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A heterogeneous optimization algorithm for reacted singlet oxygen for interstitial PDT

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Abstract

Singlet oxygen ($^1\text{O}_2$) is the major cytotoxic agent for type II photodynamic therapy (PDT). The production of $^1\text{O}_2$ involves the complex reactions among light, oxygen molecule, and photosensitizer. From universal macroscopic kinetic equations which describe the photochemical processes of PDT, the reacted $^1\text{O}_2$ concentration, $[^1\text{O}_2]_{\text{rx}}$, with cell target can be expressed in a form related to time integration of the product of $^1\text{O}_2$ quantum yield and the PDT dose rate. The object of this study is to develop optimization procedures that account for the optical heterogeneity of the patient prostate, the tissue photosensitizer concentrations, and tissue oxygenation, thereby enable delivery of uniform reacted singlet oxygen to the gland. We use the heterogeneous optical properties measured for a patient prostate to calculate a light fluence kernel. Several methods are used to optimize the positions and intensities of CDFs. The Cimmino feasibility algorithm, which is fast, linear, and always converges reliably, is applied as a search tool to optimize the weights of the light sources at each step of the iterative selection. Maximum and minimum dose limits chosen for sample points in the prostate constrain the solution for the intensities of the linear light sources. The study shows that optimization of individual light source positions and intensities is feasible for the heterogeneous prostate during PDT. To study how different photosensitizer distributions as well as tissue oxygenation in the prostate affect optimization, comparisons of light fluence rate were made with measured distribution of photosensitizer in prostate under different tissue oxygenation conditions.

Keywords

Singlet oxygen; optimization; Prostate PDT

I. INTRODUCTION

The prostate gland is an organ that is a good target for interstitial PDT. Tumors of the prostate are often confined to the prostate itself and brachytherapy techniques used for the placement of radioactive seed implants can be adapted for the placement of interstitial optical fibers.¹ Several studies have evaluated the feasibility of delivering PDT to the

prostate via this interstitial approach.^{1,2} We have initiated a motexafin lutetium (MLu)-mediated PDT of the prostate in human at University of Pennsylvania.³⁻⁵ Ideal optimization of the photodynamic linear light sources depends on knowledge of the spatial distributions of (1) tissue light opacity within the prostate, (2) photosensitizing drug concentration, and (3) tissue oxygenation. We have developed a method to determine the heterogeneous distribution of optical properties using a point source.⁶ For MLu-mediated PDT, the photosensitizer drug concentration can be determined by either interstitial fluorescence spectroscopy⁷ or absorption spectroscopy^{1,6}. The tissue oxygenation during PDT cannot be easily measured but a macroscopic model has been established to model the tissue oxygenation.⁸ Since the spatial distributions can vary in time, measurements must be done just prior to the clinical procedure. Moreover, the optical properties distribution may be affected by bleeding associated with insertion of the light sources and ideally should be monitored at a significant number of points during the entire procedure.

Accurate dosimetry calculation in photodynamic therapy (PDT) is imperative in quantifying PDT treatment efficacy. The efficacy of PDT depends on the concentration of singlet oxygen, which in turn is determined by light fluence, photosensitizer concentration, and tissue oxygen level.⁹ Direct measurement of singlet oxygen concentration is very difficult *in vivo* with large variability. As a result, to establish the correlation between the macroscopic treatment efficacy of PDT and the microscopic singlet oxygen concentration, one would need to rely on dosimetry calculation based on the *in vivo* measurements of light fluence, photosensitizer concentration, and tissue oxygen level. Accurate *in vivo* PDT dosimetry is imperative in understanding the mechanism of singlet oxygen's toxic effect and how this toxicity translates to tissue necrosis observed with PDT. Ultimately the goal of PDT dosimetry is to enable better PDT treatment planning based on optimized singlet oxygen distribution at the site of the tumor and as a result improve overall PDT treatment efficacy.

A number of optimization algorithms used in brachytherapy are of interest for prostate photodynamic therapy. In general, gradient algorithms give reproducible solutions but may be trapped in local minima far from the global minimum.¹⁰ Simulated annealing and genetic algorithms avoid getting trapped in local minima, but are relatively slow because they are stochastic algorithms.¹¹ We use a systematic search procedure based on the Cimmino feasibility algorithm¹² to obtain the locations and strengths of light sources for photodynamic treatment. The Cimmino algorithm is an iterative linear algorithm which was first applied to radiotherapy inverse problems by Censor *et al.*¹³⁻¹⁵ The algorithm is safer than most common optimization algorithms outlined above since it always converges and, if no solution exists for the inequalities (i.e. the prescribed PDT dose constraints are not all satisfied), the Cimmino algorithm reverts to a least-square solution¹⁵

Previous studies concentrate on the optimization of light fluence only under homogeneous¹⁶ or heterogeneous¹⁷ optical properties as well as optimization of PDT dose¹⁸ as a product of photosensitizer drug concentration and the light fluence for heterogeneous prostate optical properties. For the present study we concentrate on optimization of reacted singlet oxygen based on a macroscopic model for heterogeneous prostate optical properties.

