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Macroscopic Modeling of the singlet oxygen production during PDT

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Abstract

Photodynamic therapy (PDT) dose, D , is defined as the absorbed dose by the photosensitizer during photodynamic therapy. It is proportional to the product of photosensitizer concentration and the light fluence. This quantity can be directly characterized during PDT and is considered to be predictive of photodynamic efficacy under ample oxygen supply. For type-II photodynamic interaction, the cell killing is caused by the reaction of cellular acceptors with singlet oxygen. The production of singlet oxygen can be expressed as ηD , where η is the singlet oxygen quantum yield and is a constant under ample oxygen supply. For most PDT, it is desirable to also take into account the effect of tissue oxygenation. We have modeled the coupled kinetics equation of the concentrations of the singlet oxygen, the photosensitizers in ground and triplet states, the oxygen, and tissue acceptors along with the diffusion equation governing the light transport in turbid medium. We have shown that it is possible to express η as a function of local oxygen concentration during PDT and this expression is a good approximation to predict the production of singlet oxygen during PDT. Theoretical estimation of the correlation between the tissue oxygen concentration and hemoglobin concentration, oxygen saturation, and blood flow is presented.

Keywords

photodynamic therapy; singlet oxygen production; oxygen dependence of singlet oxygen quantum yield

1. Introduction

Photodynamic therapy (PDT) is a cancer treatment modality based on the interaction of light, a photosensitizing drug, and oxygen.¹ PDT has been approved by the US Food and Drug Administration for the treatment of microinvasive lung cancer, obstructing lung cancer, and obstructing esophageal cancer and Barrett's esophagus with high grade dysplasia, as well as for age-related macular degeneration and actinic keratosis.²

To quantify the photodynamic efficacy, the current state of art in clinical PDT dosimetry uses a quantity called PDT dose,³ defined as the number of photons absorbed by photosensitizing drug per gram of tissue [ph/g], i.e.,

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$$D = \int_0^t \varepsilon c \cdot \frac{\varphi(t')}{h\nu} \cdot \frac{1}{\rho} dt', \quad 1$$

where ρ is the density of tissue [g/cm^3], ϕ is the light fluence rate [W/cm^2], $h\nu$ is the energy of a photon [J/ph], c is the drug concentration in tissue [μM], ε is the extinction coefficient of the photosensitizer [$1/\text{cm}/\mu\text{M}$]. The photodynamic dose (D) does not consider the quantum yield (η) of oxidative radicals, the effect of tissue oxygenation on η , or the fraction (f) of radicals that oxidize cellular targets. Thus, it is only applicable in cases where ample oxygen supplies exist. For type-II photodynamic interaction, production of singlet oxygen is responsible for the PDT damage. The production of singlet oxygen that has damaged the cellular targets can be expressed as:⁴

$$[^1\text{O}_2]_{\text{rx}} = f \cdot \eta \cdot \rho D, \quad 2$$

where f depends on the localization of the photosensitizer at the cell level and thus depends on the photosensitizer and tissue types, the quantum yield η gives the number of singlet oxygen molecules produced per an absorbed photon, which is a constant under ample oxygen supply. However, when insufficient oxygen supply exists, η is also a function of the oxygen concentration, or pO_2 , in tissue. (We explain later why the PDT dose multiplied the tissue mass density, or ρD [ph/cm^3] is used in Eq. (2)).

The purpose of this study is to establish the relationship between the singlet oxygen concentration and the PDT dose under arbitrary oxygen supply conditions. This is achieved by solving the coupled kinetics equations describing the macroscopic process of the generation of singlet oxygen and the diffusion equations describing the light transport assuming the 3-dimensional distribution of photosensitizers can be independently characterized during PDT. Since the oxygen concentration in tissue is a local quantity that cannot be easily measured. We have also presented a model that can be used to determine the local oxygen concentration by measuring the macroscopic quantities related to oxygen supplies in the blood vessel, i.e., hemoglobin concentration, oxygen saturation, and blood flow.

