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Treatment planning using tailored and standard cylindrical light diffusers for Photodynamic therapy of the prostate

Augusto Rendon^{1,2}, J. Christopher Beck³, and Lothar Lilge^{1,2}

¹ Department of Medical Biophysics, University of Toronto, 610 University Avenue, Toronto, ON, M5G 2M9, Canada

² Ontario Cancer Institute, University Health Network, 610 University Avenue, Toronto, ON, M5G 2M9, Canada

³ Department of Mechanical and Industrial Engineering, University of Toronto, Toronto, ON, M5S 3G8, Canada, E-mail: llilge@uhnresearch.ca

Abstract

Interstitial Photodynamic therapy (PDT) has seen a rebirth, partially prompted by the development of photosensitizers with longer absorption wavelengths that enable the treatment of larger tissue volumes. Here, we study whether using diffusers with customizable longitudinal emission profiles, rather than conventional ones with flat emission profiles, improves our ability to conform the light dose to the prostate. We present a modified Cimmino linear feasibility algorithm to solve the treatment planning problem, which improves upon previous algorithms by 1) correctly minimizing the cost function that penalizes deviations from the prescribed light dose, and 2) regularizing the inverse problem. Based on this algorithm, treatment plans were obtained under a variety of light delivery scenarios using 5–15 standard or tailored diffusers. The sensitivity of the resulting light dose distributions to uncertainties in the optical properties, and the placement of diffusers was also studied. We find that tailored diffusers only marginally outperform conventional ones in terms of prostate coverage and rectal sparing. Furthermore, it is shown that small perturbations in optical properties can lead to large changes in the light dose distribution, but that those changes can be largely corrected with a simple light dose re-normalization. Finally, we find that prostate coverage is only minimally affected by small changes in diffuser placement. Our results suggest that prostate PDT is not likely to benefit from the use of tailored diffusers. Other locations with more complex geometries might see a better improvement.

1. Introduction

Photodynamic therapy (PDT) has become widely accepted for treating a variety of superficial lesions, resulting in good clinical and cosmetic outcomes. It is successfully used for treating superficial cancers of the skin (Moseley *et al.* 2006), oesophagus (Chen *et al.* 2006), upper respiratory tract (Kato *et al.* 2006, Loewen *et al.* 2006), head and neck (Biel 2006), and other locations where surface illumination is possible. However, the same success has not been achieved when treating deep-seated tumours that require interstitial light delivery, in part, due to the very steep attenuation of light in this illumination geometry. The development of photosensitizers with absorption bands at longer wavelengths, and therefore greater penetration depths, has prompted a rebirth in the field of interstitial PDT. As a result, several groups have

recently initiated clinical trials for interstitial PDT, in particular for prostate cancer (Du *et al.* 2006, Moore *et al.* 2006, Trachtenberg *et al.* 2007).

The most common light delivery strategies for deep-seated tumours use interstitially placed cylindrical light diffusers or cut end fibres, coupled to an external laser. The cylindrical diffusers are manufactured to emit with constant longitudinal emission profiles. Recently, cylindrical diffuser with customizable longitudinal profiles have become available (Vesselov *et al.* 2005). These diffusers should, in principle, enable delivering light dose distributions that match the target volume better than conventional diffusers. It is unclear, however, whether the added flexibility in the emission profile will indeed improve the light dose distribution, particularly, for prostate PDT. Tailored diffusers modulate the light dose perpendicularly to their long axis, but the prostate and organs at risk run parallel to the z -axis. We had previously established that the spatial modulation, and thus the ability to shape the light dose, is lost rapidly as a function of distance from the diffuser (Rendon *et al.* 2006). This suggests that the number of diffusers plays an important role in determining whether tailored diffusers can bring about an improvement in terms of conformality, since using more diffusers reduces the distance between the diffuser and the anatomical features that the light needs to conform to (and thus more spatial modulation remains available). This study will focus on determining whether the light dose can indeed be made to conform better to the prostate using tailored diffusers and examine how the improvement relates to the number of diffusers used.

Optimization-based treatment planning for interstitial PDT is a nascent field. Treatment planning has been traditionally performed manually, although it is clear that automation would be advantageous. Computer-based optimization can improve planning efficiency and potentially find better solutions, yet only a few groups have investigated such strategies. Altschuler *et al.* (2005) developed an optimization strategy that employs cylindrical diffusers, while the algorithm of Johansson *et al.* (2007) assumes cut end fibres. These groups have implemented similar optimization strategies, where a search over diffuser positions is combined with a Cimmino linear feasibility algorithm (Censor *et al.* 1988) to find the output powers (or irradiation times) for the diffusers. Linear feasibility algorithms are attractive to the treatment planner because, besides being computationally fast, the dose prescription can be easily implemented into the optimization framework. As shown here, the Cimmino feasibility algorithm converges to solutions that do not necessarily minimize the cost function chosen to penalize the deviation between the planned and the prescribed light doses. An alternative feasibility algorithm is introduced here to properly minimize the dose function.

Treatment planning requires knowledge of the optical properties of the tissue to ensure adequate dosimetry. Measuring μ_{eff} *in vivo* is not trivial, with uncertainties in μ_{eff} ranging from 10 to 30% (reviewed by Svensson *et al.* (2007)). Significant heterogeneities exist within the same prostate and also between patients. Optical properties further change between treatment planning and delivery, for example because of variations in blood volume fraction and oxygenation (Jankun *et al.* 2005, Zhu *et al.* 2005, Jiang *et al.* 2003, Svensson *et al.* 2007). Diffuser placement is also subject to uncertainty because of template alignment, diffuser insertion, and changes in the shape of the prostate between imaging and delivery. Studying the implications of the uncertainties in the design parameters (optical properties, diffuser placement, tissue response, etc.) is required to clarify whether careful pre-treatment planning is useful, or if instead treatment planning should primarily rely on on-line (i.e. during treatment) dosimetry.