II. METHODS AND MATERIALS

1. Heterogeneous kernel model and heterogeneous optical properties

The propagation of near-infrared light in tissues can typically be approximated by the diffusion equation¹⁹,

$$-\nabla \cdot D \nabla \phi + \mu_a \phi = S_o \quad (1)$$

where ϕ is the light fluence rate, $D=1/3 \mu_s'$ is the diffusion coefficient, S_o is the isotropic source distribution and μ_s' is the reduced scattering coefficient. In a heterogeneous medium, the light fluence rate can be calculated as

$$\phi_i = \frac{C \mu_{s,i}'}{4\pi r} \left(p_i e^{-\mu_{eff,i}(r-r_{i-1})} + q_i e^{\mu_{eff,i}(r-r_{i-1})} \right), \quad r_{i-1} < r < r_i, \quad i=1, 2, \dots, N. \quad (2)$$

where C as in the case of Eq. (2) is a constant proportional to the source power S . The expression for C , p_i , and q_i can be found elsewhere.²⁰

Measurements at multiple sites allow evaluating the variation of these optical characteristics within the prostate volume. This is done for a clinical case and the distribution of optical properties and details about how to obtain the optical properties distribution are described elsewhere.^{18,21}

2. Macroscopic modeling of singlet oxygen

A set of macroscopic rate equations can be used to describe the production of reacted singlet oxygen,⁸ i.e.,

$$\frac{d[S_0]}{dt} + \left(\xi \sigma \frac{\phi([S_0] + \delta)[^3O_2]}{[^3O_2] + \beta} \right) [S_0] = 0, \quad (3)$$

$$\frac{d[^3O_2]}{dt} + \left(\xi \frac{\phi[S_0]}{[^3O_2] + \beta} - g \left(1 - \frac{[^3O_2]}{[^3O_2](t=0)} \right) \right) [^3O_2] = 0, \quad (4)$$

$$\frac{d[^1O_2]_{rx}}{dt} - \left(\xi \frac{\phi[S_0][^3O_2]}{[^3O_2] + \beta} \right) [^1O_2] = 0. \quad (5)$$

where ϕ is light fluence rate, $[S_0]$ is the ground state sensitizer concentration, $[^3O_2]$ and $[^1O_2]$ are the ground triplet and excited singlet state oxygen concentration, respectively, and g and $[^3O_2](t=0)$ are the oxygen perfusion coefficient and the concentration of $^3O_2$ at time zero. δ is a low photosensitizer concentration correction term²²⁻²⁴. The parameters for photofrin has been determined from in-vivo mice studies and are listed in Table 1.²⁵ This set of equations can be solved for fixed light fluence rate ϕ and photosensitizer concentration, $[S_0]$ using the parameters in Table 1. The reacted singlet oxygen is a function of ϕ , $[S_0]$, and t , or $F(\phi, S_0, t)$ as shown in Figs. 1 and 2.

Figure 2 shows that, in general, the lower the light fluence rate the more efficient the production of reacted singlet oxygen for the same total light fluence. From Eqs. (3)–(5), one can derive the relationship between reacted singlet oxygen and PDT dose rate, D_{PDT}/t :

$$[^1O_2]_{rx} = \xi \int_0^t \left(\frac{[^3O_2]}{[^3O_2] + \beta} \frac{\partial D_{PDT}}{\partial t} dt \right) \quad (6)$$

Under ample oxygen supply, the reacted singlet oxygen concentration is proportional to the PDT dose.

3. Search procedure using the Cimmino optimization algorithm

The algorithms discussed below try to achieve prescribed minimum reacted singlet oxygen concentration distribution. The optimization procedure is performed in two steps: 1. optimization of PDT dose using a Cimminio algorithm. 2. Iterative procedure to optimize the distribution of reacted singlet oxygen by further optimization of the light fluence rate.

The first step use the same procedure as developed previously:¹⁸ (1) a prescribed minimum PDT dose within the prostate, and (2) PDT doses not exceeding the maximum PDT doses specified separately for the prostate, urethra, rectum, and background tissues. The contours of the prostate, urethra, and rectum in each transverse slice (parallel to the template plane and perpendicular to the linear light sources) are assumed available in computer memory. The discretized simple inverse problem can be written as

$$b_i^{min} \leq \sum_j A_{ij} x_j \leq b_i^{max} \quad (i=1, \dots, I; j=1, \dots, J) \quad (7)$$

or in matrix form as

$$\mathbf{b}^{min} \leq \mathbf{A}\mathbf{x} \leq \mathbf{b}^{max} \quad (8)$$

where I is the number of voxels (or constraint points); $\mathbf{b}^{max}$ and $\mathbf{b}^{min}$ are the PDT dose bounds on the voxels; J is the number of light sources; a component of matrix $\mathbf{A}$ denoted A_{ij} gives the PDT dose absorbed at voxel i per unit strength of light source j . A positive lower bound prescribes a minimum PDT dose for a prostate (target) voxel; it is zero for non-prostate voxels. An upper bound on PDT dose is provided for every voxel. The goal is to find the vector $\mathbf{x}$ of source strengths that satisfies the inequality constraints of the expression (8). The matrix $\mathbf{A}$ is a pre-calculated 2-D PDT dose (or kernel) table, that equals the product of the light fluence table for sources of all allowed lengths and the known drug concentration. In this study, for simplicity, the matrix is calculated for sources of fixed lengths, which are geometrically pruned based on the prostate geometry.