2. Method

The majority of photosensitizers available for PDT utilize Type II photodynamic processes, i.e., the photodynamic effect is achieved through the production of singlet oxygen.^{5, 6} The Jablonski diagram shown in Fig. 1 summarizes the underlying physical processes involved in type-II PDT. The process begins with the absorption of a photon by photosensitizer in its ground state, promoting it to an excited state. The photosensitizer molecule can return to its ground state by emission of a fluorescence photon, which can be used for fluorescence detection. Alternatively, the molecule may convert to a triplet state, a process known as intersystem crossing (ISC). A high intersystem-crossing yield is an essential feature of a good Type II photosensitizer. Once in its triplet state, the molecule may undergo a collisional energy transfer with ground state molecular oxygen (type II) or with the substrate (type I). In type II interaction, the photosensitizer returns to its ground state, and oxygen is

promoted from its ground state (a triplet state) to its excited (singlet) state. Since the photosensitizer is not consumed in this process, the same photosensitizer molecule may create many singlet oxygen molecules.

Once the singlet oxygen is created, it reacts almost immediately with cellular targets in its immediate vicinity. The majorities of these reactions are irreversible, and lead to consumption of oxygen. This consumption of oxygen is efficient enough to cause measurable decreases in tissue oxygenation when the incident light intensity is high enough. In addition to its reactions with cellular targets, singlet oxygen may react with the photosensitizer itself. This leads to its irreversible destruction (photobleaching). Photobleaching can decrease the effectiveness of PDT by reducing the photosensitizer concentration, however it can also be useful for dosimetry.⁷ Because of its high reactivity, singlet oxygen has a very short lifetime in tissue. However, a small fraction of the singlet oxygen produced may return to its ground state *via* emission of a phosphorescence photon, which can be detected optically.^{8,9}

2.1 Macroscopic kinetics rate equations

We adopted the rate equation approach first proposed by Foster *et al*¹⁰ and later refined by Hu *et al*¹¹ to describe the PDT kinetics process. We use k_i ($i = 0, 1, \dots, 7$) to designate the reaction rate. The details of the reactions associated with the reaction rates and the species involved are summarized below:

The PDT process started by the absorption of light by the photosensitizer in the ground state, S_0 , and it excites to the singlet state S_1 . The S_1 state will spontaneously decay to the ground state, S_0 , by emission of a fluorescent photon.

This is a reversible process. The monomolecular reaction rate k_0 (1/s) is proportional to the light fluence ϕ (in unit of W/cm^2): $k_0 = \varepsilon \cdot \left(\frac{\phi}{hv}\right)$, where ε is the extinction coefficient (in unit of $cm^{-1}/\mu M$), $h\nu$ is the photon energy (in unit of Joule).

The monomolecular reaction rate $k_3 = 1/\tau_3$ (in units of 1/s) is the inverse of the relaxation time τ_1 from S_1 to S_0 due to fluorescence. The photosensitizer in the ground state can interact with the singlet oxygen and produce photoproduct $[SO_2]$. The bimolecular reaction rate, k_1 (in unit of $1/s/\mu M$), describes the irreversible photobleaching reaction of the photosensitizer:

Similarly, the bimolecular reaction rate, $S \ k_2$ (in unit of $1/s/\mu M$) describe the production of singlet oxygen caused by the collisions between the photosensitizer triplet state $[T]$ and the

ground state oxygen [3O_2] to create the singlet oxygen [1O_2]. The second equation illustrates that a fraction (S) of interaction between $[T]$ and [3O_2] does not yield singlet oxygen.

The phosphorescence and inter-system crossing of the photosensitizer are described by the monomolecular reaction rate k_4 and k_5 (in units of 1/s), respectively:

The phosphorescence of singlet oxygen and the oxidation of acceptors $[A]$ are described by the reaction rates k_6 and k_7 , respectively:

Here $[S_0]$, $[S_1]$, and $[T]$ also describes the concentration of the ground, excited, and triplet state of the photosensitizer molecule, respectively. [1O_2] and [3O_2] is the concentration of singlet and triplet (ground) state of the oxygen, respectively, and $[A]$ is the concentration of all singlet oxygen acceptors except for the photosensitizer itself. $[SO_2]$, $[AO_2]$ are the concentrations of oxidation products.

