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A theoretical comparison of macroscopic and microscopic modeling of singlet oxygen during Photofrin and HPPH mediated-PDT

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Abstract

Mathematic models were developed to simulate the complex dynamic process of photodynamic therapy (PDT). Macroscopic or microscopic modeling of singlet oxygen ($^1\text{O}_2$) is particularly of interest because it is the major cytotoxic agent causing biological effects during PDT. Our previously introduced macroscopic PDT model incorporates the diffusion equation for the light propagation in tissue and the macroscopic kinetic equations for the production of the $^1\text{O}_2$. The distance-dependent distribution of $^3\text{O}_2$ and reacted $^1\text{O}_2$ can be numerically calculated using finite-element method (FEM). We recently improved the model to include microscopic kinetic equations of oxygen diffusion from uniformly distributed blood vessels and within tissue. In the model, the cylindrical blood capillary has radius in the range of 2–5 μm and a mean length of 300 μm , and supplies oxygen into tissue. The blood vessel network is assumed to form a 2-D square grid perpendicular to a linear light source. The spacing of the grid is 60 μm . Oxygen can also diffuse along the radius and the longitudinal axial of the cylinder within tissue. The oxygen depletion during Photofrin-PDT can be simulated using both macroscopic and microscopic approaches. The comparison of the simulation results have reasonable agreements when velocity of blood flow is reduced during PDT.

Keywords

Photodynamic therapy; Photofrin; dosimetry; singlet oxygen; microscopic model; macroscopic model

1. INTRODUCTION

Photodynamic therapy (PDT) combines light-activated photosensitizers, light source, and tissue oxygen to treat malignant and non-malignant diseases. During PDT, energy from the triplet-state photosensitizer excited via the absorption of light is transferred to ground-state oxygen, which produces singlet-state oxygen ($^1\text{O}_2$). Singlet oxygen is accepted to be the cytotoxic agent causing therapeutic outcomes in PDT.

Mathematical models have been developed to simulate the complex dynamic process of PDT.^{1,2,3,4,5} These models use a set of differential equations describing major photochemical and photophysical reaction pathways in PDT to calculate temporal and spatial distributions of singlet oxygen, ground-state oxygen, and photosensitizer. Tissue oxygen replenishment, PDT consumption, and metabolic consumption were included as well. In the microscopic models, oxygen can diffuse in capillaries, from capillaries into tissue, and within tissue. In contrast, oxygen diffusion is not considered in macroscopic model,⁴ and a generalized oxygen supply term implicitly including metabolic oxygen consumption is assumed everywhere in tissue.

Wang *et al*^{1,2} introduced a comprehensive microscopic PDT model. The model investigated the influence of intercapillary distance and heterogeneity of initial photosensitizer distribution on the quantities of interest during PDT such as distribution of singlet oxygen, tissue oxygen, photosensitizer, and hemoglobin-³O₂ saturation. All the simulations were performed using constant fluence rate for single capillary and its immediate surrounding tumor tissue (up to 85 μm in radial distance). Physiological responses to PDT can be affected by the combination of multiple microscopic parameters such as blood flow, total hemoglobin concentration, and the size of capillary. Hence, the influence of these parameters on PDT quantities such as tissue oxygenation is worthy of investigation. Also, temporal and spatial macroscopic distributions of those PDT quantities in the entire tumor are essential for understanding PDT mechanism.

The first objective of present work is to examine the influence of physiological parameters using the recently developed microscopic model based on a single capillary Krogh cylinder model. In addition to Wang's model,¹ the present microscopic Krogh model also incorporates axial and radial diffusion of hemoglobin in the capillary, and oxygen partial pressure is used for both calculations and boundary conditions instead of oxygen concentration. The radial distribution of light fluence rate in a simplified cylindrical geometry tumor with radius of 1 cm is calculated using diffusion theory, which is then applied to the single capillary model to obtain spatial distribution of ¹O₂, ³O₂ and S₀ in the tumor. The second objective is to make a comparison of distributions calculated using both macroscopic and microscopic models.

In this paper, both macroscopic and microscopic models are described, and simulation results of the sensitivity of microscopic parameter and the comparison of two models for photofrin-PDT are presented. In addition, PDT parameters during 2-(1-Hydroxyethyl)-2-Devinylypyropheophorbide-a (HPPH)-PDT are also obtained by using the optimization algorithm to fit the recent experimental data. These preliminary results will also be shown.