For dosimetry purposes we assume a threshold model for the biological response to PDT (Patterson *et al.* 1990). We further assume that the photosensitizer concentration is homogeneous and that the tissue is sufficiently oxygenated. Therefore, the total fluence (J/cm^2), called here light dose, determines the tissue response. Specifically, tissue necrosis occurs

above a threshold light dose, which implicitly accounts for the photosensitizer concentration. Below this dose, the tissue remains completely viable. Evidence for this model in prostate PDT largely depends on the photosensitizer used. Martin and Hahn (2004) have reviewed pre-clinical studies on dogs and early clinical results. They conclude that most studies do find a well demarcated boundary of necrosis. Some photosensitizers such as ALA (Zaak *et al.* 2003) and Motexium Lutetium (Hsi *et al.* 2001) do not show a clear relationship between depth of necrosis and light dose. Others such as SnET₂ (Selman *et al.* 2001) and WST09 (Chen *et al.* 2002) do support a threshold model.

This study is divided in two parts. Firstly, we establish under what circumstances tailored cylindrical diffusers perform better than conventional ones in PDT of the prostate. To this end, we have implemented an optimization strategy involving a modified Cimmino algorithm that adequately minimizes the cost function of the search process. Secondly, we determine the clinical implications of uncertainties in the delivery parameters, particularly the optical properties and diffuser placement.

2. Methods

2.1. Test case geometry and light dosimetry model

2.1.1. Test case—A 34 cc prostate test case was obtained by tracing T2-weighted transverse MRI slices through a prostate of a patient suited for PDT treatment. The model resolution was downsized to $1 \times 1 \times 3$ mm along the x , y and z -axes respectively. The centre of the urethra was traced and a 5 mm diameter was assumed. Only the anterior surface of the rectum was included in the test geometry (figure 1).

Diffusers are inserted in the prostate, parallel to the z -axis, using a brachytherapy template consisting of a square grid of slots spaced every 5mm. The possible (x,y) positions of the diffusers were confined to the interior of the prostate, represented by the red line on the template shown in figure 1. A total of 48 slots were valid diffuser positions.

2.1.2. Light dosimetry—Light dose (fluence) arising from a cylindrical diffuser is calculated as a convolution of a point source function and the emission profile of the diffuser. The point source function (also called kernel), $G(r)$, is adopted from the standard diffusion theory for the fluence arising from a point source emitting isotropically in an infinite medium (Arnfield *et al.* 1989):

$$G(r) = \frac{\mu_{\text{eff}}^2}{4\pi\mu_a r} \exp(-\mu_{\text{eff}} r), \quad (2.1)$$

where μ_a and μ_{eff} are the absorption and effective attenuation coefficients. This study uses relative light dose units by making $\mu_a = 1 \text{ cm}^{-1}$. Given the range of optical properties observed in the prostate, diffusion theory provides a good estimate of the light dose, provided that the fluence is measured beyond 2 mm from the diffuser.

The emission profile $S(z')$ expresses the emitted power per unit of length for a diffuser. $S(z')$ is constant for diffusers with flat emission profiles and arbitrary for tailored diffusers. By superposition, the light dose arising from diffuser k is expressed as the convolution

$$\Phi_k(\vec{r}) = \int G(x - x_k, y - y_k, z - z') S_k(z') dz', \quad (2.2)$$

where x_k and y_k specify the position of the diffuser. The light dose distribution arising from K diffusers is obtained as $\sum_{k=1}^K \Phi_k(\vec{r})$.

Equation (2.2) is discretized by sampling evenly the space coordinates x , y , and z , as well as the diffuser coordinate z' . After lexicographic indexing of the spatial coordinates by i (M voxels in total), and adding the contributions from all diffusers, (2.2) takes the form

$$\varphi_i = \sum_j^N G_{ij} s_j, \quad (2.3)$$

where s_j includes all K diffuser profiles concatenated into a single vector $\mathbf{s}$ of length N . The size of matrix $\mathbf{G}$ is therefore M -by- N .

The accuracy or the discretization was improved by sampling $S(z')$ at 0.5 mm intervals, and then re-sampling $\mathbf{G}$ at 3 mm intervals. This reduces the dimension of the problem and improves the stability of the solutions. The final discretization was 1 mm along the x and y -axes, and 3 mm along the z and z' -axes.

Observation voxels used during the optimization were defined as all voxels containing the surfaces of the prostate, the rectum and the urethra. Additional voxels were also placed inside the prostate and in the surrounding tissue (background tissue), every 5 mm along x and y , and on every z slice. These voxels were used to improve the homogeneity of the light dose within the prostate and to account for the doses to the surrounding tissues. All voxels available from the imaging were used to calculate dose volume histograms (DVH) (see footnote on page 9 and section 3.1.3). The number of observation points used for each organ is shown in table 1.

