Mathematical programming and metaheuristic approaches applied to biological-based fluence map optimization in radiotherapy

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Abstract

Intensity modulated radiation therapy (IMRT) is one of the most effective techniques in cancer treatment. Its main goal is to eradicate all clonogenic cells from the tumour without compromise of surrounding normal tissues. One specific problem in IMRT is fluence map optimization (FMO). The main goal of FMO is to find the optimal set of beamlet intensities given some clinical criteria. Both physical and biological criteria have been developed to tackle the FMO problem. Although most physical models are mathematically tractable and can be solved to optimality they do not include some important clinical considerations as, for example, radio-biological tissue response. On the other hand, biological models although more meaningful usually do not have desirable mathematical features. In this paper we carry out a comparison between metaheuristics and exact methods applied to an unconstrained non-linear biological model based on the well-known generalized equivalent uniform dose. We compare the results in terms of objective function value, time and the obtained dose volume histogram. We apply our algorithms to a non-clinical prostate case.

Key words: radiation therapy, fluence map optimization, generalized equivalent uniform dose, mathematical optimization, metaheuristics

1 Introduction

The main goal in radiation therapy is to eradicate all clonogenic cells from the tumour without compromise of surrounding normal tissues. However, because of the physics of radiation delivery, there is a trade-off between tumour control and normal tissue damage. The most common form of radiation treatment is intensity modulated radiation therapy (IMRT). IMRT allows the radiotherapist to modulate radiation across a beam, which is particularly important for volumes with non-convex shapes

in difficult anatomical situations (Ehrgott et al. 2008). Radiation modulation is possible thanks to a specific physical device called a multi-leaf collimator (MLC) which is able to block the radiation from specific beams. Therefore, IMRT can generate convenient dose distributions to deliver more radiation to the target while sparing surrounding organs at risk (OARs).

IMRT treatment planning is usually divided into three sequential sub-problems: beam angle optimization (BAO), fluence map optimization (FMO) and sequencing of the MLC. In BAO the main goal is to define an optimum number of delivery angles and their orientations (Ehrgott and Johnston 2003). FMO aims to find an optimal set of beamlet intensities given some clinical criteria. Usually hundreds of beamlets are involved in the FMO problem. Finally the sequencing problem aims to find the optimal delivery sequence of the previously defined fluence intensities seeking mainly to reduce the time of patient exposure to radiation.

In this paper we solve the FMO problem. FMO has been tackled from both physical and biological points of view. The former approach, also known as dose-volume approach, links the delivered dose to both tumour and normal tissues with tumour control and complications for the OARs, respectively. Dose-volume models usually maximize the dose delivered to the target and minimize the dose to the OARs subject to both bound constraints and dose-volume constraints (DVC). Most of the physical models are linear, mixed-integer, or quadratic models (Ehrgott et al. 2008). This allows scholars to find clinically acceptable treatment plans using well known exact techniques such as linear and quadratic programming. This approach, although it is very well-known, presents several weaknesses. From a mathematical point of view one can argue that some of its parameters (e.g. weights in quadratic models) have neither clinical nor physical meaning (Ehrgott et al. 2008). Moreover, measures such as mean delivered dose do not take into account the effect of hot/cold spots that can have huge consequences on the tumour control and radiation-related complications after the treatment (Thomas et al. 2005). From a clinical point of view dose-volume models do not consider some important aspects of radio-biological response e.g. cell fraction survival, oxygenation, repopulation, and radio sensitivity.

Biological models, also known as dose-response, relate the delivered dose to the biological response of the irradiated structures. Their main goal is to maximize the tumour control probability (TCP) while minimize the normal tissues complication probability (NTCP) of OARs. Some authors have pointed out the advantages of biological models over physical ones (Thomas et al. 2005; Wu et al. 2002).

