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Optimization in Surgical Operation Design*

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Abstract

A new treatment of some oncological diseases is brachytherapy that means the insertion of low level radiation isotopes into the organ to be healed. This cure has much less intensive side effects than traditional radiation therapy, while it is just as much effective. The problem is to determine how to position the 50-90 capsules in such a way that the tissue to be healed obtains at least a given level of dose, while the surrounding other organs absorb a dose less than a prescribed level. The related nonlinear optimization problem is of moderate dimensional (120-270). The resulting global optimization problem is very redundant, and it shows several forms of symmetries as well. The first test results obtained for an artificial model are reported.

Keywords: Operation design, Sphere packing

MSC: 90C,65K

1. Introduction

Some kinds of cancers can be treated by a new method, by inserting low radiation level material into the given organ. This technique, called brachytherapy was accepted by the Hungarian health care authorities a few years ago, and has been used in the developed world since a decade.

Usually 50-90 pieces of small capsules (called seeds, see Figure 1) are inserted that contain the radiating material. The operation requires local anesthesia, and

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can also be carried out in an ambulant way. Brachytherapy has minimal side effects compared to traditional radiation therapy, while it is at least as effective.

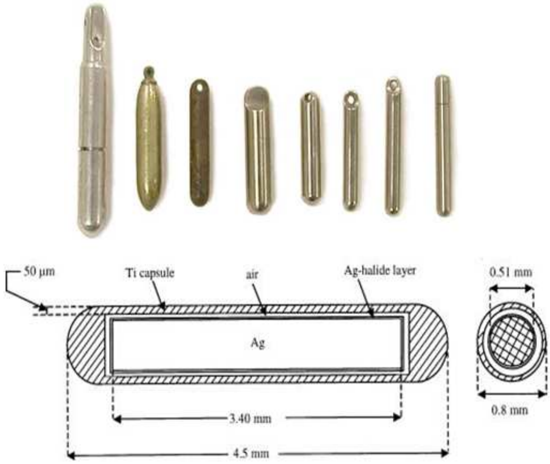

Figure 1: Seeds to be inserted containing the isotopes, and the structure of the seeds

Brachytherapy costs around 5,000 Euros per patient. The remained pieces of the ordered set of seeds are now handled as dangerous waste that requires expensive handling.

Brachytherapy is used for cancers in the brain, thyroid gland, neck, breast, and prostate. The healing effect is based on the phenomenon that tumor cells are less effective in repairing new errors in the genes. The applied radiation dose is comparable with that of the diagnostic imaging procedures such as CT and xray.

The optimization method we develop can help in answering the following questions:

- How to position a given number of seeds with known common radiation intensity in such a way, that provides the required radiation dose to the tissue with tumors, while the surrounding other tissues receive only minimal radiation?
- Which setting of the seeds allows to have a successful therapy with a minimal number of seeds?
- The present surgical operation design method requires 0.5-1.5 hours of computation, during which the patient waits anesthetized. Can this part of the therapy be speeded up somewhat?
- Is it possible to provide an acceptable solution with seeds of different radiation intensity (and hence saving much money)?

We applied the following simple model for the computational tests: The tumorous tissue to be treated is modeled by a sphere with the center at the origin, and with a radius of 2.5. The other tissues that should obtain as small amount of radiation as possible are outside the sphere, and are in a vertical cylinder around the axe z with a diameter of 1. The radiation dose is assumed to be identical within each cube of side length 0.25 (with the resolution of 20), and the dose is calculated in its center. This resolution was also changed slightly during our experiments as needed. A surgical operation design is regarded to be acceptable, if at least 90% the tissue classes get doses fulfilling the set conditions: the tumorous tissue obtains radiation dose of 110 units, and the tissues to be saved get at most 90 units of radiation.

