Singlet Oxygen Modeling of PDT incorporating Local Vascular Oxygen Diffusion

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Abstract: Based on a previously developed model that incorporates the macroscopic kinetic equations for the generation of the singlet oxygen, the distance-dependent reacted singlet oxygen concentration, $[^1O_2]$ can be numerically calculated using finite-element method (FEM). We have improved the model to include oxygen diffusion from uniformly distributed blood vessels to the adjacent tissue. In the model, the cylindrical blood capillary has radius in the range of 2.5 - 10 μm and a mean length of 220 μm. The blood vessel network has varying vascular densities, i.e., the spacing between vascular cylinders is varying between 18 and 60 um. The forward calculation is performed using COMSOL. In conclusion, our model incorporating local vascular oxygen diffusion proves the validity of the formulation of the oxygen supply term in the macroscopic singlet oxygen model, $g(1-[^3O_2]/[^3O_2]_0)$, where g is oxygen supply rate and $[^3O_2]_0$ is the initial oxygen concentration before PDT.

Keywords: Singlet oxygen, vascular modeling, oxygen supply rate, macroscopic modeling, finite element method.

1. Introduction

Photodynamic therapy (PDT) is an emerging treatment modality for malignant and non-malignant conditions. PDT combines a light source, a light-activatable photosensitizer (PS) and molecular oxygen ($^3O_2$). As shown in figure 1, during PDT, photosensitizer is excited by light at a certain wavelength, and then, the excited-state sensitizer transfers its energy to the ground-state molecular oxygen, which results in singlet-state oxygen – singlet oxygen ($^1O_2$). Singlet oxygen is considered as the major cytotoxic agent causing biological and therapeutic outcomes in type-II PDT. The photosensitizer (PS) considered in this study is Photofrin, the earliest FDA approved photosensitizer in the USA.

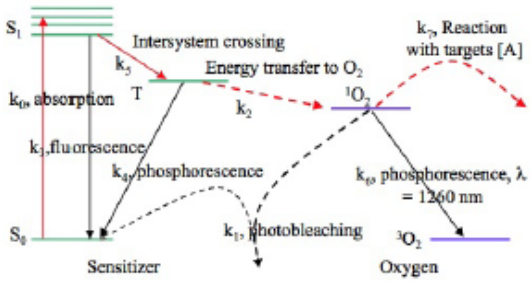

Figure 1. Jablonski Diagram for type II PDT interaction.

2. Theory

Based on the Jablonski diagram shown in Fig. 1, the diffusion equation describing the generation of singlet oxygen can be expressed as [1,2]:

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

$$\frac{d[S_1]}{dt} = -(k_3 + k_5)[S_1] + k_0[S_0] \quad (2)$$

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

$$\frac{d[^3O_2]}{dt} = -S_\Delta k_2[T][^3O_2] + k_6[^1O_2] + g\left(1 - \frac{[^3O_2]}{[^3O_2]_0}\right) \quad (4)$$

$$\frac{d[^1O_2]}{dt} = -k_1[S_0][^1O_2] + S_\Delta k_2[T][^3O_2] - k_6[^1O_2] - k_7[A][^1O_2] \quad (5)$$

$$\frac{d[A]}{dt} = -k_7[A][^1O_2], \quad (6)$$

where $[S_0]$, $[S_1]$, $[T]$, $[^3O_2]$,$[^1O_2]$, and $[A]$ are the concentrations (in μM) of ground state PS, singlet state PS, triplet state PS, and the ground triplet state of oxygen, the singlet oxygen, and the concentration of tissues to be destroyed. The photochemical parameters are defined in Table 1 along with the units. Since many of these photochemical parameters are unknown for a specific PS, it is a common practice to simplify Eqs. 1-6 by assuming $d[S_1]/dt$=0, $d[T]/dt$=0, and $d[^1O_2]/dt$ = 0 since the decay times are known to be very short (ns to μs time scale) while the main

interest of our modeling is in the seconds to hours time scale.

Table **1**: photochemical parameter definitions

Symbol	Definition (unit)
k_0	PS absorption rate, = $\varepsilon\phi/\nu$ (1/s)
k_1	Photobleaching rate (1/μM·s)
k_2	Reaction rate of $^3O_2$ with T (1/μM·s)
k_3	Rate of S_1 to S_0 (1/s)
k_4	Rate of T to S_0 (1/s)
k_5	Rate of S_1 to T (1/s)
k_6	Rate of $^1O_2$ to $^3O_2$ (1/s)
k_7	React. rate of $^1O_2$ and tissue (1/μM·s)
S_Δ	Fraction [$^1O_2$] from [T] and [$^3O_2$] reaction (unitless)
ε	Extinction Coefficient (cm^{-1}/μM)
g	Max. oxygen supply rate (μM/s)