In this paper we solve an unconstrained FMO model based on the generalized equivalent uniform dose (gEUD) (Wu et al. 2002). Although the gEUD function is convex (Choi and Deasy 2002) we cannot state the same for our unconstrained model (Olafsson, Jeraj, and Wright 2005). Therefore, we propose the use of metaheuristics as an alternative to exact methods. Concretely, two evolutionary algorithms are implemented, the CHC (Eshelman 1991) and differential evolution (DE) (Storn and Price 1997) algorithms. In addition, the conjugate-based method L-BFGS-B (Zhu et al. 1997) is deployed and compared with the latter algorithms in terms of objective function value, time and the obtained dose-volume histogram (DVH).

This paper is organized as follows. In Section 2 the main concepts related to both IMRT and FMO problems are introduced. In Section 3, we present the biological model used for our study. In Section 4, the optimization methods are explained. Finally, we discuss the results in Section 5 and we highlight some conclusions and

future work in Section 6.

2 Preliminaries

In IMRT region R (target or OAR) is divided in $|R|$ small volumes called *voxels*. The source of radiation is a set of fixed beam angles K which are divided in J beamlets or *bixels*. Information about the effect produced by one unit of intensity from *bixel* j on *voxel* i in region R is defined by the dose deposition matrix A^R. In this paper we assume that A^R is given. Below we present the formula to calculate the dose deposited at each *voxel* i for some vector w of beamlet intensities in Equation 1:

$$D_i^R = \sum_{j=1}^{J} A_{ij}^R w_j \qquad \forall i = 1, 2, ..., |R| \tag{1}$$

where D_i^R is the total dose deposited at *voxel* i in region R by the intensity vector w. Therefore, to solve the FMO problem we need to find a set of beamlet intensities w_j that produce a dose vector D^R that meets given clinical criteria. For a more comprehensive explanation of IMRT concepts see Ehrgott et al. (2008).

Some exact methods have been developed to solve the FMO problem. Linear programming, mixed integer programming, quadratic programming, non-linear programming (NLP) and multi-objective optimization have been proposed before (Ehrgott et al. 2008). Particularly most of the strategies to solve biological FMO models are based on conjugate gradient methods. Those approaches, although fast, do not ensure optimality (Aleman et al. 2010).

Metaheuristics have been mainly used to solve BAO (Bertsimas et al. 2012). There are also many multi-objective metaheuristic proposals which integrate the BAO and FMO problem but considering dosimetric deviation functions as the optimization objectives (Schreibmann et al. 2004). Regarding the use of metaheuristics to solve biological FMO models, only the work of Harmann and Bogner was found (Hartmann and Bogner 2008).

3 A biological FMO model based on gEUD

The biological NLP model used in this paper is based on the concept of gEUD. gEUD can be defined as the biologically equivalent dose that, if delivered uniformly, leads to the same response as the actual non uniform dose distribution (Niemierko 1997). One advantage of gEUD is the penalization of hot/cold spots in OAR/target regions without the need of several parameters as in other biological models.

Different models have been proposed using gEUD concept. Wu et al. (2003) presented a model which combines a dose-response formulation with DVC. Some authors have suggested the superiority of gEUD-based models over dose-volume optimization in terms of OAR sparing with equal or even better target coverage (Thomas et al. 2005; Choi and Deasy 2002). For a complete analysis of these functions see Romeijn, Dempsey, and Li (2004), and Choi and Deasy (2002).

This paper is focused on an unconstrained gEUD-based model proposed originally in Wu et al. (2002). Using this model, solutions that improve the sparing of critical structures while maintaining the target dose can be obtained (Wu et al. 2002; Olafsson, Jeraj, and Wright 2005). Furthermore gEUD based models provide

a large search space making it easier for the optimization system to balance competing requirements in search of a better solution (Choi and Deasy 2002; Wu et al. 2002). The mathematical expression of gEUD is shown in Equation 2:

$$gEUD(w;R,a) = \frac{1}{|R|}(\sum_{i=1}^{|R|} D_i^a)^{\frac{1}{a}} \tag{2}$$

where $|R|$ is the number of voxels of the structure R, a is the structure-dependent parameter and D_i corresponds to the i-th element of intensity vector D^R. For target structures a should be negative, whereas for normal structures a should be greater than 1. As $abs(a)$ increases the function becomes more sensitive to cold/hot spots in targets/OARs, respectively. Therefore, for those normal tissues that allow certain levels of radiation without a functional compromise (also called parallel structures), parameter a should be set close to 1. For serial structures (those that must be irradiated as little as possible) values for parameter a should be set greater than 10 (Thomas et al. 2005; Wu et al. 2002). Then, gEUD can be seen as a link between physical and biological models because it behaves as biological ones do but it depends highly on the intensities and also on the structure dependent parameter, a.