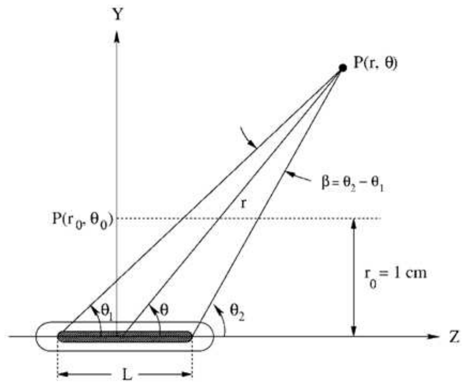

Figure 2: Dose calculation for a not point-like radiation source

Dose calculation details are from the paper of Tibor Major and Jenő Julow [3] (illustrated on Figure 2). The half life of the isotope iodine-125 is around 60 days, the emitted average energy density is 35,5 keV, and it is actually gamma-radiation. The half life of the isotope iridium-192 is about 74 days, its produced average energy density is 370 keV, and it emits beta-radiation. In our simplified model we do not calculate with the anisotropy (see Figure 3 for typical curves) of the radiation sources [7].

2. Optimization model

Let $S_{\text{in}} = \{(x, y, z) \mid x^2 + y^2 + z^2 \leq 2.5^2,\ z^2 \geq 0.25\}$ be the set that models the tissue to be treated, and $S_{\text{out}} = [-2.5, 2.5]^3 \backslash S_{in}$ is the set of tissues that are to be saved. Then the optimization problem can be formulated as

$$\max_{x_i, y_i, z_i \in [-2.5, 2.5]^3} \frac{(\text{vol}(\{s \in S_{\text{in}} \mid D(s) \geq 110\}) + \text{vol}(\{s \in S_{\text{out}} \mid D(s) \leq 90\}))}{(\text{vol}(S_{\text{in}}) + \text{vol}(S_{\text{out}}))},$$

where $D(s)$ is the cumulative dose obtained at point s from the seeds, and $\text{vol}(S)$ denotes the volume of the set S. The function $D(s)$, that calculates the summed

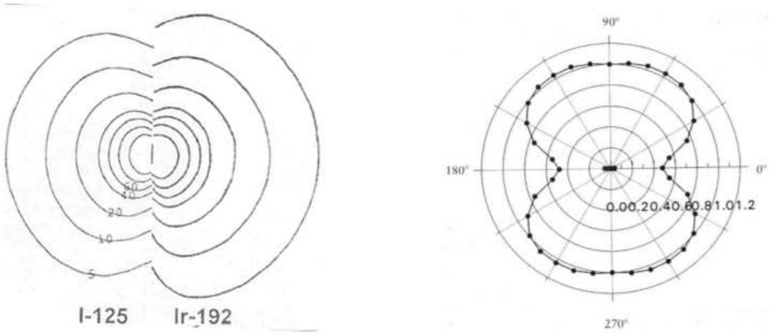

Figure 3: Curves with equivalent dose values for the isotopes iodine-125 and iridium-192, and illustration of anisotrophy caused by the not point-like radiation source

up dose from the point-like radiation sources, is proportional with the reciprocal of the square of the distance to the seed. The simulated radiation intensities were set in such a way that the plausible number of 40 seeds could already provide the necessary amount of doses for the tissues to be healed. The prescribed threshold dose value of 110 units are provided in this model within a sphere around a single seed with a radius of about 0.3. The respective volume is around 0.11.

The volume of the set S_{in} is ca. 65, while that of S_{out} is about 60 (52% and 48% of the search domain, respectively). The reference point distribution, where we measure the dose is slightly different from these. The proportion of the volumes implies that when we do not use any seeds, then the objective function has a value of 48% – of course without having any curing effect. To keep the doses for the set S_{out} below 90%, it makes sense to allow the positions of the seeds away from the boundary of the sets by a distance of $1/3$, since the dose inside of a sphere with radius $1/3$ is 90. Of course there exists a strong cumulative effect of radiation arriving from different seeds. On the other hand, seeds beyond a distance of 1 unit have a dose contribution less than 10; for a distance of 2 units already below the value of 2.5.

The cumulative dose constraints mean basically a kind of generalization of sphere covering of bounded bodies [6]. In this way the optimal surgery operation design problem belongs to discrete geometrical optimization [5].

The algorithm development was made in a Matlab environment. The final implementation is planed to be in a high level programming language like C. The GLOBAL algorithm [1], a multistart clustering method was used for optimization. Due to the high dimensionality of the problem, the random walk type simple local search technique, UNIRANDI was applied, instead of the more sophisticated BFGS quasi-Newton algorithm. Since the problem is highly symmetric, such as the circle packing problem, similar tricks should be used to have an efficient and effective algorithm.