2. THEORY AND METHOD

2.1 PDT mechanism

The major photochemical reaction pathways during PDT can be summarized by a set of differential equations as shown in (1) to (6). The variable notations are defined in Table 1.

$$\frac{d[S_0]}{dt} = -\frac{\sigma_c \phi}{h\nu} [S_0] + k_f [S_1] + k_p [T_1] + k_{ot} [T_1] [^3O_2] - k_{os} ([S_0] + \delta) [^1O_2], \quad (1)$$

$$\frac{d[S_1]}{dt} = \frac{\sigma_c \phi}{h\nu} [S_0] - k_f [S_1] - k_{isc} [S_1] - k_{sa} [A] [S_1], \quad (2)$$

$$\frac{d[T_1]}{dt} = k_{isc} [S_1] - k_p [T_1] - k_{ot} [T_1] [^3O_2] - k_{ta} [A] [T_1], \quad (3)$$

$$\frac{d[^3O_2]}{dt} = -S_\Delta k_{ot} [T_1] [^3O_2] + k_d [^1O_2], \quad (4)$$

$$\frac{d[^1O_2]}{dt} = S_\Delta k_{ot} [T_1] [^3O_2] - k_d [^1O_2] - k_{oa} [A] [^1O_2] - k_{os} ([S_0] + \delta) [^1O_2], \quad (5)$$

$$\frac{d[A]}{dt} = -k_{oa} [A] [^1O_2]. \quad (6)$$

In the quasi-steady state, the lifetimes of S_1 , T and 1O_2 are so short compared to the time for bulk variations of sensitizer and oxygen concentration that their instantaneous concentrations can be assumed in dynamic equilibrium. Hence, the time derivatives of ground-state sensitizer S_0 and oxygen 3O_2 can be simplified and expressed as equations (7) and (8), given that the parameters are defined in Table 2. Note that a term Γ_s representing tissue oxygen replenishment source is included in equation (8) in addition to PDT reactions. The details on the derivation can be found elsewhere^{4,6}

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

$$\frac{d[^3O_2]}{dt} + \xi \frac{\phi [S_0] [^3O_2] (1 + \sigma ([S_0] + \delta))}{[^3O_2] + \beta} = \Gamma_s. \quad (8)$$

The differential equation for singlet oxygen $[^1O_2]_{rx}$ can be derived as equation (9) by manipulating the above equations.⁴ The cumulative concentration of reacted singlet oxygen is the integration of equation (9) over time.

$$\frac{d[^1O_2]_{rx}}{dt} - \left(\xi \frac{\phi [S_0] [^3O_2]}{[^3O_2] + \beta} \right) = 0. \quad (9)$$

2.2 Three-dimensional cylinder tumor model

The tumor is simplified using a three-dimensional cylindrical geometry tissue with radius of 1 cm. A linear light source (LS) is placed along the longitudinal axis of the cylinder. The spatial distribution of energy light fluence rate is calculated using diffusion approximation theory, as expressed in (10) where S_L represents power of light source, μ_a is absorption coefficient, and μ'_s is reduced scatter coefficient.

$$\mu_a \phi - \nabla \cdot \left(\frac{1}{3\mu'_s} \nabla \phi \right) = S_L. \quad (10)$$

Initial distributions of both photosensitizer and ground-state oxygen are assumed to be uniform within tumor. For cylindrical symmetric geometry, the distributions of quantities are only radially dependent in this study.

2.3 Microscopic model for PDT

In microscopic model, the tumor has uniformly distributed blood capillaries aligned parallel to the linear light source. The intercapillary distance between two adjacent capillaries is large enough so that each capillary can supply oxygen only to its immediate concentric surrounding tissue. Hence, a Krogh cylinder model can be adopted for a single capillary and its surrounding tissue.³ A three dimensional Krogh model can be simplified as 2-D cylindrical symmetric model illustrated in figure 1. In figure 1, R_c is radius of capillary, R_t is half of intercapillary distance, and L is length of capillary. Table 3 shows values for the benchmark conditions and definitions of the physiological parameters in the microscopic model. Blood flows along the z with a velocity of v_z .