The kinetics of the above processes can be described by the coupled differential equations:

$$\frac{d[S_0]}{dt} = -k_0[S_0] - k_1[^1O_2][S_0] + k_2[T][^3O_2] + k_3[S_1] + k_4[T] \quad 3$$

$$\frac{d[S_1]}{dt} = -(k_3 + k_5)[S_1] + k_0[S_0] \quad 4$$

$$\frac{d[T]}{dt} = -k_2 [T] [^3O_2] - k_4 [T] + k_5 [S_1] \quad 5$$

$$\frac{d[^3O_2]}{dt} = -S_{\Delta} k_2 [T] [^3O_2] + k_6 [^1O_2] + P \quad 6$$

$$\frac{d[^1O_2]}{dt} = -k_1 [S_0] [^1O_2] + S_{\Delta} k_2 [T] [^3O_2] - k_6 [^1O_2] - k_7 [A] [^1O_2] \quad 7$$

$$\frac{d[A]}{dt} = -k_7 [A] [^1O_2]. \quad 8$$

Where P is the oxygen diffusion and perfusion rate and can be treated as a known constant. S_{Δ} is the fraction of interaction between $[^3O_2]$ and $[T]$ that resulted in production of singlet oxygen. The values of the various parameters for Photofrin are listed in Table 1.

It should be emphasized that the first term in Eq. (3), $k_0[S_0]$ is the rate of PDT dose, as that defined in Eq. (1), multiplied by the tissue mass density ρ . The light fluence rate, ϕ , describes the light propagation in tissue and follows a diffusion equation:

$$\nabla (1/3\mu'_s) D \nabla \phi - \mu_a \phi = S, \quad 9$$

where $\mu_a = \mu_0 + \epsilon[S_0]$ (in cm^{-1}) and μ'_s (in cm^{-1}) are the absorption and reduced scattering coefficients in tissue, and S (in W) is the source strength. For a point source in an infinite turbid medium, one can provide an analytical solution to Eq. (9) as:

$$\phi = \frac{3\mu'_s S}{4\pi r} e^{-\mu_{eff} r}, \quad 10$$

where S is the light source strength (in W), r is the radial distance from the point source, and $\mu_{eff} = \sqrt{3\mu_a \mu'_s}$ is the effective attenuation coefficient. For a given photosensitizer, the reaction rates ($k_0 - k_7$) are considered constants.

The rate equation is implemented in the COMSOL finite-element modeling (FEM) package (COMSOL AB, Stockholm, Sweden). The calculation time is in seconds for the rate equation alone and tens of minutes for the time and spatially coupled differential equations.

2.2 Oxygen dependence of the singlet oxygen quantum yield

The life time of the singlet and triplet states of photosensitizer ($[S_1]$ and $[T]$) and the singlet oxygen ($[^1O_2]$) are very short (ns – μs time scale) since they either decay or react with cellular targets immediately after they are created. Thus, it is reasonable to set the time dependences, $d[S_1]/dt$, $d[T]/dt$, and $d[^1O_2]/dt$ to be zero for Eqs. (4), (5), (7). Thus, the coupled kinetics equations (3) – (8) can be rewritten as:

$$[{}^1O_2] = S_{\Delta} \left(\frac{k_5}{k_5 + k_3} \right) \cdot \left(\frac{[{}^3O_2]}{[{}^3O_2] + k_4/k_2} \right) \cdot \left(\frac{1}{k_6 + k_7[A]} \right) \cdot k_0 [S_0] \quad 11$$

$$[S_1] = \left(\frac{1}{k_5 + k_3} \right) \cdot k_0 [S_0] \quad 12$$

$$[T] = \left(\frac{k_5}{k_5 + k_3} \right) \cdot \left(\frac{1}{k_2[{}^3O_2] + k_4} \right) \cdot k_0 [S_0] \quad 13$$

$$\frac{d[S_0]}{dt} = - \left(\frac{k_5}{k_5 + k_3} \right) \left(\frac{[{}^3O_2]}{[{}^3O_2] + k_4/k_2} \right) \left(\frac{k_1[S_0]}{k_6 + k_7[A]} \right) \cdot k_0 [S_0] \quad 14$$

and

$$\frac{d[{}^3O_2]}{dt} = - S_{\Delta} \left(\frac{k_5}{k_5 + k_3} \right) \left(\frac{[{}^3O_2]}{[{}^3O_2] + k_4/k_2} \right) \left(\frac{k_7[A]}{k_6 + k_7[A]} \right) \cdot k_0 [S_0] + P \quad 15$$