3. First results

A representative Matlab setting of the algorithm parameters in the computational testing were the following (without the tricks utilizing the symmetries and redundancies):

```
» LB = [-3; -3; ...  -3];
» UB = [3; 3; ...  3];
» OPTS.N100 = 500;
» OPTS.NG0 = 2;
» OPTS.NSIG = 6;
» OPTS.MAXNLM = 3;
» OPTS.METHOD = 'unirandi';
» FUN =@brachy;
» [X0,F0,NC,NFE] = GLOBAL(FUN, LB, UB, OPTS);
```

The arrays LB and UB contain the lower and upper bounds for the decision variables, the seed coordinates. For the algorithm we generate 500 sample points in one iteration round, out of which we keep the best 2 as starting points for the local search. The number of significant precise digits is set to be 6 for the local search. The maximum number of local minima is limited to 3 this time. The local search method selected was UNIRANDI, and the objective function was given as a Matlab subroutine named `brachy.m`. The last row requires to print the sets of found local minimizer points, the respective minimum values of the objective function, the number of clusters recognized and the number of function evaluations.

First experiment. This time we allowed for all seeds to move within the search domain $[-2.5, 2.5]^3$. A typical result when the algorithm settings were: resolution 0.2, 10 seeds with respectively elevated radiation intensity, number of sample points: 500, tolerance value 10^{-8}. At most 3 local minima was allowed, the local search method was UNIRANDI, and the running time was limited to 25 seconds.

```
» [X0,F0,NC,NFE] = GLOBAL(FUN, LB, UB, OPTS);

*** TOO MANY CLUSTERS ***
NORMAL TERMINATION AFTER 1414 FUNCTION EVALUATIONS

LOCAL MINIMA FOUND: 3

F0 =
-0.8023
-0.6991
-0.6976
```

```
X0 =
0.2743 -0.8013 2.3628
1.2200 0.7336 0.3030
-0.4384 1.2329 -0.1015
...
```

Of course, increasing number of seeds means larger dimension of the optimization problem. Since the complexity of the solution is proportional to the exponential of the dimension, realistic size problems cannot be solved with this kind of brute force search. According to our experiences, the solution quality became worse as the dimensionality increased. This could be partly due to the decreasing relative size of the set of feasible solutions. We were able to detect that the resolution of the search space influences the CPU time in a cubic way.

We can also force a unique identification of the seeds. This would be in accordance with what we have learned in the determination of optimal circle packing [4, 5]. Also other, less dimension sensitive global optimization methods can help, such as the Multilevel Coordinate Search [2].

Second experiment. The next step of algorithm development was to utilize the known sparsest covering structure of spheres in the space. This reduces the dimensionality of the optimization problem substantially, since only a handful of parameters should be optimized. We laid a simple rectangular grid over the search domain, and some grid points were regarded to be the seeds. Only those grid points were accepted that were in the set S_{in}, and at least in a distance of $1/3$ to its borders. The number of seeds depend on the grid resolution, that was the main parameter of the model to be optimized. We also allowed shifts of the grid along the coordinate axes.

This time the resolution was 30, the number of sample points within an iteration round was 1000. We asked for more precise local search with 16 significant digits, and we allowed 5 local minima hoping for a stable result quality. One of the results obtained after a 7 minutes long computation is:

```
» [X0,F0,NC,NFE] = GLOBAL(FUN, LB, UB, OPTS);

*** TOO MANY CLUSTERS ***
NORMAL TERMINATION AFTER 2781 FUNCTION EVALUATIONS

NUMBER OF LOCAL MINIMA FOUND: 5

   F0 =
-0.8589
-0.8574
-0.8565
-0.8563
```

```
-0.8544

X0 =
0.8907 0.9001 0.8946 0.9023 0.8858
0.4797 0.4481 0.4465 0.4831 0.3634
0.4756 0.4485 0.1172 0.4680 0.4993
0.3965 0.2276 0.2605 0.1792 0.0657
```

The result is quite promising regarding the closely 86% objective function value achieved. It was reached by 47 seeds, which is realistic. The relative measure of the points in S_{in} and S_{out} that fulfilled the conditions were 75.7% and 94.1%, respectively. These figures indicate that there are more reserves for improvement in covering the set S_{in} with radiation, than for decreasing the doses obtained by points in S_{out}.