In blood, hemoglobin is normally contained in the red blood cell (RBC), in which hemoglobin saturation and desaturation occur. After oxygen unloads from oxy-hemoglobin, it diffuses into blood through the RBC cell membrane and then into tissue. Here, one assumption in the microscopic model is that no oxygen diffusion barrier is in RBC cell membrane. The distribution of hemoglobin within the capillary is assumed to be uniform. Typical hemoglobin concentration in a red blood cell is $5000 \mu\text{M}$.⁹ If the volume concentration of red blood cells in the capillary, normally referred to as hematocrit, is 50%, total hemoglobin concentration in capillary is $2500 \mu\text{M}$.

In capillaries, the governing oxygen transport equations are described in equations (11) and (12),¹⁰ where oxygen concentration has been expressed using oxygen partial pressure via Henry's law in (13). S is the oxy-hemoglobin saturation relation in equilibrium, which is described using Hill's equation (14) in this study. C_H is the total hemoglobin concentration in the capillary. Γ_{rec} , as expressed in (15),¹⁰ is the reaction of unloading oxygen from oxy-hemoglobin, where k is the dissociation rate constant, and $f(P_{\text{O}_2})$ is oxy-hemoglobin fractional saturation curve which is equal to S for saturation in equilibrium. Γ_{rec} will not be used in the final calculation as it is eliminated by manipulating equations (11) and (12).

$$\alpha_c \frac{\partial P}{\partial t} = \alpha_c D_c \nabla^2 P - \vec{v} \cdot \alpha_c \nabla P + \Gamma_{\text{rec}}, \quad (11)$$

$$C_H \frac{\partial S}{\partial t} = C_H D_H \nabla^2 S - \vec{v} \cdot C_H \nabla S - \Gamma_{\text{rec}}, \quad (12)$$

$$[{}^3\text{O}_2] = \alpha P. \quad (13)$$

$$S = \frac{P^n}{P^n + P_{50}^n}. \quad (14)$$

$$\Gamma_{\text{rec}} = k \times C_H \frac{f(P_{\text{O}_2}) - S}{1 - f(P_{\text{O}_2})}. \quad (15)$$

If the oxygen unloading from hemoglobin is an instantaneous process, equations (11) and (12) can be added to obtain equation (16), and then equation (14) can be substituted into (16). Subsequently, the transient governing equation for oxygen in the capillary can be obtained as equation (17), and the corresponding steady-state equation is (18).

$$\alpha_c \frac{\partial P}{\partial t} + C_H \frac{\partial S}{\partial t} = \alpha_c D_c \nabla^2 P + C_H D_H \nabla^2 S - \vec{v} \cdot \alpha_c \nabla P - \vec{v} \cdot C_H \nabla S \quad (16)$$

$$(\alpha_c + K C_H) \frac{\partial P}{\partial t} = (\alpha_c D_c + K C_H D_H) \nabla^2 P - (v_z \alpha_c + v_z K C_H) \frac{\partial P}{\partial z} + C_H D_H M \left(\left(\frac{\partial P}{\partial r} \right)^2 + \left(\frac{\partial P}{\partial z} \right)^2 \right), \quad (17)$$

$$(\alpha_c D_c + K C_H D_H) \nabla^2 P = (v_z \alpha_c + v_z K C_H) \frac{\partial P}{\partial z} - C_H D_H M \left(\left(\frac{\partial P}{\partial r} \right)^2 + \left(\frac{\partial P}{\partial z} \right)^2 \right), \quad (18)$$

$$\text{where: } M = \frac{n(n-1)P_{50}^n P^{(n-2)} (P^n + P_{50}^n) - 2n^2 P^{(2n-2)} P_{50}^n}{(P^n + P_{50}^n)^3}, \quad (19)$$

$$K = \frac{n P^{n-1} P_{50}^n}{(P^n + P_{50}^n)^2}. \quad (20)$$

In addition, the boundary conditions in the microscopic model are given in equations (21) to (24).

$$P|_{z=0, r \in [0, R_c]} = P_{\text{ts}}, \quad (21)$$

$$\alpha_c D_c \nabla P|_{r=R_c^-} = \alpha_t D_t \nabla P|_{r=R_c^+}, \quad (22)$$

$$P|_{r=R_c^-} = P|_{r=R_c^+}, \quad (23)$$

$$\nabla P|_{\text{others}} = 0. \quad (24)$$

The governing equation for ground-state oxygen in tissue is given by equation (25), where q_0 is the maximum metabolic oxygen consumption rate in the Michaelis-Menten relationship.¹¹ The second term on the left-hand side calculates the PDT consumption as discussed in section 2.1.