We have replaced $k_1[S_0] + k_7[A]$ by $k_7[A]$ in Eq. 15 since $k_1[S_0] \ll k_7[A]$. Equation (11) describes the relationship between the singlet oxygen concentration and the PDT dose rate, $\dot{D} = k_0 \cdot [S_0] / \rho$. Once the time dependence of the singlet oxygen concentration $[{}^1O_2]$ is known, one can solve Eq. (8) for the destruction of the acceptors:

$$[A] = [A_0] \cdot e^{-k_7 \int_0^t [{}^1O_2] dt}. \quad 16$$

Thus, the threshold value of cumulative singlet oxygen production for sufficient cellular target killing is $k_7 \int_0^t [{}^1O_2] dt = 4.6$ assuming $[A]/[A]_0 = 10^{-2}$. However, this quantity $k_7 \int_0^t [{}^1O_2] dt$ has no unit. To maintain the unit of concentration (μM) for singlet oxygen production, an alternative quantity is the concentration of singlet oxygen that has interacted with the tissue, $[{}^1O_2]_{rx}$. By integrating Eq. (8) and setting $[{}^1O_2]_{rx}$ to equal to the reduction of cellular targets as a fraction of acceptors $[A]$:

$$[{}^1O_2]_{rx} = -f \cdot \int_0^t \frac{d[A]}{dt} dt = f \cdot k_7 \int_0^t [A] [{}^1O_2] dt, \quad 17$$

where f is the fraction of acceptors $[A]$ that is the cellular target. Substituting Eq. (11) into Eq. (17) and compared the results with Eq. (2), we can determine the expression for the singlet oxygen quantum yield as:

$$\eta = S_{\Delta} \left(\frac{k_5}{k_5 + k_3} \right) \cdot \left(\frac{[{}^3O_2]}{[{}^3O_2] + k_4/k_2} \right) \cdot \left(\frac{k_7[A]}{k_6 + k_7[A]} \right), \quad 18$$

$$[^1O_2]_{rx} = f \cdot \int_0^t \eta \cdot \rho \dot{D} dt. \quad 19$$

Equation 18 is the expression of singlet oxygen quantum yield under the condition of arbitrary tissue oxygen concentration $[^3O_2]$ during PDT. $\rho = 1 \text{ g/cm}^3$ for tissue. To use this expression for a particular photo sensitizer, one needs to know the parameters $k_5/(k_5+k_3)$, k_4/k_2 , and $k_7[A]/k_6$ (see Table 3). Under ample oxygen supply, Eq. 19 returns to the form of Eq. 2. The local tissue oxygenation $[^3O_2]$ cannot be directly measured using absorption spectroscopy. We provide some preliminary result of microscopic modeling of the diffusion process to correlate the tissue oxygenation with the measured quantities inside the blood vessel, such as total hemoglobin concentration, the oxygen saturation, SO_2 , and the blood flow speed.

2.3 Tissue oxygen concentration vs. THC, SO_2 , and blood flow

Governing Equations—Tumor tissue is represented as an array of uniformly spaced Krogh cylinders with capillaries along the axes. Each cylinder is assumed to be supplied oxygen exclusively from the capillary within it (Fig 2.).

In the capillary, the equations governing oxygen transport are:

$$\alpha_c D_c \nabla^2 P = \vec{u} \cdot \alpha_c \nabla P + C_H \vec{u} \cdot \nabla S \quad 20$$

where P (mmHg) is the partial pressure of oxygen in the capillary, α_c ($\mu\text{M/mmHg}$) is the oxygen solubility in the capillary, D_c ($\mu\text{m}^2/\text{s}$) is the diffusion coefficient of oxygen in the capillary, u ($\mu\text{m/s}$) is the speed of blood flow, C_H (μM) is the oxygen carrying capacity of hemoglobin at 100% saturation and S is the fractional hemoglobin saturation described using Hill equation:¹⁵

$$S = \frac{P^n}{P_{50}^n + P^n} \quad 21$$

where P_{50} is the pO_2 at which hemoglobin is 50% saturated and n is a constant describing the cooperative binding of oxygen to hemoglobin.¹⁵⁻¹⁷