This time the objective function is of lower dimension, and the BFGS local search procedure can be applied. This results in a 30% drop in the necessary number of function evaluations, which is the main factor of computation time. On the other hand, with this approach the average result quality was around 83%. Since the sparsest covering of the space by spheres in a mesh is that related to the face-centered cubic grid.

Third experiment. In this series of tests we have repeated the previous procedure with the face-centered cubic arrangement in stead of the last cubic setting. With this approach, we were able to produce regularly solutions above the 85% level.

where	occurance numbers									
in	< 20	< 40	< 60	< 80	< 100	< 110	< 120	< 140	< 160	> 160
	0	0	0	50	1159	841	880	1462	1428	6220
out	< 20	< 40	< 60	< 80	< 90	< 100	< 120	< 140	< 160	> 160
	0	1130	4961	5287	1636	757	516	180	118	375

Table 1: The distribution of dose values for an approximate 85.5% solution of the brachytherapy seed positioning problem

Next we investigated the distribution of measured doses at the mesh points for a 85.5% solution. The results are comprised in Table 1. As it can be seen, only 841 measuring grid points have dose values between 100 and 110 units in the set S_{in}, 1159 points between 80 and 100, and just 50 points below the dose value of 80. Due to the much higher dose values achieved in some points of S_{in}, it seems to be possible to rearrange the seeds in such a way, that most of these weakly radiated measuring points become acceptable.

As it concerns the tissue S_{out} to be saved from radiation, we have 757 measuring points with dose values between 90 and 100, and altogether 1189 points above 120 radiation units. This situation is again promising: too close seeds to the set S_{out} should be moved more into the inside of S_{in}. Only $4.5\% \times 30^3 = 1215$ points should be pushed beyond the two limit dose values. We could achieve a closely

0.5% improvement in the objective function value by starting a simple Nelder-Mead simplex local search from the approximate solution discussed in this subsection, at the cost of a few minutes of CPU time. This time the high dimension original problem formulation was used, and all seed positions could move. A natural idea is to restrict the dimensionality of the search, and to change the subsets of seed coordinates in a systematic way.

Effect of resolution. In this study we have fixed the optimization algorithm parameters: 500 sample points per iteration round, 2 best sample points kept, 16 significant digits asked from the local search, and BFGS local search technique. The only difference between the runs were the setting of resolution, it changed between 10 and 60. The results are summarized in Table 2.

resolution	10	20	30	40	50	60
CPU time (s.)	3	15	45	120	300	480
optimum found	88.30%	85.70%	86.00%	84.71%	84.53%	84.17%

Table 2: The effects of increasing the resolution of dose measurements

The main consequence of the test is that although the achieved optimum values in general decreased slightly with increasing resolution, yet the optima do not changed much in realistic higher resolution values. The CPU time needed grows closely in a cubic way. The moral is that resolution values around 40 provide good results at moderate computational complexity.

Further research. As a first step, a refinement optimization will be applied for the solution obtained in the first phase, allowing to divert the seeds form the grid structure. Once we have acceptable solutions for real life application, we turn to more realistic problem formulation, introducing the linear positioning of the seeds with proper space keeping, and having a unique direction for the positioning device. The anisotropy and the form and size of the seeds should be taken into account. Finally a high level programming language implementation should also be prepared.

4. Summary

We have achieved 80% quality solutions for the oversimplified model (10 seeds, point-like radiation source) with minimal computation time. The solution quality became worse with increasing the dimensionality – possibly partly due to the decreasing relative size of the set of feasible solutions. The face-centered cubic grid model ensured a closely acceptable solution quality with up to 86% objective function value. The computation times experienced are still promising (taking into account that the interpreter mode functioning of Matlab results in a much slower execution than a high level language implementation). The resolution of the search space influences the CPU time in a cubic way.

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