$$\frac{\partial [^3\text{O}_2]}{\partial t} + \left(\xi \frac{\phi [S_0] [^3\text{O}_2] (1 + \sigma ([S_0] + \delta))}{[^3\text{O}_2] + \beta} \right) = D_t \nabla^2 [^3\text{O}_2] - q_0 \frac{[^3\text{O}_2]}{[^3\text{O}_2] + \alpha_t P_m}. \quad (25)$$

In the microscopic model, velocity of blood flow is hypothesized to decrease with increased treatment time in order to simulate PDT-induced physiological response. The reduction form is hypothesized as equation (26), where M is the decay constant. The irradiance-dependent parameter B is the ratio of the final to initial velocities, which can set the low limit of blood flow. At time $t = 0$, the initial velocity is v_z . For instance, a B value of 0.3 for 75 mW/cm² means that the blood flow velocity is reduced to 30% of its initial value at this irradiance, which is reasonable consistent with some experimental findings in mice.¹² A value of 0.2 is determined for 150 mW/cm² to make a reasonable agreement between macroscopic and microscopic Krogh models.

$$v = (1 - B) * v_z * e^{-M * t} + B * v_z. \quad (26)$$

2.4 Macroscopic model for PDT

In addition to PDT mechanism described in section 2.1, oxygen replenishment in macroscopic model was hypothesized as shown in equation (27).⁴ Note that this term implicitly includes metabolic consumption of tissue oxygen.

$$\Gamma_s = g \left(1 - \frac{[^3\text{O}_2]}{[^3\text{O}_2](t=0)} \right) \quad (27)$$

With PDT mechanism, the differential equation for ground-state tissue oxygen during PDT in the macroscopic model can be expressed by equation (28).

$$\frac{d [^3\text{O}_2]}{dt} + \left(\xi \frac{\phi [S_0] [^3\text{O}_2] (1 + \sigma ([S_0] + \delta))}{[^3\text{O}_2] + \beta} \right) = g \left(1 - \frac{[^3\text{O}_2]}{[^3\text{O}_2](t=0)} \right) \quad (28)$$

2.5 Initial conditions and simulation procedures

In this work, two models are first compared in the same Krogh cylinder model using parameters given in tables 2 and 3. Note that there is no capillary in the macroscopic model. Then, the spatial and temporal distributions of tissue oxygen in the tumor are calculated by sweeping light fluence rate in the Krogh cylinder.

For the microscopic model, steady-state solution of ground-state oxygen in Krogh cylinder is first calculated using equations (18) and (25) without PDT consumption term to obtain initial conditions before solving transient-state equations. In contrast, a uniform initial oxygen concentration is assumed in the macroscopic model. Physiological parameters in the microscopic model listed in table 3 are chosen in the ranges published in literature so that the mean oxygen concentration at the steady state in the Krogh cylinder is the same as that in the macroscopic model, which is assumed to be 40 mmHg oxygen partial pressure in tissue. Initial concentrations of sensitizers in both models are the same, which is 7 μM . A constant fluence rate is assumed in the Krogh cylinder as the cylinder is considerably smaller in comparison to the whole tumor tissue. Both sensitizer and singlet oxygen are limited to the tissue only by applying the insulation boundary conditions.

In the single capillary Krogh cylinder, temporal distributions of mean tissue oxygen, singlet oxygen, and sensitizer are calculated and compared at fluence rates of 75 and 150 mW/cm^2 for total radiant exposures of 30 J/cm^2 for both macroscopic and microscopic models. In the comparison, the reduction in blood flow velocity is necessary to have reasonable agreement between two models.

Then, one of physiological parameters including C_H , v_z and R_c in the microscopic model is increased or decreased by a factor of two so that the influence of that parameter on temporal distribution of mean oxygen can be examined. Finally, the spatial and temporal distributions ground-state oxygen in the entire tumor are compared for two models.

Photosensitizer Photofrin is chosen for the present simulations because the photochemical parameters listed in Table 2 are well studied. Both models were developed and simulated using COMSOL v4.3a.