2.2. Solution to the inverse problem

The inverse problem of treatment planning corresponds to finding s_j given some specification of the light dose φ_i . The specification used here prescribes a set of upper and lower light doses d_i^U and d_i^L for each observation voxel i . These doses, summarized in table 1, correspond to the thresholds of necrosis for the respective organs based on clinical findings at our institution using WST09. These values were converted from J/cm^2 to arbitrary light dose units by requiring that the prostate threshold dose be 100 units [Sean Davidson, personal communication]. An upper light dose prescription for the prostate was also added to improve homogeneity.

Define the residual at each observation point as

$$r_i(\mathbf{s}) = \begin{cases} 0 & \text{if } d_i^L \leq \mathbf{G}_i \cdot \mathbf{s} \leq d_i^U \\ d_i^L - \mathbf{G}_i \cdot \mathbf{s} & \text{if } \mathbf{G}_i \cdot \mathbf{s} \leq d_i^L \\ d_i^U - \mathbf{G}_i \cdot \mathbf{s} & \text{if } d_i^U \leq \mathbf{G}_i \cdot \mathbf{s}, \end{cases} \quad (2.4)$$

where $\mathbf{G}_i \cdot \mathbf{s}$ is the standard inner product between the i th row of $\mathbf{G}$ and $\mathbf{s}$. The inverse problem is solved by minimizing

$$f(\mathbf{s}) = \sum_{i=1}^M w_i |r_i(\mathbf{s})|^2 \quad (2.5)$$

subject to $s_j > 0$ for $i = 1, 2, \dots, N$.

The constraint ensures that all powers remain positive. The optimal solution is specified by the powers (or emission profiles for tailored diffusers), lengths and positions of the diffusers.

The cost function (2.5) expresses the weighted sum of all square deviations from the prescribed dose range, and it is similar to equation (4) in (Altschuler *et al.* 2005):

$$f_{\text{Altschuler}}(\mathbf{s}) = \sum_{i=1}^M w_i |r_i(\mathbf{s})|.$$

Since $f(\mathbf{s})$ is an upper bound to $f_{\text{Altschuler}}(\mathbf{s})$ for all but $r_i(\mathbf{s}) < 1$, and voxels with such deviations are extremely uncommon (less than 0.5% of all voxels, data not shown), minimizing $f(\mathbf{s})$ invariably also minimizes $f_{\text{Altschuler}}(\mathbf{s})$. This property was verified extensively under multiple conditions for the inner loop algorithm (defined below). For better comparison with the work from Altschuler *et al.* (2005), we have calculated $f_{\text{Altschuler}}(\mathbf{s})$ when reporting the optimal costs in figure 2.

Importance weights are introduced for each organ, where w_i is equal to the weight of the organ it belongs to, divided by the number of observation voxels in that organ. Here, all organs receive equal weights (0.25), and each voxels receives a weight of 0.25 divided by the number of voxels in the organ it belongs to (see table 1).

We have solved two different problems for each type of diffuser (flat and tailored). (I) The free parameters are the template positions and the powers (or emission profiles) for diffusers that extend across the maximum z dimension of the prostate at a given slot. (II) Diffuser lengths and z locations are also free parameters. The four possible problem scenarios are summarized in table 2.

An algorithm with several nested loops was implemented to minimize $f(\mathbf{s})$. The outer collection of loops optimizes the lengths and positions of the diffusers, while the inner loop optimizes the powers or power emission profiles. The listing below summarizes the algorithm.

```
% Outer loops
loop(over 20 starting positions) % INITIALIZATION
do % until convergence is achieved
  loop(over random permutation of diffusers) % SEARCH OVER TEMPLATE SLOTS
  choose diffuser
  loop(over empty slots)
  ;move diffuser to slot
  do % LENGTH AND Z POSITION (only for type II problems)
    loop(over random permutation of diffusers)
    trim/extend diffusers
  % Inner loop returns optimal cost
```

```

cost=feasibility algorithm % modified Cimmino algorithm
while(no convergence at slot)
while(no convergence)

```

2.2.1. Outer loops—These loops consists of: initialization of the diffuser positions, search over the possible positions, and, for type II problems, search over the lengths and z positions of the diffusers. At any iteration of these nested loops the inner loop is called to optimize the powers/emission profiles of all diffusers simultaneously.

Initialization: A multi-start approach was implemented to improve the chances of finding a global minimum. For type I problems, optimization was started from twenty initial, randomly chosen, sets of positions. To speed up type II problems, the 10 sets of positions yielding the lowest costs during the optimization of 1T were used as starting points.

Search over x,y positions (template slots): The algorithm chooses a diffuser randomly while fixing the positions of other diffusers. Then it proceeds to find the minimum cost position for that diffuser over all the available template slots. This is repeated for the other diffusers. The whole process is repeated until the cost converges, with typically 3 to 5 iterations needed.

Search over lengths and z positions: Only type II problems implement this additional search step. For each set of template positions a diffuser is chosen randomly and its length is set to fully extend along the z dimension of the prostate, at the given slot. First, the distal end is reduced by 3 mm at a time until the cost no longer decreases. The proximal end is then trimmed following the same procedure. An extension phase follows the trimming, where the distal and then the proximal ends are extended by 3 mm intervals until the cost ceases to decrease. This four-step loop is repeated for that diffuser until the cost ceases to decrease, and then repeated with the remaining diffusers. The whole process is then repeated until cost convergence is obtained.

