and rectum points. For the results reported herein, the objective function weights for the 0/1 variables associated with uniformity and contour points were set equal to 1; and the weights for the 0/1 variables associated with urethra and rectum points were set equal to the number of uniformity points. Selecting the weights in this fashion essentially ensures that the dose contribution to urethra and rectum points will lie within the specified bounds.

For Model 2, the objective function weights for the 0/1 variables associated with the rectum points were set equal to 1; those associated with the urethra points, 100; those associated with the uniformity points, 1; and those associated with the contour points, to the ratio of the number of uniform points over the number of contour points. This selection helped in maintaining a relatively even balance in the percentage of uniformity points and contour points for which the

dose levels achieved their target bounds, while at the same time yielding high achievement for the urethra and rectum points.

The optimization module first reads in the data specifying the type and location of each point, as well as the candidate seed positions and source exposure rate constants. Employing the modeling language AMPL [14], the associated MIP problem instance is generated in a standard format, which is then read by the optimization solver. The optimization solver incorporates state-of-the-art mixed integer programming techniques [15, 16]. In particular, we note that the solver has a fast heuristic that is effective in quickly generating feasible integer solutions.

Due to the intrinsic difficulty of solving mixed integer programs to proven optimality, we report only the best result obtained after running the solver for 5 and 1 CPU minute(s) for Models 1 and 2, respectively. Model 1 required a longer running time since the associated problem instances proved to be more difficult to obtain feasible solutions. We ran both models long enough so as to obtain between 3 and 5 integer feasible solutions. Tables 3a and 3b show, for each patient, the percentage of rectum points, urethra points, contour points, and uniformity points for which dose level was within the specified bounds, when the "best" solution out of those generated was selected.

Table 3a. Solution Statistics for Model 1: Percentage of Points Satisfying Bound Conditions

Pt	Rectum	Urethra	Contour	Uniformity
1	100	100	46	45
2	100	100	44	42
3	100	100	35	44
4	100	100	41	35
5	100	100	50	42
6	100	100	33	37
7	100	100	48	41
8	100	100	46	44

Table 3b. Solution Statistics for Model 2: Percentage of Points Satisfying Bound Conditions

Pt	Rectum	Urethra	Contour	Uniformity
1	60	100	58	48
2	100	100	52	52
3	100	100	45	43
4	100	100	50	55
5	29	100	70	53
6	100	100	35	40
7	100	100	56	50
8	100	100	51	46

Table 4 shows a comparison of results from a treatment plan selection method currently in use at a regional hospital to results from Models 1 and 2. For this evaluation, an extremely fine grid of points within each slice of the diseased organ was used. These "region of interest points" lie within the boundary specified by the contour points, and are spaced less than 1 millimeter apart. The total number of region of interest points for each patient is listed in the column labeled n. As with the uniformity points, the lower and upper bounds for the radiation dosage to each region of interest point are 100% and 150% of the target dose level, respectively. Achievement of both lower and upper bound criteria is reflected in Table 4; for each method, the column labeled L (U) records the percentage of points achieving at least 100% (at most 150%) of target dose level.

Table 4. Comparison of Solution Statistics: Percentage of Points Satisfying Lower/Upper Bound Conditions

		Current		Model 1		Model 2	
Pt	n	L	U	L	U	L	U
1	340117	96.1	46.7	95.3	55.2	92.6	53.3
2	292278	93.0	47.7	93.3	57.3	93.4	52.9
3	292278	93.2	54.5	87.5	56.0	82.8	45.8
4	167426	98.3	53.6	98.5	64.1	92.9	57.7
5	312495	96.0	41.4	96.2	52.6	95.2	50.3
6	400160	84.9	49.7	86.1	54.6	80.7	45.8
7	212043	98.0	52.8	98.8	68.2	91.3	48.3
8	226625	96.6	54.1	96.6	64.0	91.7	50.6

Observe from Table 3a that using the selected objective function weights for the 0/1 variables associated with rectum and urethra points in Model 1 resulted in all of these points achieving their associated target dose level bounds. Although this was not the case for Model 2 (see Table 3b), on average, the percentages of contour points and uniformity points satisfying the respective bounds were higher in Model 2 than in Model 1. Note however, that whereas contour and uniformity points are actually associated with model constraints, the region of interest points are not. Hence, the region of interest points serve as unbiased test points for the treatment plans. With this in mind, Table 4 indicates that Model 1 performed consistently better than Model 2 on the eight cases considered. More importantly, Model 1 was competitive with the current method in achieving the lower bound conditions, while consistently achieving a higher percentage of points satisfying the upper bounds.

SUMMARY AND CONCLUSION

The goal of these preliminary studies is to obtain raw measurements on the performance of the proposed techniques. Although mixed integer programs are technically difficult to solve to optimality, discrete variables, and in particular, 0/1 variables, are powerful tools for modeling real applications. In this application, the models formulated provided flexibility in choice of the number

and type of seeds, as well as in prioritizing the importance of dose level achievement for various organs and tissue within the diseased area. The results obtained indicate that integer programming is a viable approach for generating treatment plans for brachytherapy. Planned future work includes studying the effect of the objective function weights for the various models, investigating other MIP formulations, and applying the technique to brachytherapy treatment for other type of cancers. In addition, we will continue to seek effective computational strategies for solving the MIP models developed and displaying the results graphically in terms of isodose and target contour representations, so as to facilitate physicians and radiation physicists in obtaining good treatment plans "on the fly."

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