The governing equation in the tumor tissue is given by:

$$\alpha_t D_t \nabla^2 P = q(P) \quad 22$$

where α_t ($\mu\text{M/mmHg}$) is the oxygen solubility in the tumor tissue, D_t ($\mu\text{m}^2/\text{s}$) is the diffusion coefficient of oxygen in the tumor tissue, $q(P)$ ($\mu\text{M/s}$) is the oxygen consumption rate per unit volume of the tissue cylinder. With Michaelis-Menten kinetics, $q(P) = q_0 P / (P + P_m)$, where q_0 ($\mu\text{M/s}$) is the oxygen demand, i.e., the consumption when the oxygen supply is not limiting, and P_m is the pO_2 at which consumption is half of the demand.^{16, 18} Notice that PDT consumption of oxygen is not considered in the above equations, thus the conclusion is only valid before (or after) PDT treatment.

Boundary Conditions—At the capillary-tissue interface, both pO_2 and oxygen flux must be continuous.¹⁶ $P|_{r=R_c^-} = P|_{r=R_c^+}$, and $\alpha_c D_c \nabla P|_{r=R_c^-} = \alpha_t D_t \nabla P|_{r=R_c^+}$. P is initially in equilibrium with tumor arterial blood, so $P|_{r=0, y \in [0, R_c]} = P_{ts}$ where P_{ts} is the tumor oxygen supply pO_2 . At all the other boundaries, the flux of dissolved oxygen per unit area is zero,¹⁶ described as an insulation boundary $\nabla P|_{\delta\Omega} = 0$. The differential equation is solved using COMSOL FEM package.

Parameter values—Parameter values are chosen to represent blood flow in various tumor tissues and are listed in Table 2.

3. Results and Discussion

3.1 Macroscopic modeling of singlet oxygen production

Figure 3 shows the time dependence of singlet oxygen production [1O_2], the oxygen consumption [3O_2], and the photosensitizer consumption [S_0] by solving the coupled rate equations (Eqs. (3) - (8)) for parameters listed in Table 1. For comparison, the production of triplet state [T] and the excited state [S_1] of the photosensitizer are also shown. The light fluence rate is 100 mW/cm^2 .

There are three time regions for temporal changes (Fig. 3). In the first time region (for time less than 1 ms), the initial rise of [S_1], [T], and singlet oxygen [1O_2] is very rapid, within 1 μs (Fig. 3a). In the second time region (for time in the region of 0.1 ms to 30 seconds), one observes a rapid decrease of triplet and singlet oxygen concentrations, [3O_2] and [1O_2], and a corresponding increase of [T] (Fig. 3b). In the third region (for time > 30 seconds), photobleaching of the photosensitizer dominates and one observes a decreases of [S_0], [S_1], [T] and a corresponding increase. If one is only interested in the second and the third time regions, then one can set $d[S_1]/dt$, $d[T]/dt$, and $d[^1O_2]/dt$ to zero for equations 4, 5, and 7, and solve for the equilibrium concentration of the excited states of oxygen and photosensitizer relative to their ground states.

For Photofrin, the time it takes to consume most of oxygen is in the order of 20 seconds. To illustrate this process, linear time scale is used in Fig. 3b. In this plot, the concentrations are renormalized by the respective maximum concentrations so that they can all be shown in the linear scale. There is significant consumption of oxygen, with the final oxygen concentration ($[^3O_2] > 0$) determined by the diffusion and perfusion rate of oxygen (P). The production of singlet oxygen decreases with time due to consumption of oxygen and finally reaches a saturation concentration determined by $P/k_7[A] (=5.3 \times 10^{-2} \mu\text{M})$. With the consumption of oxygen, the concentration of the triplet state (T) increases with time before reaching an equilibrium value.

Beyond the initial time region ($t > 30$ seconds), the singlet oxygen and triplet oxygen concentrations will increase with time due to the photobleaching of photosensitizer. This is illustrated in Fig. 3c where the concentrations are normalized to the respective concentrations at $t = 40$ seconds. For this Photofrin concentration ($8.5 \mu\text{M}$ or 5 mg/kg), the

photobleaching of the photosensitizer is quite low (Fig. 3c), the concentration of S_1 (proportional to fluorescence signal) decrease slowly with increasing time.