2.2.2. Inner loop—The inner loop implements a feasibility algorithm that attempts to find a solution that satisfies all the constraints (i.e. a solution such that $f(\mathbf{s}) = 0$). Since feasible solutions are uncommon because the number of constraints is much larger than the number of design parameters, such a solution cannot be found, and the algorithm reverts to minimizing $f(\mathbf{s})$ in a least-square sense. We employ the following linear feasibility algorithm:

Linear feasibility algorithm: Choose $\lambda = \rho(\mathbf{G}^T \mathbf{W} \mathbf{G})^{-1}$ and start with $\mathbf{s}^0 = \mathbf{0}$. Then iterate:

$$\tilde{\mathbf{s}}^{k+1} = \mathbf{s}^k + \lambda \left(\sum_{i=1}^M w_i r_i(\mathbf{s}^k) \mathbf{G}_i \right) \quad (2.6)$$

$$\mathbf{s}^{k+1} = \begin{cases} \tilde{s}_j^{k+1} & \text{if } \tilde{s}_j^{k+1} \geq 0 \\ 0 & \text{if } \tilde{s}_j^{k+1} < 0 \end{cases} \quad (2.7)$$

until $k > 80$ or $\|f(\mathbf{s}^{k+1}) - f(\mathbf{s}^k)\| < 10^{-3}$.

Here $\rho(\mathbf{A})$ is the spectral norm of matrix $\mathbf{A}$ (square-root of the largest eigenvalue of $\mathbf{A}\mathbf{A}^T$), and $\mathbf{W}$ is the M -by- M matrix with diagonal entries equal to the weights w_i . Equation (2.7) ensures

that powers emitted at all fibre positions remain positive. In contrast to the Cimmino algorithm by Censor *et al.* (1988), our algorithm replaces the per-row normalization term $\sum_j^N |\mathbf{G}_{ij}|^{-2}$ in Cimmino's algorithm, by a λ that normalizes the iteration for all rows.

The stopping criteria has been empirically found to provide a compromise between low costs and smooth solutions. Smooth solutions are desired because they are easier to manufacture and avoid segments with very high emission powers that can lead to tissue heating. Before using feasibility type algorithms, a simulated annealing algorithm was used to find the diffuser powers, but this approach led to very noisy diffuser profiles (Rendon *et al.* 2007). The present algorithm not only corrects this, but also offers a parameter to adjust the degree of smoothness desired, namely the number of iterations. The value of $k = 80$ proved adequate for all optical properties and number of diffusers tested.

Other groups have previously proposed using the Cimmino feasibility algorithm (Censor *et al.* 1988) to optimize the diffuser outputs (Altschuler *et al.* 2005, Johansson *et al.* 2007). However, De Pierro and Iusem (1985) have shown that, for the inconsistent case, the Cimmino algorithm minimizes

$$\sum_i^M w_i \frac{|r_i(\mathbf{s})|^2}{\sum_j^N |\mathbf{G}_{ij}|^2} \quad (2.8)$$

rather than (2.5), making the comparison of different diffuser positions in the outer loops inconsistent. Furthermore, it is arguable that this cost function represents any desirable dose penalty, since the term in the denominator tends to zero for voxels far from any source, and thus weighing such voxels much more than other closer ones. Our algorithm uses a single normalization for all voxels (taking the spectral norm), thereby avoiding these two problems.

2.3. Sensitivity analysis

The sensitivity to changes in optical properties of the light dose distributions for the solutions to all scenarios was analyzed by calculating the fluence rate distribution resulting from changing μ_{eff} by $\Delta\mu_{\text{eff}} = \pm 0.3 \text{ cm}^{-1}$. The value of the uncertainty is chosen at the lower range of experimental uncertainties observed by other investigators (see Introduction section). The resulting light dose distributions for these two extremes were compared with the nominal solution. The sensitivity to diffuser placement was also determined. Optimal diffuser positions were perturbed by adding a noise vector in the x, y -plane uniformly drawn from $(-0.3, 0.3) \times (-0.3, 0.3) \text{ cm}$. 100 such samples were generated.

3. Results

3.1. Diffuser comparisons

To determine whether tailored diffusers performed better than standard ones and under which scenarios, we solved the inverse problem for each scenario, with four different optical properties ($\mu_{\text{eff}} = 1.5, 2.5, 3.0$, and 3.5 cm^{-1}) and 5 to 15 (5 to 21 for 1F) diffusers. These optical properties were chosen to cover the effective attenuation coefficient of prostate at wavelengths used with current photosensitizers in clinical trials (760 nm - WST09 (Weersink *et al.* 2005), 732 nm - Motexium Lutetium (Altschuler *et al.* 2005), 660 nm - mTHPC (Svensson *et al.* 2007): 2.5, 3.0, and 3.5 cm^{-1} respectively). The 1.5 cm^{-1} value was chosen to study the effects of a large penetration depth. First we looked at the differences in the minimum cost achieved.

Subsequently, the resulting light dose distribution were compared by looking at the iso-dose contours and the dose volume histograms (DVH)[‡].

3.1.1. Cost versus number of diffusers—Figure 2 shows the costs obtained for all scenarios as a function of the number of diffusers. Scenario 2T performs better than all others, although 2F and 1T display very similar costs. The costs for scenario 1F are considerably larger in comparison to the other scenarios. Scenario 1F is the closest to standard clinical implementations (e.g. by Weersink *et al.* (2005)). In summary, there is a large gain for using tailored diffusers under type I problems, however, this improvement can also be achieved by relaxing the lengths of the diffusers.

