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Tumor reactive singlet oxygen approach for Monte Carlo modeling of photodynamic therapy dosimetry

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ABSTRACT

Photodynamic therapy (PDT) is an emergent technique used for the treatment of several diseases. It requires the interaction of three components: a photosensitizer, a light source and tissue oxygen. Knowledge of the biophysical aspects of PDT is important for improving dosimetry protocols and treatment planning. In this paper we propose a model to simulate the spatial and temporal distribution of ground state oxygen ($^3O_2$), cumulative singlet excited state oxygen $(^1O_2)_{rx}$ and photosensitizer, in this case protoporphyrin IX (PpIX) in an ALA mediated PDT treatment. The results are analyzed in order to improve the treatment dosimetry. We compute the light fluence in the tissue using Monte Carlo simulations running in a GPU system. The concentration of $^3O_2$, $(^1O_2)_{rx}$ and the photosensitizer are calculated using this light fluence and a set of differential equations describing the photochemical reactions involved in PDT. In the model the initial photosensitizer concentration depends on tissue depth and type, moreover we consider blood vessel damage and its effect in the ground state oxygen concentration in the tissue. We introduce the tumor reactive single oxygen (*TRSO*) as a new dosimetry metric. It represents the amount of singlet oxygen per tumor volume that reacts, during the treatment, with the molecules in the tumor. This quantity integrates the effect of the light irradiance, the optical properties of the tumor and the normal tissue, the oxygen consumption and supply, and the photosensitizer biodistribution on the skin.

1. Introduction

Photodynamic therapy (PDT), is a common therapeutic procedure for the treatment of many diseases. Among them, basal cell carcinoma, retinal diseases, gastric tumors, Bowen's disease and non-malignant skin conditions like actinic keratosis [1,2,3,4]. Its main advantages reside in being minimally invasive and having almost no systemic toxicity. The technique requires three components: a photosensitive compound (photosensitizer), a light source and ground state oxygen. Its therapeutic effect is connected with the cytotoxic role of the excited singlet state oxygen in the cells.

Most PDT treatments are based on empirically administered photosensitizers and light doses. However, the large variation in the photosensitizer distribution, its complex pharmacokinetics, the heterogeneity on the optical properties of the tissue and the tissue's oxygenation are usually neglected. Therefore, it is often difficult, if not impossible, to adjust the single session and/or the whole course of the treatment, for a better outcome. It is not a surprise that the search for basic principles and simple models that may help to better understand, optimize and particularize the treatment to the specific requirements of each patient is a very active field of research [5].

Of particular importance is the concept of PDT dose used in the clinical practice, defined as the number of photons absorbed by the photosensitizer per gram of tissue. This quantity is usually calculated based on the photosensitizer extinction coefficient, the initial drug concentration, the light irradiation fluence rate and the treatment time [6]. However, the acceptance of PDT for the clinical routine would be greatly facilitated by a dosimetry metric that incorporates the interactions among the irradiation light fluence rate, the oxygenation of the tissue, and the photosensitizer distribution. The goal is to establish a dosimetry measure to optimize the PDT treatment based on the specificity of the disease and the patient characteristics. Three general strategies are under investigation, all of them based on the cumulative dose of singlet oxygen generated during the PDT that is used as an estimator of the tissue damage. *Direct dosimetry* relies on the detection of singlet oxygen itself through its emission at 1270 nm [7]. *Implicit dosimetry* uses an indirect quantity such as the fluorescence of the photosensitizer, as an indicator of the cumulative singlet oxygen [8]. Finally, *explicit dosimetry* refers to the measurement of quantities such as light distribution, photosensitizer and oxygen concentration, to calculate the PDT dose [9,10].

Following this last strategy we propose in this work a mathematical model of PDT that may orient the search of a dosimetry metric. In

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particular we propose the minimal fluence needed to destroy a tumor as a possible alternative in this direction. This quantity is calculated based on the Tumor Reaction Single Oxygen, *TRSO*, which represent the amount of singlet oxygen per tumor volume that reacts, during the treatment, with the molecules in the tumor. This quantity integrates, as in previous reports in the literature [11,12,13,14], the oxygen consumption and supply, the non-uniform initial photosensitizer distribution and the destruction of blood vessel by the PDT treatment. Moreover, we differentiate tumor and cancer tissues in terms of their different uptake of the photosensitizer and optical properties. We also calculate these quantities for several tumor depths and analyze their behavior and the consequences for PDT treatment.

The rest of the work is organized as follows. In Section 2 we describe the model and introduce the mathematical techniques used to study the PDT: first the calculation of the fluence in the tissue and then the pharmacokinetic equations that describe the dynamics of the chemical species involved. In this section we also introduce the concept of Tumor Reactive Singlet Oxygen *TRSO*, as a proper metric for the dosimetry of PDT. Then we present the results of our simulations in Section 3 and their implications are analyzed in Section 4. Finally the conclusions are brought in.

2. Methods

When the photosensitizer is excited by light of a specific wavelength it returns to the ground state releasing energy. This energy is transferred to the ground state oxygen in the tissue, $^3O_2$, to produce singlet oxygen, $^1O_2$, considered to be the major cytotoxic agent responsible for cell death [15]. Fig. 1 shows a diagram of these photochemical processes.