2.6 *In vivo* mouse studies for HPPH-PDT

To quantify the PDT parameters for the macroscopic model of HPPH-PDT. *In vivo* mouse experiments were performed. During these experiments, 25 female C3H mice (about 9 weeks old) were intradermally injected with radiation-induced fibrosarcoma (RIF) tumors in the right shoulders. When the measured radius of tumor was about 4 mm, mice were given HPPH (0.25 mg/kg) via tail vein injection. After 24 hours incubation time, mice were irradiated with a 665 nm linear light source (2 cm). The source was placed in one of two parallel catheters inserted into the tumor.

Prior to delivery of light, optical properties of tumor was measured using a point source coupled to a 665 nm diode laser and an isotropic point detector. The fluorescence spectra of HPPH were also measured interstitially prior to PDT using 405 nm excitation light. The spectra were then analyzed using singular value decomposition (SVD) method. The same

procedures were performed for phantom experiments with known HPPH concentration. Calibrating the SVD results from *in vivo* experiments with the data from phantom experiments, the HPPH concentration in the tumor was quantified. Note that the measured optical properties were used to correct the attenuation of fluorescence due to absorption of tumor tissue.¹³

Some preliminary results are shown in this paper, which includes the total radiant exposures of about 50 J/cm at 12, 30 and 75 mW/cm and 20 J/cm at 30 mW/cm. Necrosis radius of each tumor was determined in the same method as described by Wang *et al.*⁴

3. RESULTS AND DISCUSSIONS

3.1 Temporal distributions of PDT parameters in a Krogh cylinder

Figure 2 shows the simulation results of the temporal distributions of volume-averaged $^3\text{O}_2$, $^1\text{O}_2$ and S_0 at fluence rates 75 and 150 mW/cm² using both macroscopic and microscopic models. Total radiant exposure of 30 J/cm² is delivered. In the macroscopic models, the varied maximum oxygen supply rates g were 0.4, 0.7 and 1 $\mu\text{M/s}^4$ in figure 2, and 0.7 $\mu\text{M/s}$ for figures 3, 4, and 5. The results of microscopic model without blood flow reduction produce less oxygen depletion than that macroscopic model does. After examining physiological parameters in the microscopic model within reasonable ranges in the literature data (results are not shown), the reasonable agreement between two models can be reached when blood flow is reduced with treatment time. The magnitude of this reduction is irradiance-dependent, which agrees with some experimental findings.¹² The discrete blood flow reduction at different treatment time was used by Wang *et al.*¹⁴

The sensitivities of volume-averaged ground-state tissue oxygen concentration in a Krogh cylinder to physiological parameters in the microscopic model are also investigated at fluence rates 75 and 150 mW/cm². To better compare results, mean $[^3\text{O}_2]$ is normalized. The results are shown in figures 3. As seen, greater total oxy-hemoglobin concentration, capillary radius and initial blood flow velocity can result in slower and less oxygen depletion. Oxygen depletion is more sensitive to capillary size at the same fluence rate. The sensitivities of oxygen depletion to these parameters are reduced as fluence rate increases because oxygen consumption due to PDT is much greater at higher fluence rate.

Finally, the radial distribution of light fluence rate in the cylindrical tumor is calculated, and then the results are applied to the Krogh cylinder model so that temporal and spatial distribution of $[^3\text{O}_2]$ are obtained for both models and shown in figure 4. Figure 5 shows the comparison at 30 J/cm. At higher light source strength 150 mW/cm, oxygen depletion range expands to greater radial distance than that at 75 mW/cm. One can also see the g value of 0.7 $\mu\text{M/s}$ in the macroscopic model produce better agreement with the microscopic model at 75 mW/cm. This g value may overestimate oxygen concentration at higher irradiance.

3.2 Preliminary results of HPPH-PDT mouse studies

Figure 6(a) shows necrosis radius versus radiant exposure. At about 50 J/cm, the greatest necrosis is observed at the lowest irradiance 12 mW/cm at which less oxygen depletion occurred.

The optimization algorithm was developed by our group and introduced by Wang *et al*⁴ to obtain PDT parameters. The optimization was performed on these preliminary data, and the results of fitting the calculated singlet oxygen spatial profiles to the true necrosis radius are shown in figure 6(b). The obtained parameters are listed in table 4.