For 1F, notice that the cost plateaus after a number of diffusers that depends on μ_{eff} (around 15 for $\mu_{\text{eff}} = 1.5 \text{ cm}^{-1}$ and 19 for $\mu_{\text{eff}} = 3.5 \text{ cm}^{-1}$). The cost also seems to plateau as the number of diffusers increases for the remaining scenarios, but not as strongly as for scenario 1F.

The stability of the algorithm is also addressed in figure 2. The error bar correspond to the lower 75 percentile of the costs obtained from the multi-start step. Notice that the spread of the cost values is small. Scenarios 1T, 2F, and 2T often have overlapping cost ranges for given number of diffusers and optical properties.

3.1.2. Light dose distributions—As an example, figure 3 shows the light dose distribution arising from the solutions to scenarios 1F and 1T for 7 diffusers (profiles shown in figure 4). For all numbers of diffusers examined, prostate coverage, and sparing of the rectum and urethra appear similar between tailored and flat diffusers. The 62.5 iso-dose line crosses deeper into the rectum for scenario 1F. Under-dosing of the apex ($z \leq 0.6 \text{ cm}$) of the prostate remains problematic for both cases, and increasing the number of diffusers does not appear to resolve this; although, more diffusers result in a more homogeneous prostate coverage. In agreement with the similarities in the cost, light dose maps for type II problems are very similar to those for scenario 1T (data not shown).

In our test case, only the rectum most adjacent to the prostate is over-dosed (z between 1.2 and 1.8 cm). Furthermore, sparing seems to improve with increasing μ_{eff} . This is expected since larger μ_{eff} lead to light penetrating less into surrounding structures.

3.1.3. DVH base comparison—The volumetric distributions of the light dose for the prostate, rectum and urethra are summarized in figure 5 using DVHs. As shown, the main impact of increasing the number of diffusers is to improve prostate coverage without over-dosing more rectum. Also, the volume of over-dosed urethra decreases as more diffusers are used, but overall, the urethra receives larger doses as more diffusers are employed.

In terms of the different scenarios, DVHs for 1T are better than 1F, while further improvement with type II problems is minimal. Scenario 1F performs worse than the other ones in terms of prostate coverage and rectal over-dose, particularly for $\mu_{\text{eff}} = 1.5 \text{ cm}^{-1}$. This is consistent with the early plateauing of the cost for scenario 1F relative to the other scenarios (figure 2). Under scenario 1F, the urethra receives on average lower doses. However, as shown in figure 3, this is at the cost of prostate coverage.

3.1.4. Dose conformality and homogeneity—Coverage of the prostate and over-dosing of critical organs can be combined into a single metric by scaling the diffuser output powers by a single multiplier, such that 95% of the prostate receives 100 dose units (the prostate

[‡]A DVH, more properly called a cumulative dose volume histogram, expresses the percentage of the volume of an organ that has received more than a given dose. It is useful to summarize the volumetric distribution of the light doses.

necrosis threshold). This metric measures how conformal the delivery is, directly reflecting the therapeutic index. Dose scaling, in effect, transfers prostate under-dosing to over-dosing of the organ of interest. In medical physics, this procedure is termed dose re-normalization (Lind *et al.* 1999).

The re-normalized DVHs for the rectum and urethra are shown in figure 6, panels (A) to (C). Although scenario 1T performs marginally better than the other scenarios, improvement is only evident with respect to 1F (compare error bars in panel B). This is contrary to what was anticipated from the cost comparison (figure 2), where solutions to scenario 1T were at most equivalent to those obtained for scenario 2F, and always inferior to those of 2T.

For all scenarios rectal over-dosing decreases by about 30% for every 5 additional diffusers used. For the urethra, in contrast, increasing the number of diffusers only has a positive effect for large values of μ_{eff} . For scenario 1F with $\mu_{\text{eff}} = 1.5 \text{ cm}^{-1}$, there is no improvement in the rectal over-dose as the number of diffusers increases, in agreement with the plateauing of the cost. For this scenario as well, increasing the number of diffusers does not decrease urethral over-dose with $\mu_{\text{eff}} = 3.5 \text{ cm}^{-1}$.

Dose homogeneity is calculated as the fraction of prostate receiving more than 300 dose units after re-normalization (figure 6(D)). It is an important measure which partially accounts for treatment efficacy, as lower fluence rates are encountered by the majority of the organ, thus leading to less de-oxygenation (Henderson *et al.* 2006). A 20–30 % reduction is observed for every 5 extra diffusers employed for a μ_{eff} of 3.5 cm^{-1} . The improvement is less evident for smaller attenuation coefficients. As expected, smaller μ_{eff} offer better dose homogeneity.

3.2. Sensitivity analysis

Next, we investigated the sensitivity of the solutions to uncertainties in the model parameters. To study the effects of changes in the optical properties between treatment planning and delivery, light doses were calculated with μ_{eff} different from the one used in the optimization (with $\Delta\mu_{\text{eff}} = \pm 0.3 \text{ cm}^{-1}$). The effects of diffuser misplacement were modelled by perturbing the diffuser x, y -positions randomly.

3.2.1. Changes in optical properties—The light dose distribution is extremely sensitive to changes in the optical properties. This is shown in figure 7 A, where a change of only 0.3 cm^{-1} (on the lower end of experimental uncertainty *in vivo*) alters the prostate coverage by about 15% with respect to the nominal value. Reducing μ_{eff} results in more over-dosing to the rectum, which is independent of the number of diffusers (figure 7(B)). These results also hold for the other optical properties not shown in figure 7.