The NLP unconstrained model used in this paper is based on the gEUD concept presented above. Equations 3,4, and 5 show this model:

$$\min_{w \geq 0} f(w) = -\ln L\left(w;\, T,\, a_T,\, v_T,\, eud_0^T\right) - \ln U\left(w;\, N,\, a_N,\, v_N,\, eud_0^N\right) \tag{3}$$

where:

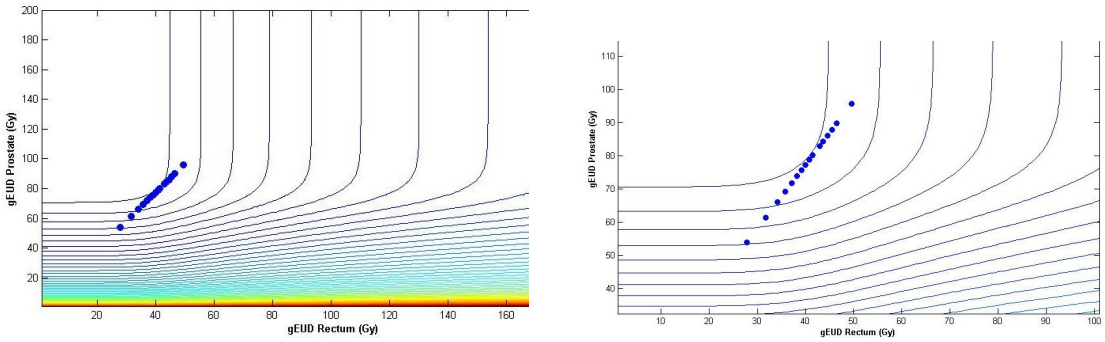
$$L\left(w;\, T,\, a_T, \nu_T,\, eud_0^T\right) = \left(\left(1 + \frac{gEUD\,(w;T,a)}{eud_0^T}\right)^{\nu_T}\right)^{-1} \tag{4}$$

$$U\left(w;\, N,\, a_N, \nu_N,\, eud_0^N\right) = \left(\left(1 + \frac{eud_0^N}{gEUD\,(w;N,a)}\right)^{\nu_N}\right)^{-1} \tag{5}$$

Parameters eud_0^T and eud_0^N correspond to the prescribed EUD values for target and normal tissues respectively. Parameters T and N denote the target and normal tissue, respectively. Then $|T|$ and $|N|$ correspond to the number of voxels of structures T and N, respectively. Finally, $\nu > 0$ is a user-defined parameter that indicates the importance of each structure.

In order to analyze the objective function f we present a contour plot of Equation (3) in Figure 1a. These contour plots are in the EUD space generated by prostate and rectum structures only. Based on contours in Figure 1a we can easily realize that the objective function is convex in EUD space. However, nothing can be said about its convexity in the intensity space (Choi and Deasy 2002). In Figure 1b (a zoom in of Figure 1a) we can see a set of optimal solutions to our problem in terms of EUD. Each point in the graph corresponds to a specific combination of importance factors (weights) for each structure. A distinctive feature of Figure 1b is that all optimal solutions are on the same straight line.

Figure 2 shows the contours for gEUD as a function of just two intensities for both target and rectum (hereafter denoted by $gEUD^T$and $gEUD^{OAR}$). As we can see in Figure 2, the $gEUD^T$ and $gEUD^{OAR}$ functions are concave and convex respectively. Convexity/concavity of the function $gEUD^R$depends on the value of parameter a



(a) Optimal solutions represented in the EUD space.

(b) Optimal solutions on a straight line (zoom in).

Figure 1: Contour plots in EUD space of function $f(w)$.