2.1 Macroscopic model for singlet oxygen

The resulting macroscopic model for the generation of singlet oxygen can be expressed as [2,4]:

$$\frac{d[S_0]}{dt}+\left(\frac{\xi\sigma\phi([S_0]+\delta)[^3O_2]}{[^3O_2]+\beta}\right)[S_0]=0 \quad (7)$$

$$\frac{d[^3O_2]}{dt}+\left(\frac{\xi\phi[S_0]}{[^3O_2]+\beta}\right)[^3O_2]=g\left(1-\frac{[^3O_2]}{[^3O_2]_0}\right) \quad (8)$$

$$\frac{d[^1O_2]_{rx}}{dt}=\left(\frac{\xi\phi[S_0]}{[^3O_2]+\beta}\right)[^3O_2] \quad (9)$$

where $[^1O_2]_{rx}$ is the reacted cumulative singlet oxygen ($=\int_0^t d[A]/dt\cdot dt$), $[^3O_2]_0$ is the initial oxygen concentration at t = 0, and ϕ is the light fluence rate. The definition and the values (for Photofrin) of the other parameters are listed in Table 2.

Table **2**: Definitions and values (for Photofrin) [2]

Parameter	Value	Definition
ξ ($cm^2mW^{-1}s^{-1}$)	3.7 x 10^{-3}	$S_\Delta k_5/(k_3+k_5)\varepsilon/h\nu/(k_6/k_7[A]+1)$
σ (μM^{-1})	2.97 x 10^{-5}	$k_1/(k_7[A])$
δ (μM)	33	_
β (μM)	8.7	k_4/k_2

2.2 Model for local vascular oxygen diffusion

One drawback of the macroscopic model (Eqs. (7)-(9)) is that the oxygen supply term (last term in Eq. 4) is assumed to be uniformly distributed everywhere without consideration of oxygen diffusion through vasculatures. Thus its functional form, $g(1-[^3O_2]/[^3O_2]_0)$, needs to be validated. In reality, the oxygen supply is accomplished via diffusion of oxygen released from the blood vessels. Figure 2 shows a uniformly distributed Krogh's cylindrical blood vessel model [1], which can be described by the radius of capillary, R_c (μm), the radius of the tissue layer, R_t (μm), and the average length of the capillary, l_c (μm). R_t determines the vascular density (numbers of capillaries per volume) in a particular tissue model.

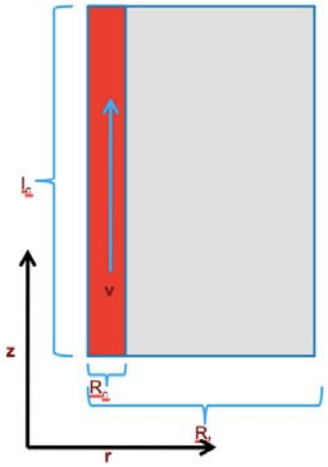

Figure 2. Krogh's 3D cylindrical blood vessel model in 2D using the axial symmetry.

The diffusion equation governing the free oxygen $[^3O_2]$ and bounded oxygen in hemoglobin in the capillary can be expressed as [4,5]:

$$\frac{d[^3O_2]}{dt}+\left(\frac{\xi\phi[S_0]}{[^3O_2]+\beta}\right)[^3O_2]=D_c\nabla^2[^3O_2]-\vec{v}\cdot\nabla[^3O_2]+\Gamma_{rec} \quad (10)$$

$$C_H\frac{dS}{dt}=C_H D_H\nabla^2 S-C_H\vec{v}\cdot\nabla S-\Gamma_{rec} \quad (11)$$

where S is the oxygen saturation, i.e., the ratio of oxy-hemoglobin to the total hemoglobin, which follows the Hill's curve in equilibrium condition (when Γ_{rec} = 0):

$$f([^3O_2])=\frac{[^3O_2]^n}{[^3O_2]^n+[^3O_2]_{50}^n} \quad (12)$$

$$\Gamma_{rec} = C_H k_H \frac{f([^3O_2]) - S}{1 - f([^3O_2])} \quad (13)$$

The diffusion equation governing the oxygen in the tissue region is [3-4]:

$$\frac{d[^3O_2]}{dt} + \left(\frac{\xi\phi[S_0]}{[^3O_2]+\beta}\right)[^3O_2] = D_t\nabla^2[^3O_2] - g_0\frac{[^3O_2]}{[^3O_2]+[^3O_2]_m} \quad (14)$$

The vascular parameters used in the diffusion equations are listed in Table 3 [1]. Notice the general conversion between the oxygen concentration and pressure are: $[^3O_2]_t = \alpha_t P_t$, $[^3O_2]_c = \alpha_c P_c$, for the tissue and capillary regions respectively. This should be used obtain $[^3O_2]_m$ in Eq. 14 and $[^3O_2]_{50}$ in Eq. 12 from the corresponding P_m and P_{50} listed in Table 3, respectively.