As the light fluence rate increases, the production of singlet oxygen also increases (Fig. 4a). The time it takes to produce the singlet oxygen is roughly the same. However, the occurrence of the initial rapid consumption of singlet oxygen delays with decreasing light fluence rates during PDT (Fig. 4a). The reacted singlet oxygen concentration increases linearly with time for fluence rates ($\phi > 10 \text{ mW/cm}^2$) (Fig. 4b).

For a point source within 1 mW power in a homogeneous phantom with a mean optical properties of $\mu_a = 0.3 \text{ cm}^{-1}$ and $\mu_s' = 14 \text{ cm}^{-1}$,²² the coupled differential equation can be solved to determine both the spatial and time dependence of the singlet oxygen concentration, as shown in Fig. 5a. Clearly the radial distribution of the reacted singlet oxygen concentration is very different from that of the light fluence rate (Fig. 5b).

3.2 Relationship between singlet oxygen production and PDT dose

A more general method of establishing a PDT dosimetry protocol is to use the concept of the reacted singlet oxygen concentration, $[^1\text{O}_2]_{\text{rx}}$, as determined in Eq. (19). This equation correlates the measured PDT dose rate with $[^1\text{O}_2]_{\text{rx}}$, without the need of any kinetics modeling. Oxygen dependence of the singlet oxygen quantum yield for a particular photosensitizer depends on the three ratios: $k_5/(k_3+k_5)$, k_4/k_2 , and $k_7[A]/k_6$. Table 3 summarizes the known ratios for two photosensitizers based on literature. Since the ratio $k_7[A]/k_6 \gg 1$, the expression for the singlet oxygen quantum yield (Eq. 18) can be simplified as:

$$\eta = S_{\Delta} \cdot \left(\frac{k_5}{k_5 + k_3} \right) \cdot \left(\frac{[^3\text{O}_2]}{[^3\text{O}_2] + k_4/k_2} \right). \quad 23$$

One can come to two conclusions based on this expression and Table 3. Firstly, the value of the singlet oxygen quantum yield under ample oxygen supply (second term in parenthesis = 1) has similar values for photofrin and mTHPC. It remains to be seen whether this value is photosensitizer independent. Secondly, as long as the tissue oxygen concentration is larger than k_4/k_2 , or 12 μM , the effect of oxygen consumption can be ignored. This situation applies to cases where PDT effect is mostly vascular, i.e., the damage to the blood vessel dominates, since the tissue oxygen concentration in blood vessel is usually larger than 100 μM (see Fig. 6).

We emphasize that the spatial distribution of the reacted singlet oxygen concentration,

$$[^1\text{O}_2]_{\text{rx}} = f \cdot \int_0^t \eta \cdot \dot{D} dt,$$

can be determined using the measured 3D distribution of light fluence rate and the photosensitizer concentration in real-time. This further underscores the importance of explicit PDT dosimetry of these quantities in real-time.

3.3 Tissue oxygen concentration vs. THC, SO₂, and blood flow

Macroscopic measurement of total hemoglobin concentration (THC), oxygen saturation (SO₂) and blood flow in blood vessel needs to be correlated to the local tissue oxygen concentration in order to determine the singlet oxygen quantum yield (Eq. 23). This correlation is complicated because it depends on the exact geometrical shape of the capillary and the spacing between capillaries. For a cylindrical capillary, one can calculate the oxygen concentration in tissues surrounding the vessel, as shown in Fig. 6 using parameters listed in Table 1. This figure shows that there is tissue oxygen concentration decreases with increasing distance from the blood vessel. One also observes decrease of oxygen concentration along the blood vessel length.