(Choi and Deasy 2002). When only two beamlets are considered in the optimization procedure, the optimal solutions lie, again, on a straight line.

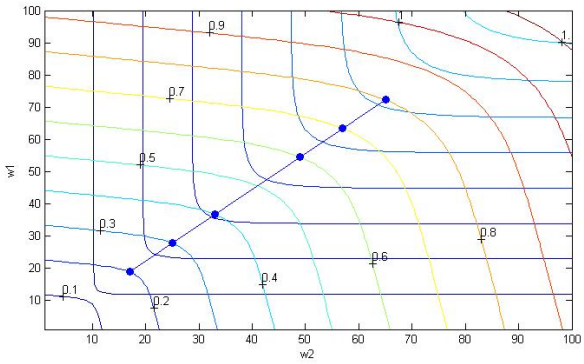


Figure 2: *gEUD* contours plot for target and rectum.

Further research must be done in order to understand the meaning of these features as well as their implications.

4 Optimization strategies

4.1 L-BFGS-B algorithm

L-BFGS-B (Zhu et al. 1997) is a limited-memory quasi Newton optimization algorithm for solving large non-linear unconstrained optimization problems. The L-BFGS-B algorithm allows us to include bounds on decision variables which meets our requirement of $w_j \geq 0$. Basically, L-BFGS-B algorithm builds and iteratively refines a quadratic model of the function being optimized. Using the information from gradients calculated at previous iterations the algorithm calculates positive definite Hessian approximations. This approximate Hessian matrix is then used to make quasi-Newton step. For a more detailed explanation of the algorithm see (Zhu et al. 1997).

The algorithm requires computation of the first derivative of the objective function. Gradient vectors can be calculated as follows (Olafsson, Jeraj, and Wright 2005).

$$\frac{\partial\left(-ln\, L\left(w;\, T,\, a_T,\, v_T,\, eud_0^T\right)\right)}{\partial w_j} = -\frac{v\cdot(1-L)}{|T|\cdot gEUD\,(w;T,a)^a}\sum_{i=1}^{|T|}\left(D_i^{a-1}A_{ij}\right) \qquad (6)$$

$$\frac{\partial\left(-ln\, U\left(w;\, N,\, a_N,\, v_N,\, eud_0^N\right)\right)}{\partial w_j} = \frac{v\cdot(1-U)}{|N|\cdot gEUD\,(w;N,a)^a}\sum_{i=1}^{|N|}\left(D_i^{a-1}A_{ij}\right) \qquad (7)$$

where $gEUD$, L and U were defined in Equations 2, 4 and 5 respectively.

4.2 Metaheuristics

Differential Evolution (DE)

DE (Storn and Price 1997) is a parallel direct search method based on evolutionary algorithms (EAs). DE combines simple arithmetic operators with the classical crossover, mutation, and selection operators within an easy to implement scheme and with few control parameters. The fundamental idea of DE is a scheme for generating trial solutions by adding the weighted difference vector between two population members to a third one. The DE algorithm is summarized in the following steps:

Population initialization: Initialize each solution k of the first generation of the population ($t = 1$), $w_j^k(t)$, according to a uniform probability distribution.

Mutation or differential operation: Then, the algorithm generates a differential vector z_j^k for each $w_j^k(t)$ solution of the population at generation t according to Equation (8):

$$z_j^k = w_j^{r_1}(t) + F\cdot[w_j^{r_2}(t) - w_j^{r_3}(t)], \qquad (8)$$

where k is the solution's population index at generation t; r_1, r_2, r_3 are three randomly generated integers (for the k^{th} solution) with uniform distribution and their values are lower than or equal to the population size, and mutually different. F is the *mutation factor* ($F > 0$) which controls the amplification of the difference between two individuals and which is normally fixed for the run of the algorithm.