During the course of time, the photosensitizer is consumed, either in its ground state by the reaction with the singlet oxygen, or in the excited triplet state by the reaction with the substrate molecules on the tissue. This process is called photobleaching and can be monitored using fluorescence studies. On the other hand, the oxygen is consumed via the reactions with the photosensitizer, but also through metabolic pathways. Moreover, it may enter into the system through the blood vessels. The whole dynamics of the system is therefore complex and hard to describe, especially if the heterogeneity of the tissue is taken into account. It is well understood however, that to model the PDT two processes should be accounted for, first the interaction of light with the tissue and second the chemical dynamics of the molecular species involved in the reactions. We describe below in details how we addressed both problems.

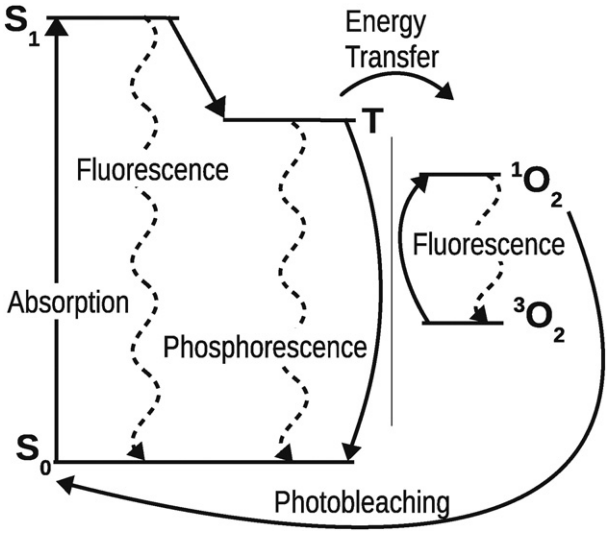

Fig. 1. Simplified Jablonski diagram showing the main photochemical reactions that take place during PDT. A light photon of a specific wavelength is absorbed by a photosensitizer molecule, exciting the molecule from its ground singlet state,S_0, into a higher excited singlet state, S_1. After that, the molecule can relax going back to the ground state by emitting fluorescent photons. Alternatively through inter system crossing (ISC) the molecule may cross into a excited triplet state, T_1. The lifetime of the molecule in the excited triplet state is longer than that achieved in the excited singlet state and thus the molecule is more likely to react with its surroundings. Energy is transferred from the excited triplet state photosensitizer, T_1 to molecular oxygen, $^3O_2$, thus generating highly reactive singlet oxygen, $^1O_2$. It is believed that $^1O_2$ is the main cytotoxic agent involved in PDT.

2.1. Local Tissue Fluence Calculation

The propagation of light in heterogeneous materials is determined by the radiation transport equation (RTE) [16]. But, for almost all cases of practical interest an analytic solution of the RTE is not possible and the use of approximate methods is mandatory. The simplest and most widely used approach is to replace the RTE with a diffusion equation for the fluence rate [17]. This approximation requires that the point of interest is far from the source of light and the boundaries of the system and assumes that the radiance is isotropic. Unfortunately these assumptions are often unrealistic for PDT protocols because biological tissues scatter light not isotropically, mainly in the forward direction.

A general approach to solve the RTE with all its complexities is the Monte Carlo method (MC) [5]. An accurate description of the technique can be found in the literature [18,19,20]. In this model a photon packet with a given weight, proportional to its energy, is launched into the tissue. At each time step, the packet moves in a direction and with a step size defined by specific probability functions. At every interaction point, the weight of the packet is reduced according to the absorption probability of the material in which it is moving. When hitting a layer boundary, the photon packet is either transmitted through or reflected following the Snell's law and the Fresnel's equations. The process repeats until the photon packet leaves the tissue or its weight fall bellow a given threshold value. In the former case a Russian roulette gives the photon packet one chance out of ten of surviving with their weight multiplied by 10 in order to ensure energy conservation. When a sufficient number of packets are launched, the cumulative distribution of all photon paths should provide an accurate approximation to the true solution of the light transport problem.

The main limitation of the method is the requirement of extensive computations. Fortunately, in the last few years several techniques have been developed to speed up and simplify the simulations. In the delta-scattering technique, the maximum total attenuation coefficient from the layers involved in the simulation is used to sample the step size everywhere. Furthermore, a null event, to evaluate the probability of the occurrence of an actual interaction event, had to be sampled at each interaction location in order to correct the underestimation of the step size introduced. Using this technique the photon packet was traced without directly dealing with photon crossing the interfaces between different types of tissues [18,21]. Liu et al. [12] and Salas-García et al. [22] used this delta-scattering method to model light propagation in tissue for PDT treatment.

Moreover, the implementation of Monte Carlo algorithms using Graphic Processing Units, GPU, have shown that simulations may be up to 600 times faster than on a single standard Central Processing Unit, CPU [23] providing an effective framework to study complex systems. In this work we made extensive use of these GPU based algorithms. We used two NVIDIA M2075 Graphic Computing Modules each with 448 cores and 6 GB of global memory.

Fifty runs were made to calculate the light fluence distribution of tumors with depth ranging from 0.0005 cm to 0.25 cm for a total execution time of 5275 s representing 105 s per run. We launched 10^9 photon packets for each simulations. The initial coordinates of the photon packet were calculated using a random number generator, to mimic a planar light source with an irradiance of 150 mW/cm^2. The simulated region was a cylinder of 0.4 cm depth and 0.2 cm radius and the tumor was represented using a semi-infinite three layer model inside