Importantly, when dose is re-normalized to ensure adequate prostate coverage, rectal over-dosing is restored closely to the nominal case (figure 7 C). This suggests that the shape of the light dose distribution does not vary much; instead, it is only the absolute values of the fluence rate that changes. Further supporting this observation, the over-dosed volume of background tissue is also restored to within 10 % of the nominal value by re-normalization (data not shown). The same does not hold for the urethra. While re-normalization partially recovers the nominal distribution, the values fluctuate much more than for the rectum (not shown). Since the DVH for the urethra falls very steeply close to the threshold dose (figure 5), small variations of the light dose drastically change the volume over-dosed. On average, 80% of the urethral volume is over-dosed after re-normalization.

3.2.2. Diffuser placement—Figure 8 shows a comparison between the nominal solution and the average of the 25% top and bottom tails of the distribution ($\pm 1 \text{ SD}$) of simulated diffuser misplacements. The results of this simulation are largely insensitive to the type or number of

diffusers. The other optical properties not shown in figure 8 behave similarly to the one depicted, with curves in (B) and (C) slightly shifted down as μ_{eff} increases.

Remarkably, Figure 8 A shows that a large percentage of diffuser shifts do not affect prostate coverage significantly, suggesting that many nearby local minima exist, or alternatively, that the cost function (2.5) is shallow near the optimum.

Rectal over-dose is sensitive to placement errors in a different way. This organ is easily overdosed by placing a diffuser closer than planned. In this sense, rectal overdose differs from prostate coverage in that it does not require the concerted effort of all diffusers. Re-normalizing (figure 8 B) reveals that solutions with better conformality exist (in terms of rectal sparing). Such solutions are possible because the resolution of diffuser placement in this simulation (1 mm) is finer than for the template (5 mm). In contrast, the dose distribution at the urethra is on average deteriorated with respect to the nominal case (not shown).

4. Discussion

The main goal of this study was to determine whether using tailored diffusers can improve light delivery for interstitial PDT, particularly for prostate treatment. This was carried out by comparing the light dose distributions resulting from four different treatment scenarios (table 2). For all scenarios, the diffuser positions (template slots), and the power or emission profile (for tailored diffusers) were optimized. Under scenarios 1F (flat) and 1T (tailored) the length of the diffuser was constraint to the z dimension of the prostate at a given template slot. For scenarios 2F and 2T this length was also optimized.

Under each scenario, the light dose was optimized to best conform to a prescribed set of constraints. The effects of variations of the optical properties or the placement of the diffusers on the light dose distributions were also studied to determine the robustness of these solutions to uncertainties in the parameters of the model.

4.1. Tailored versus standard diffusers

Altschuler *et al.* (2005) compared different light delivery strategies for PDT of the prostate using standard diffusers. The authors optimized treatment plans for strategies ranging from fixed diffuser lengths and placement, to our scenario 2F. They found that optimizing more delivery parameters (i.e., individual diffuser powers, diffuser positions, and lengths) improved the light dose distribution in terms of prostate coverage, and urethral and rectal sparing. We have proposed here that using tailored diffusers makes the light dose conform to the prostate even more, thereby improving the selectivity of the treatment. We have extended the work of Altschuler *et al.* (2005) to compare flat and tailored diffusers under their best light delivery strategies, called here type I and type II problems.

Scenario 1T performs better than scenario 1F for all optical properties investigated, and particularly for small μ_{eff} (figures 5 and 6). This scenario achieves lower costs resulting from improvements in terms of prostate coverage and rectal sparing. This suggests that using tailored diffusers does represent an advantage over standard ones, specially because scenario 1T is already an improvement over what is done in the clinic. However, once the lengths and positions along the z -axis are also optimized (type II problems), the advantage of using tailored diffusers is less clear. Interestingly, scenario 1T seems to marginally outperform both 2F and 2T scenarios after dose re-normalization is performed (figure 6).

Regardless of the diffuser type, the best way to improve the dose distribution is to increase the number of diffusers (figure 2). Using more diffusers results in better prostate coverage without compromising rectal sparing (figure 5). In fact, figure 6 A shows that for every five additional

diffusers, the volume of rectum over-dosed seems to be reduced by 30%, irrespective of the optical properties.

Improvement with more diffusers, however, seems to plateau (figure 2). This is particularly evident for scenario 1F with $\mu_{\text{eff}} = 1.5 \text{ cm}^{-1}$ where no improvement is observed after 7 diffusers. Figure 2 A shows that the plateauing starts later (more diffusers) for larger μ_{eff} , and that, as more diffusers are used, similar costs can be achieved irrespective of μ_{eff} . This behaviour seems to be also present with scenarios 1T, 2F, and 2T, albeit to a lesser extent.

For smaller μ_{eff} (1.5 and 2.5 cm^{-1}), tailored diffusers conform better to the prostate as evidenced by lower over-dosed rectum (figure 6(A)) and background tissue (not shown), after re-normalization. However, this is only true when using between 9 and 13 diffusers. Two opposing principles may explain the improved conformality in this range of diffusers. Increasing the number of tailored diffusers is expected to improve conformality since less spatial modulation is lost as diffusers are placed closer to the prostate surface. In contrast, the improvement achieved by using more diffusers plateaus until no discernable differences are observed between all scenarios. A more complex geometry would be better suited for tailored diffusers to conform to, possibly expanding the range of the number of diffusers for which there is an advantage. Other cancer locations that have critical structures that may occupy a small volume, such as nerve tracts or important blood vessels, may see a greater benefit from employing tailored diffusers; although, this will be difficult to quantify using DVHs, as these tiny volumes become averaged out.