Recombination operation: In order to increase the diversity of the new trial solution $w_j^k(t+1)$, a recombination operator is applied by replacing certain intensity values of solution $w_j^k(t)$ by the values of the previously generated differential vector z_j^k. The values to be replaced are randomly selected with a uniform distribution according to the *recombination rate* $CR \in [0, 1]$. The replacement is done as follows:

$\forall j$ *intensity value of* $w_j^k(t)$*:*

If $Rand(j) \leq CR$ *then* $w_j^i(t+1) = z_j^k$

Otherwise, $w_j^k(t+1) = w_j^k(t)$

Selection operation: If the new trial solution $w_j^k(t+1)$ is better than $w_j^k(t)$, then the latter is replaced by the new trial solution.

After preliminary experimentation, the DE variant which uses a binomial discrete recombination (DE/Random/1/bin) showed better performance than the one using an exponential recombination (DE/Random/1/exp). For more details about these DE variants, see Das and Suganthan (2011). Therefore, we will use the DE/Random/1/bin algorithm in the experimentation with parameters CR and F set to 0.9 and 0.5, respectively.

Real-coded CHC

Originally, CHC (Eshelman 1991) was proposed as a binary-coded EA combining a selection strategy with high selective pressure and several components inducing a strong diversity. However, as the FMO problem is a real-valued parameter problem, we have extended the above CHC scheme to deal with real-coded solutions. The main components of the real-coded CHC are:

An elitist selection: The solutions of the population are merged with the new population and the best individuals are selected to compose the new population.

A highly disruptive crossover: The blend crossover (BLX-α) crossover operator guaranteeing that the two trial solutions are always at the maximum binary-converted Hamming distance from their two parents, thus proposing the introduction of a high diversity in the new population and reducing the tendency of premature convergence. For more details about the BLX-α crossover operator see (Eshelman and Schaffer 1993).

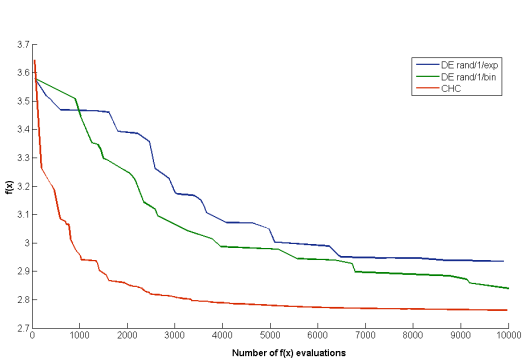
An incest prevention mechanism: Before mating, the Hamming distance between the potential parents is calculated and if half this distance does not exceed a fixed difference threshold, they are not allowed to mate and no trial solution coming from them is included in the population. Therefore, only the most diverse potential parents are mated. However, the required diversity automatically decreases as the population naturally converges.

Besides, CHC is also characterized by a restart mechanism to encourage the achievement of a suitable and fast rate of convergence. For our experimentation we set the population size to 50 individuals and $\alpha = 0.5$ for the BLX-α operator.

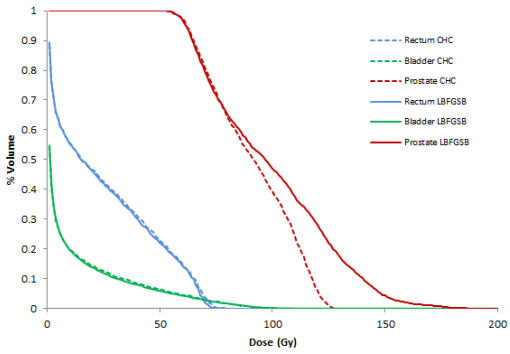
5 Computational experiments

In the section we present and analyse the results obtained by the algorithms when applied to the prostate case. The target corresponds to the prostate plus some margin and OARs are bladder and rectum. Four a priori fixed coplanar beam angles were considered with a total of 116 beamlets whereas the total number of voxels is more than 22,000. Equation (3) is determined by parameters a, ν and eud_0. For the target, a, ν and eud_0 are -8, 12 and 74, respectively. The values for the bladder are 2, 5 and 30; and the values for rectum are 8, 6 and 40, respectively.

In order to enrich the experimentation with a low quality baseline for the approaches presented in the paper, a random search algorithm is implemented. The



(a) Convergence of the DE and CHC algorithms.