The second step of optimization will use the PDT dose optimization result from Cimmino algorithm and convert the resulting light fluence $\phi(x,y,z)$ and photosensitizer concentration $c(x,y,z)$ and convert to reacted singlet oxygen for a specific time t using the function $F(\phi,c,t)$ as discussed in section II.2.

To check the effect of optimizations, the clinical optical properties were chosen. Three different PS drug concentrations are considered: (i) uniform ($c = 1$); (ii) linear (Fig. 3); (iii) clinical PS drug distribution (Fig. 4). Notice that all drug concentration are normalized distribution such that $c = 1$ corresponding to the average PS distribution. It is noteworthy to point out the similarity between the absorption coefficient map at 732 nm and the photosensitizer drug distribution (Fig. 4). Previous studies have shown that the drug concentration (in mg per kg body mass) is proportional to the absorption coefficient.^{7,26}

III. RESULTS AND DISCUSSIONS

Figure 5 compares computer runs of optimized 100% isodose distributions for PDT dose to the 3D prostate volume using light source weight based on Cimmino algorithm assuming the actual optical properties distribution and the heterogeneous kernel (Eq. 2) and three different distribution of photosensitizer concentration. The most optimal PDT dose distribution does not provide information about the dose rate effect. However, it is not necessary to know the absolute photosensitizer concentration (only the relative distribution) in order to obtain the optimal PDT dose distribution.

Figures 6 and 7 shows that one can optimize the light fluence rate further, based on initial PDT dose optimization plan and assigning the absolute light fluence rate (100 mW/cm^2 and 20 mW/cm^2 , respectively, for Figs. 6 and 7). The corresponding singlet oxygen concentration coverage for lower light fluence rate is better than that for higher light fluence rate, even if the total light fluence rate (or PDT dose) is the same.

IV. CONCLUSION

The question addressed is whether any significant advantage may derive from methods that weight each CDF source separately and/or choose the geometry of the light sources as well. In summary, our comparison shows that: (1) it is important to measure the optical properties of a patient because it determines the light fluence distribution. This effect is more predominant than inclusion of photosensitizer drug concentration. (2) Optimization of individual light source strength using the Cimmino algorithm is feasible for optimizing reacted singlet oxygen concentration for heterogeneous prostate PDT, provided light fluence rate is correctly accounted for. (3) The heterogeneous Cimmino optimization with the drug concentration may significantly alter the light fluence rate distribution to obtain the most optimal singlet oxygen concentration distribution. The Cimmino optimization is fast enough for this problem to obtain clinical real-time optimization (less than 300 s).

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Figure 1. Reacted singlet oxygen vs. light fluence rate at time of (a) 1000 sec and (b) 4000 sec for photosensitizer concentrations (PS) from bottom to top: 0.1, 0.2, 0.3, ... 1.9, 2.0, 3.0, ... 20.0 μM .

Figure 2.
Reacted singlet oxygen vs. (a) time and (b) fluence different fluence rate for PS concentration of 7 μ M.

Figure 3.

Normalized linear photosensitizer (PS) drug distribution used for the solid lines for PDT dose distribution as shown in Figs. 5 and 6. The drug concentration changes by 3 times from $c = 1$ for $x = 0$ to $c = 3$ for $x = 2.5$ cm.

Figure 4.

Normalized clinical photosensitizer (PS) drug distribution used for the solid lines for PDT dose distribution as shown in Figs. 5 and 6.

Figure 5.

Optimized PDT dose using 12 sources for a prostate PDT treatment assuming uniform, linear, and clinic distribution of the photosensitizer.

Figure 6.

Optimized reacted singlet oxygen concentration using 12 sources for a prostate PDT treatment assuming uniform, linear, and clinic distribution of the photosensitizer at time $t = 1000$ s for light fluence rate of 100 mW/cm^2 to cover the entire prostate gland.

Figure 7.

Optimized reacted singlet oxygen concentration using 12 sources for a prostate PDT treatment assuming uniform, linear, and clinic distribution of the photosensitizer at time $t = 4000$ s for light fluence rate of 20 mW/cm^2 to cover the entire prostate gland.

Table 1

modeling parameters for photofrin obtained from in-vivo studies²⁵

Parameters:	ξ	σ	β	g
Values:	$2.1 \times 10^{-3} \text{cm}^2/\text{mWs}$	$7.6 \times 10^{-5} \mu\text{M}^{-1}$	$11.0 \mu\text{M}$	$0.69 \mu\text{M/s}$