We have assumed here that any diffuser profile can be manufactured. Using current technology (Vesselov *et al.* 2005), this is not the case, with special difficulty in fabricating diffusers with large peak powers towards their distal end. Previously, we have proposed including an additional non-linear constrained optimization step to design such diffusers while ensuring that they can be manufactured (Rendon *et al.* 2007). This strategy can easily be adopted with the present algorithm. Other constraints in the present algorithm can be included to ensure that the peak powers per segment of diffuser do not lead to photothermal effects.

In principle, scenario 1T should also encompass 2T. However, this was not observed, and solutions to 1T are quite different from those of scenario 2T. This is a likely consequence of the regularization of the solutions that imposes some degree of differentiability, forcing the emission profiles to not have zero values.

4.2. Uncertainties in μ_{eff} and diffuser placement

Several groups have measured the optical properties of the prostate, both in animals and humans. Reports coincide to find sizable variations of the optical properties within the prostate and among different subjects (see for example (Muschter 2003), (Martin and Hahn 2004) and references therein). Furthermore, light delivery has been shown to affect the optical properties at some wavelengths (630 nm (Chen *et al.* 1997) and 670 nm (Ballangrud *et al.* 1997)), but not at longer ones (732 nm (Zhu *et al.* 2003) and 763 nm (Chen *et al.* 2002)). These data suggest that oxygen consumption plays a big role in this phenomenon since haemoglobin displays strong absorption in the 600 to 700 nm region. This variability implies that pre-treatment planning may be limited, since most likely, optical properties encountered during light delivery will differ from those used for treatment planning. Because of the observed inherent variability, on-line dosimetry has been proposed by several groups including (Zhu *et al.* 2005) and (Jankun *et al.* 2004).

The sensitivity analysis performed here suggests that, if optical properties are assumed to vary homogeneously, the shape of the light dose distribution remains nearly constant, and only the absolute values of the fluence rate vary. In agreement with this result, we had previously

investigated the robustness of the fluence rate distribution arising from a single tailored diffuser and found it to be largely insensitive to changes in μ_{eff} (Rendon *et al.* 2006). As a result, not only can pre-treatment planning provide an optimal starting condition for light delivery, but also, variations in the optical properties can be dealt with during light delivery, thereby recovering the planned light dose distribution. These findings, however, still need to be corroborated by directly comparing the light dose distributions.

Recently, Johansson *et al.* (2007) have tested their on-line dosimetry system by simulating (based on finite element methods) heterogeneous changes in the optical properties by adding small random changes in the absorption coefficient over and otherwise constant field, and calculating new irradiation times for their treatment fibres using a Cimmino algorithm. In agreement with our results, they find that prostate coverage can be nearly recovered to nominal values.

An additional parameter studied was diffuser misplacement. Prostate coverage was found quite robust in terms of diffuser displacement in the x , y -axis (figure 8 A). On average, prostate coverage for the top 25 percentile of the perturbed solutions is at most 5% less than for the nominal solution. This means that placing diffusers accurately during light delivery is not as critical as expected. Furthermore, it suggests that finding a global optimum is not only very difficult but also not necessary, since many nearby diffuser positions lead to practically the same dose distribution.

Uncertainty in other parameters was not studied. It would be of special interest to understand the effect of changes in prescribed threshold doses. However, interpreting results from such variations is difficult, given the absence of adequate models that relate the tumour control and normal tissue complication probabilities to the light dose. In any case, this is certainly something that has to be addressed in the future as more clinical data becomes available.

4.3. Optimization strategy

Initially, we implemented Cimmino's algorithm but found that, for large μ_{eff} the algorithm was not minimizing the cost, as evidenced by the cost worsening as the number of diffusers increased. The reason is that Cimmino's algorithm minimizes (2.8) rather than the true cost (2.5) (De Piero and Iusem 1985). Based on results by Jiang and Wang (2003) for linear systems of equations (rather than for linear systems of inequalities required for the feasibility problem), we modified the Cimmino algorithm to minimize (2.5) in the infeasible case. While preliminary evidence suggests that our feasibility algorithm does minimize (2.5), to our knowledge this has not been mathematically proven. Therefore, our algorithm performs nearly as fast as the Cimmino one, minimizes the correct cost function, and has desirable regularization properties that are required when the solutions have very large number of parameters.

Overall, we find that our algorithm is slower than the one reported by Altschuler *et al.* (2005). On an Intel Core 2 Duo (2 GHz.) computer with 2 Gb RAM scenarios 1F and 1T take approximately 150 and 180 seconds respectively (for 12 diffusers and with $\mu_{\text{eff}} = 2.5 \text{ cm}^{-1}$). Type II problems require much longer computation times because of the additional search step (between 4 hours and 3 days, for all 10 initial conditions). Our goal, however, was not to find a fast algorithm but one that would likely find a global minimum, or alternatively, that would have a small spread of optimal costs. This was necessary to reliably compare solutions for the different scenarios studied. Judging from the smooth shape of the cost as a function of the number of diffusers (figure 2), this goal was achieved.

5. Conclusions

In conclusion, tailored diffusers with lengths set to the length of the prostate (scenario 1T), performed as well as or better than tailored or standard diffusers which had their length also optimized (scenarios 2F and 2T). However, the improvement offered by tailored diffusers will likely be masked by the effects of the variations of optical properties found in clinical practise. In contrast, we find that small variations in diffuser placement have little effect in the resulting light dose distribution, particularly in terms of prostate coverage.