A preliminary simulation is performed to correlate the mean tissue oxygen concentration vs. the mean tissue oxygen saturation for various conditions. The mean tissue oxygen concentration is calculated as a volumetric average of the tissue oxygen concentration from $r = 0$ (center of the blood vessel) to outer boundary: $[O_2] = \pi \int_0^z \int_0^{R_t} [O_2] dr^2 dz / V$. In Fig. 7a, the blood flow speed (u) is varied between 50 and 200 $\mu\text{m/s}$. It seems that the relationship between mean tissue oxygenation and the mean tissue oxygen saturation SO₂ are not affected much by the blood flow speed change, when oxygen partial pressure at tumor oxygen supply end is low ($P_{ts} < 50$ mmHg). On the other hand, when the supply is highly oxygen saturated, the difference in blood flow leads to an approximately 12% difference in mean tissue oxygen concentration. In Fig. 7b, metabolic oxygen consumption rate is varied. The difference in mean tissue oxygen concentration due to different metabolic consumption rate is more pronounced when less saturated oxygen is supplied than when the highly saturated blood is fed to the tumor tissue. However, the difference is not significant for low oxygen consumptions ($q_0 \leq 10$ $\mu\text{M/s}$). Thus one can use an average oxygen consumption rate (5 $\mu\text{M/s}$) for all simulations. In Fig 7c, the total (tissue averaged) hemoglobin concentration is defined as: $[Hb]_{tot} = (C_H / 4)(R_C / R_t)^2$, assuming the hemoglobin concentration in the blood vessel (C_H) and inter-capillary distance (tissue cylinder radius R_t) remain constant, and R_C varies from 4 μm to 20 μm . It demonstrates that total hemoglobin concentration has no effect on the relationship between the mean tissue oxygen concentration and SO₂. As shown in Fig 7c., four curves overlapping each other, indicating that mean tissue oxygen saturation can be the only input parameter needed to estimate the corresponding mean tissue oxygen concentration. Our geometry may not be representative for the complex tumor vascular architecture since all the simulations are performed on the Krogh single cylinder geometry. Further simulations with complex geometry should be performed. Also notice that these simulations are performed before photodynamic therapy. Additional consumption of oxygen occurs during PDT and these curves cannot be used to estimate the mean tissue oxygen concentration.

4. Conclusions

We have shown that using a set of rate equations, one can calculate the production of singlet oxygen. Under 3D heterogeneity of light fluence rate, photosensitizer concentration, and tissue oxygenation, it is suggested to use the reacted singlet oxygen as a dosimetry quantity to monitor and optimize during PDT. Our simulation of PDT kinetics shows low

photobleaching rate during clinical PDT and also showed a marked difference between light fluence rate distribution and the reacted singlet oxygen concentration, $[^1\text{O}_2]_{\text{rx}}$. Preliminary study has shown that one can correlate the tissue oxygenation with the macroscopic quantity measured in the blood vessel, such as SO_2 . Further studies are necessary to determine the relationship between the mean oxygen concentration and the macroscopic measurement during PDT.

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Figure 1. Jablonski diagram of photosensitized singlet oxygen formation by Type II photosensitizer. The rate constants for monomolecular transition (solid lines) and bimolecular energy transfer (dashed lines) are indicated.

Figure 2.
Schematics of the capillary cylinder used in our model.

Figure 3.

The time dependence of $[^1\text{O}_2]$, $[^3\text{O}_2]$, $[S_0]$, $[S_1]$, and $[T]$ for parameters listed in Table 1 for Photofrin: (a) The concentrations of various components in log time scale (10^{-10} – 10^4s); (b) The concentrations normalized by the maximum concentrations in linear time scale; (c) The concentration normalized by the concentration at $t = 40\text{s}$ in linear time scale. Spatial distributions for light fluence rate, photosensitizer concentration, and oxygenation are assumed to be homogeneous.

Figure 4.

Time dependence of (a) the singlet oxygen concentration $[^1O_2]$ and (b) the reacted singlet oxygen concentration $[^1O_2]_{rx}$ as a function of light fluence rate (in unit of mW/cm²).

Figure 5.

(a) Time and spatial dependence of the singlet oxygen concentration $[{}^1\text{O}_2]$ (μM) and (b) light fluence rate distribution for a point source. For comparison, the reacted singlet oxygen concentration at 1000s and 2000s are also plotted.

Figure 6.

Radial profile of pO_2 for $q_0=5\mu M/s$, at upstream end ($z=0\mu m$), midpoints ($z=20, 40$, and $80\mu m$) and downstream end ($z=160\mu m$) of the tumor tissue cylinder. The tumor supply pO_2 used here is $P_{ts} = 100 \text{ mmHg}$.