(b) DVH plots for the solutions obtained by L-BFGS-B and CHC.

random search algorithm randomly generates solutions to the FMO problem until a stopping criteria is achieved (number of evaluations of the objective function). Each solution w_j^k is generated by randomly setting each intensity with a value within a range $[LB_{w_j}, UB_{w_j}]$. The best solution is always maintained, being the output of the algorithm.

In Table 1 the final objective values reached by the algorithms as well as the EUD values for each organ are shown. Each algorithm was run 10 times to study the stability of its results. Then, we show the mean and standard deviation of the results in all the runs. In addition, the time spent by the algorithms are listed in the last column of the table. The time of the metaheuristic algorithms is fixed by the number of evaluations which is their stopping criterion.

Table 1: Mean and standard deviation of the objective function, EUD values, and elapsed time in the 10 runs of the metaheuristic and mathematical methods.

Method		$f(x)$	EUD(Prostate)	EUD(Bladder)	EUD(Rectum)	Time (s)
Random search	$\overline{x}$	3.697	73.993	22.370	62.887	213.736
	σ	0.105	1.492	2.039	1.887	0.036
DE	$\overline{x}$	2.952	74.068	21.034	55.551	215.834
	σ	0.040	1.285	0.724	1.001	0.043
CHC	$\overline{x}$	2.778	74.258	20.620	54.094	214.025
	σ	0.006	0.229	0.129	0.188	0.055
L-BFGS-B	$\overline{x}$	2.706	74.490	20.488	53.577	53.300
	σ	0.001	0.044	0.034	0.031	3.622

As can be observed, the best results are obtained by the L-BFGS-B method. The value of the objective function after 53 seconds is 2.706. CHC is the best metaheuristic algorithm obtaining better results than DE. Clearly, the random search baseline is easily outperformed by all the methods, showing that this FMO problem cannot be solved by means of a simple random-based algorithm.

The objective function and EUD values achieved by the L-BFGS-B method and the CHC algorithm are very similar. For instance, the difference in the objective function is just 0.072 and the EUD values are also close. However, the L-BFGS-B method is faster than all the metaheuristic algorithms. It only spends 53 s to obtain these results when CHC needs almost four times longer, that is 214 s.

The evolution of the objective function values in the metaheuristic algorithms can be analysed from Figure 3a. The descent of the objective value is plotted through

the function evaluations of the DE and CHC algorithms. The maximum number of evaluations was 10,000. The better performance of the CHC algorithm with respect to the DE algorithm is clear. But what it is more important is the rapid descent of the objective function value in the first 2,000-3,000 evaluations. Although the metaheuristic algorithms are still improving the objective value during the last 8,000 evaluations, these improvements are small, needing more time than the L-BFGS-B method in achieving the same results.

Doses obtained by L-BFGS-B and CHC are presented in a DVH plot in Figure 3b. This tool is widely used in radiotherapy to evaluate the performance of treatment plans. We can see how the irradiated volumes of the organs are very close in the cases of CHC and L-BFGS-B. The most important difference is that the solution provided by CHC presents a more homogeneous irradiation to the prostate than those one provided by L-BFGS-B.

6 Conclusions and future work

In this work we have compared two different strategies to solve the a gEUD based model for the FMO problem. The well known L-BFGS-B algorithm was compared with two metaheuristics, the CHC and DE evolutionary algorithms. The algorithms were compared according to the objective function value, computational time, and the DVH generated by their solutions.

We found that in terms of objective function and the EUD values, the L-BFGS-B method was just slightly better than the metaheuristics. CHC showed better results than DE and although the CHC algorithm is slower than the L-BFGS-B method, it is quite competitive for the problem. Moreover, in terms of DVH we can conclude that the CHC algorithm tends to generate more uniform doses for the target than the L-BFGS-B method.

Despite these promising results, moreE experimentation and optimization analysis must be done. Other metaheuristics exploiting some of the features we drafted in this paper could be a fruitful research area. Furthermore, solving BAO and biological-based FMO models by combining mathematical and metaheuristics could be another very interesting research field.

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