Our results suggest that prostate PDT does not profit significantly from using tailored diffusers. Other locations with more complicated geometries, such as tumours of the brain or head and neck that require interstitial light delivery, still remain interesting candidates to test whether tailored diffusers can deliver more conformal light doses.

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Figure 1.

Description of the geometry of the test case. The prostate is indicated in red, the rectum in blue and the urethra in green. The template grid is shown on the x, y -plane. The maximum projection of the prostate (and cross sections of the urethra and rectum at the same height) is superimposed on the template. Only rectal surface at positions $y > -1$ cm was considered.

Figure 2. Comparison of the cost obtained from solving the different scenarios. The minimum values + 75 percentile (error bars) of the costs obtained for the solutions to the various starting conditions are shown. (A) shows the cost for scenario 1F (◊) for up to 21 diffusers. (B) shows the remaining scenarios for 5 to 15 diffusers: (○) scenario 1T, (+) scenario 2F, and (×) scenario 2T. The colours correspond to the four different μ_{eff} used. From top to bottom: 3.5, 3.0, 2.5, and 1.5 cm^{-1} .

Figure 3.

Fluence rate map for scenarios 1F (top) and 1T (bottom) for 7 diffusers, with $\mu_{\text{eff}} = 2.5 \text{ cm}^{-1}$. The red line corresponds to the prostate, the green to the urethra, and the blue to the rectum. The black lines are contour levels at 100 (inner curve) and 62.5 (outer curve) dose units. The numbering of the diffusers corresponds to that in figure 4.

Figure 4.

Sample of emission profiles for scenarios 1F (top) and 1T (bottom) with $\mu_{\text{eff}} = 2.5\text{cm}^{-1}$ and 7 diffusers. Each box corresponds to a diffuser of up to 4.8 cm in length. The y-axis scale is the same for both plots and normalized to the maximum power density for 1T. Notice that 1T delivers higher peak powers. The fluence rate maps for these diffusers are shown in figure 3.

Figure 5.

Comparison of the DVHs for prostate, rectum, and urethra for all scenarios: 1F ($\cdots$), 1T ($—$), 2F ($- \cdot -$), and 2T ($- -$). The optical properties and number of diffusers are indicated. The relative positions of the curves for the two values of μ_{eff} are consistent across the rows (number of diffusers). Curves for other values of μ_{eff} in the range 1.5 – 3.5 cm^{-1} fall between these two sets of lines. The vertical lines indicate the target minimum dose for the prostate and the maximum permissible doses for rectum and urethra.

Figure 6.

Measures comparing the conformality and homogeneity of the solutions to scenarios: 1F $\circ(\cdot \cdot \cdot)$, 1T $\circ(\text{---})$, 2F $+(\text{---})$, and 2T $\times(\text{---})$, as a function of the number of diffusers and two different optical properties. Doses have been re-normalized so that 95% of the prostate receives 100 units of dose, and all panels show percent volumes after re-normalization. (A) Rectum receiving more than 62.5 dose units. (B) Same as (A) with $\mu_{\text{eff}} = 2.5 \text{ cm}^{-1}$, and data points corresponding to the mean $\pm 1\text{SD}$ of the solutions obtained from the multi-start step. (C) Urethra receiving more than 100 dose units. (D) Prostate receiving more than 300 dose units. Curves for other values of μ_{eff} in the range 1.5–3.5 cm^{-1} fall between the two sets of lines for each figure.

Figure 7.

Sensitivity of the fluence rate distribution to changes in μ_{eff} of $\Delta\mu_{\text{eff}} = \pm 0.3 \text{ cm}^{-1}$ for all scenarios: 1F ($\cdots$), 1T (—), 2F ($-\cdot-$), and 2T ($--$). Only $\mu_{\text{eff}} = 2.5 \text{ cm}^{-1}$ is shown for 5 to 15 diffusers. The relative percent change with respect to the nominal solution is shown for three measures: (A) percent prostate receiving dose above 100 units; (B) percent rectum receiving dose above 62.5 units; and (C) percent rectum receiving a *re-normalized* dose above 62.5 units.

Figure 8.

Sensitivity of the fluence rate distribution to displacements of the diffusers in the x,y -plane of up to ± 3 mm in both directions, as a function of number of diffusers, for $\mu_{\text{eff}} = 2.5 \text{ cm}^{-1}$. The relative percent change with respect to the nominal solution for the top and bottom 25 percentiles of the distribution (± 1 SD) of each measure are shown: (A) percent prostate receiving dose above 100 units, and (B) percent rectum receiving a *re-normalized* dose above 62.5 units. Solutions to scenarios 1F *, 1T ○, 2F +, and 2T × are shown. Notice the change in the y-axis scale

Table 1

Lower and upper light dose constraints (arbitrary units), and number of observation voxels for each organ. The weights per voxel are also shown.

Organ	d^L	d^U	voxels	$w_i \times 10^{-4}$
prostate	100	1000	786	3.18
rectum	0	62.5	277	9.03
urethra	0	100	65	38.5
background	0	100	1319	1.90

Table 2

Nomenclature of the problems solved in this study.

Problem Type	Scenario	Diffuser	Design Parameters
I	1F	Flat	x,y ; powers
I	1T	Tailored	x,y ; power profiles
II	2F	Flat	x,y,z ; lengths; powers
II	2T	Tailored	x,y,z ; lengths; power profiles