Figure 7.

Tissue oxygen concentration vs. SO_2 under different (a) blood flow velocity (u), (b) metabolic oxygen consumption rate (q_0), and (c) various THC concentrations ($[Hb]_{tot}$). $R_c = 4 \mu\text{m}$ for (a) and (b) and varies for (c). $R_t = 50 \mu\text{m}$ for all cases.

Table 1

Parameters used in the macroscopic kinetics equations for Photofrin.

Sym.	Definition	Values	References
k_0	PS absorb. rate at $\phi=100$ mW/cm ²	1.9 s^{-1}	12
k_1	Photobleaching rate	$1.2 \times 10^5 \text{ l}/\mu\text{M}\cdot\text{s}$	11
k_2	Reaction rate of $^3\text{O}_2$ with T	$100 \text{ l}/\mu\text{M}\cdot\text{s}$	¹³ for $k_4/k_2=12.1 \mu\text{M}$
k_3	Rate of S_1 to S_0	$2.0 \times 10^7 \text{ l/s}$	¹³ for $k_5/(k_5+k_3)=0.80$
k_4	Rate of T to S_0	1250 l/s	10
k_5	Rate of S_1 to T	$8.0 \times 10^7 \text{ l/s}$	11
k_6	Rate of $^1\text{O}_2$ to $^3\text{O}_2$	$1 \times 10^6 \text{ l/s}$	11
k_7	Reaction rate of $^1\text{O}_2$ with [A]	$2.6 \times 10^6 \text{ l}/\mu\text{M}\cdot\text{s}$	¹³ for $k_1/k_7[A]=56.5 \text{ M}^{-1}$
ε	Extinction coefficient of $[\text{S}_0]$	$0.0036 \text{ cm}^{-1}/\mu\text{M}$	12
S	Fraction $^1\text{O}_2$ from reaction [T] and $[\text{S}_0]$	0.5	13
P	Oxygen Diffusion and Perfusion rate	$1.66 \times 10^{-2} \mu\text{M/s}$	11
$[\text{S}_0]_i$	PS concentration	$8.5 \mu\text{M}^* (= 5 \text{ mg/kg})$	14
$[\text{S}_1]_i$	Init. Con.	$0 \mu\text{M}$	11
$[\text{T}]_i$	Init. Con.	$0 \mu\text{M}$	11
$[^3\text{O}_2]_i$	Init. Con.	$83 \mu\text{M}$	13
$[^1\text{O}_2]_i$	Init. Con.	$0 \mu\text{M}$	11
$[\text{A}]_i$	Init. Con.	$830 \mu\text{M}$	11

* $1 \mu\text{M} = 6.022 \times 10^{14} \text{ cm}^{-3}$.

Table 2

Summary of parameter values used in the oxygen diffusion model.

Parameter	Description	Value	References
R_c	Capillary radius	4~10 μm	19
R_t	Tissue radius	18~65 μm	20
z	Length of capillary	220 μm	16
u	Blood velocity in capillary	50~750 $\mu\text{m/s}$	16, 18
C_H	Plasma oxygen carrying capacity	9000 μM	16
a_c	Oxygen solubility in plasma	1.527 $\mu\text{M/mmHg}$	16
a_t	Oxygen solubility in tissue	1.295 $\mu\text{M/mmHg}$	16
P_{50}	Half maximum hemoglobin saturation	26mmHg	20
p_m	Half maximum oxygen consumption	1mmHg	20
P_{ts}	Tumor supply $p\text{O}_2$	20~40 mmHg	19
n	Hill constant	2.7	17
D_c	Oxygen capillary diffusion coefficient	1120 $\mu\text{m}^2/\text{s}$	16
D_t	Oxygen tissue diffusion coefficient	1700 $\mu\text{m}^2/\text{s}$	16
q_0	Oxygen consumption	2~16 $\mu\text{M/s}$	21

Table 3
Parameters for selected photosensitizers

Photosensitizers	$k_3/(k_3+k_5)$	k_4/k_2 (μM)	$k_7[A]/k_6$
Photofrin	0.80	12	10^3 - 10^4
mTHPC	0.89	8.7	10^3 - 10^4
References	13	13	11