Table **3**: Vascular parameters [1,4]

Parameter	Definition	Value
R_c	Capillary radius	2.5~10 μm
R_t	Tissue radius	18~65 μm
l_c	Length of capillary	220-300 μm
v	Blood velocity in capillary	50~750 μm/s
C_H	Plasma oxygen carrying capacity	2500 μM
α_c	Oxygen solubility in plasma	1.527 μM/mmHg
α_t	Oxygen solubility in tissue	1.295 μM/mmHg
P_{50}	Half maximum hemoglobin saturation	26mmHg
P_m	Half maximum oxygen consumption	1mmHg
P_{ts}	supply pO_2	100 mmHg
n	Hill constant	2.46
D_c	Oxygen capillary diffusion coefficient	1120 μm^2/s
D_t	Oxygen tissue diffusion coefficient	1700 μm^2/s
q_0	Oxygen consumption	2~16 μM/s

The boundary conditions (see Fig. 2) are:
In flow: $P = P_{ts}$ at z = 0, $r < R_c$;
Continuum: $P_c = P_t$, $\nabla[^3O_2]_c = \nabla[^3O_2]_t$ at $r = R_c$;
Insulation: $\nabla P = 0$ at all others with $r = R_t$ set as periodical boundary.

The initial oxygen distribution at $t = 0$ is calculated using steady-state Eqs. (10) – (14) with $\phi = 0$, i.e., no treatment light and $d[^3O_2]/dt = 0$. The resulting $[^3O_2]$ distribution is then used as initial conditions at t = 0. At start of PDT, we assumes $[S_1] = [T] = [^1O_2] = 0$. $[S_0] = 7$ μM for Photofrin [2]. We have also fixed blood velocity in capillary to be 100 μm/s in all our simulations.

To simplify the calculation, we have also assumed that $S \approx f([^3O_2])$, i.e., the oxygen saturation follows Hill's curve and thus $\Gamma_{rec} \approx 0$. We further ignored the PDT oxygen consumption inside the capillary, i.e., the second term in Eq. 10 is 0 during PDT, thus by summing Eqs. (10) and (11), we obtained in the capillary region [4]:

$$\frac{d[^3O_2]}{dt} + C_H\frac{dS}{dt} = D_c\nabla^2[^3O_2] + C_H D_H\nabla^2 S - \vec{v}\cdot\nabla[^3O_2] - C_H\vec{v}\cdot\nabla S \quad (15)$$

This equation along with $S = f([^3O_2])$ (Eq. 12) is used in our calculations to approximate the solution for Eqs. (10) and (11) inside capillary.

2.3 Validation of the oxygen supply rate

To validate the oxygen supply rate in the macroscopic model (Eq. 8 right hand side), we solve the differential equations (Eqs. 7, 9, 14, 15) to account for the actual oxygen diffusion through the local vasculature. Once the solution is obtained, we calculate the volume average quantities over the tissue cylinder (R_t) for $[^3O_2]$, $[^3O_2]_{ave}$ and volume average over the tissue cylinder (R_t) for the left hand side of Eq. 8 as the oxygen supply rate. Because the spatial scale of light transport (~ 1 mm) is much larger than the spatial scale of oxygen diffusion (~ 65 μm = 0.065 mm), we have set also the light fluence rate ϕ to be a constant within the Krogh cylinder during the PDT.

3. Results

The finite-element calculation is implemented in COMSOL multiphysics v4.3b. Figure 3 shows calculated mean oxygen supply term vs. $[^3O_2]/[^3O_2]_0$ for various light fluence rates. The slope of the linear fit gives the value of g = 1.7 μM/s.

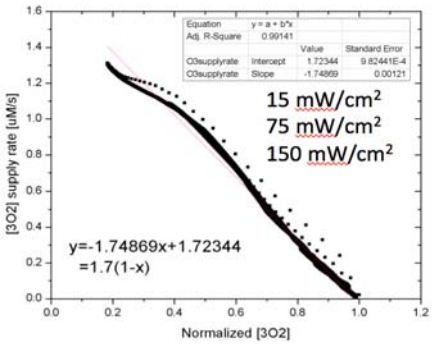

Figure 3. Vascular model prediction of $[^3O_2]$ supply term vs. $[^3O_2]/[^3O_2]_0$ for ϕ = 15, 75, 150 mW/cm^2. Capillary parameters used: l_c = 300 μm, R_c = 2.5 μm, R_t = 60 μm, v = 100 μm/s.

Figure 4 shows calculated mean oxygen supply rate vs. $[^3O_2]/[^3O_2]_0$ for various capillary geometry conditions: R_c = 2.5 – 10 μm and R_t = 18 – 60 μm, ϕ = 75 mW/cm^2, and l_c = 220 μm. The slope of the linear fit gives the values of g in table 4.

Table **4**: g (μM/s) vs. R_t and R_c (Fig. 4)

$R_t \setminus R_c$ (μm)	2.5	4	10
18	12.6	23.2	146
30	6.24	10.2	41.4
60	2.53	4.23	11

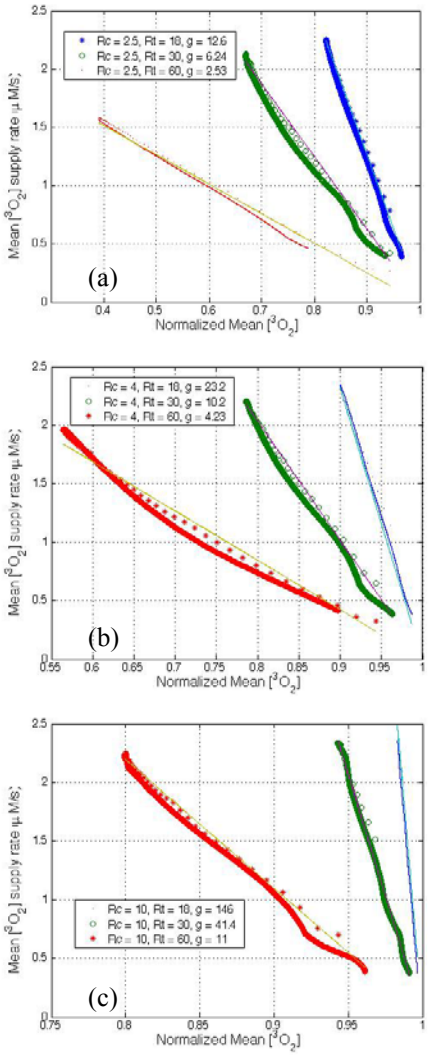

Figure 4. Vascular model prediction of $[^3O_2]$ supply rate vs. $[^3O_2]/[^3O_2]_0$ for ϕ = 75 mW/cm^2.and capillary radius: (a) R_c = 2.5 μm, (b) R_c = 4 μm, and (c) R_c = 10 μm. Other parameters used: l_c = 220 μm, R_t = 16, 30, 60 μm, and v = 100 μm/s.

4. Discussion

Figure 3 shows that a universal dependence between the oxygen supply rate and the volume averaged $[^3O_2]$, $g(1\text{-}[^3O_2]/[^3O_2]_0)$, which is independent of the light fluence rate and oxygen concentrations. The slope of the curve gives the value of g.

Figure 4 shows that g varies with the capillary radius R_c and the tissue radius R_t. An empirical formula can be obtained to calculate g for various values of R_c and R_t:

$$g[\mu M/s] = \frac{59400 R_c[\mu m](R_c[\mu m]+0.573)}{l_c[\mu m](R_t[\mu m]-4.2)^2} \qquad (16)$$

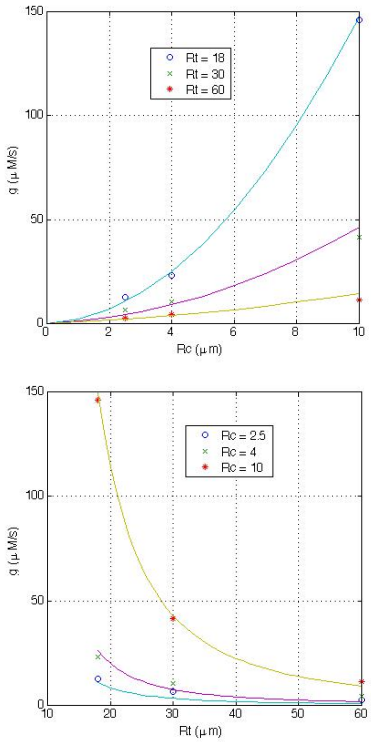

Figure 5. g vs. (a) R_c and (b) R_t for vascular conditions in Fig. 4 Other parameters used: l_c = 220 μm, ϕ = *75 mW/cm^2,* and v = 100 μm/s.

The result of the empirical formula compared to the actual data is shown in Fig. 5.

5. Conclusions

Our model incorporating local vascular oxygen diffusion confirms the form of oxygen supply term to be $g(1\text{-}[^3O_2]/[^3O_2]_0)$. However,

the value of g predicted from our current model parameters is generally higher than those obtained from PDT experiment, $g = 0.7$ μM/s [2, 6]. Our model (Eq. 16) anticipates g to decrease with increasing capillary radius, R_c, and decreasing spacing between capillary R_t.

6. References

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7. Acknowledgements

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