4. CONCLUSION

Both macroscopic and microscopic models are summarized in this work. The agreement between two models can be reached in a single Krogh cylinder model with the reduction in blood flow in the microscopic model. The sensitivities of microscopic parameters were studied via comparing normalized volume-averaged tissue oxygen concentration in the Krogh cylinder. Temporal and spatial distributions of tissue oxygen were also investigated for both models and better agreement is found at 75 mW/cm. These results may be helpful to understand influence of physiological parameters such as capillary size in PDT and provide some evaluations of accuracy of macroscopic PDT model.

Acknowledgments

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Figure 1.
A schematic of the Krogh cylinder model.

Figure 2.

Comparison of macroscopic and microscopic models in the Krogh cylinder model.

Figure 3.
Parameter sensitivity tests in the Krogh cylinder model.

Figure 4. Temporal and spatial distributions of $^3\text{O}_2$ for macroscopic and microscopic model
 (a): Macroscopic model at 75 mW/cm; (b): Macroscopic model at 150 mW/cm; (c):
 Microscopic model at 75 mW/cm; (d): Microscopic model at 75 mW/cm.

Figure 5. Spatial distributions of $^3\text{O}_2$ for macroscopic and microscopic model in tumor at 30 J/cm

(a): Light source strength 75 mW/cm; (b) Light source strength 150 mW/cm

Figure 6. HPPH mouse studies results

a). Necrosis radius versus radiant exposure; b). Fitting results of singlet oxygen distribution profiles

Table 1

Definitions of the notations and variables in the photobleaching reaction equations.

Symbol	Definition	Units
$[S_0]$	Ground-state sensitizer	M
$[S_1]$	Singlet excited-state sensitizer	M
$[T_1]$	Triplet excited-state sensitizer	M
$[^3O_2]$	Triplet ground-state oxygen	M
$[^1O_2]$	Singlet excited-state oxygen	M
$[A]$	Molecular substrate	M
k_f	$S_1 \rightarrow S_0$	s^{-1}
k_p	$T_1 \rightarrow S_0$	s^{-1}
k_{isc}	$S_1 \rightarrow T_1$	s^{-1}
k_d	$^1O_2 \rightarrow ^3O_2$	s^{-1}
k_{ot}	Bimolecular rate constant for reaction of 3O_2 with T_1	$M^{-1}s^{-1}$
k_{os}	Bimolecular rate constant for reaction of 1O_2 with S_0	$M^{-1}s^{-1}$
k_{oa}	Bimolecular rate constant for reaction of 1O_2 with A	$M^{-1}s^{-1}$
k_{sa}	Bimolecular rate constant for reaction of S_1 with A	$M^{-1}s^{-1}$
k_{ta}	Bimolecular rate constant for reaction of T_1 with A	$M^{-1}s^{-1}$
ϕ_t	Sensitizer triplet yield	
S	Fraction of T_1 and 3O_2 reactions that produce 1O_2	
σ_c	Absorption cross section of S_0	cm^{-2}
Φ_D	1O_2 quantum yield	
φ	Energy fluence rate at the excitation wavelength	$J\ cm^{-2}$

Table 2PDT parameters.⁴

Parameter	Value	Definition
$\xi(\text{cm}^2\text{mW}^{-1}\text{s}^{-1})$	3.7×10^{-3}	$S_{\Delta} \left(\frac{k_{isc}}{k_{isc}+k_f} \right) \frac{\sigma_c}{h\nu} \frac{k_{oa} [A]/k_d}{k_{oa} [A]/k_d+1}$
$\alpha(\mu\text{M}^{-1})$	2.97×10^{-5}	$k_{os}/k_{oa} [A]$
$\delta(\mu\text{M})$	33	
$\beta(\mu\text{M})$	8.7	k_p/k_{ot}
$\mu'_s(\text{cm}^{-1})$	13.46	optical scattering coefficient
$\mu_a(\text{cm}^{-1})$	1.03	optical absorption coefficient

Table 3

Physiological parameters.

Parameter	Value	Description
R_t	60	radius of cylindrical tissue (μm)
R_c	2.5^7	radius of cylindrical capillary (μm)
D_t	1700^8	$^3\text{O}_2$ Diffusion coefficient in tissue ($\mu\text{m}^2/\text{s}$)
D_c	1240^1	$^3\text{O}_2$ diffusion coefficient in capillary ($\mu\text{m}^2/\text{s}$)
α_t	1.295^8	$^3\text{O}_2$ solubility in tissue ($\mu\text{M mmHg}^{-1}$)
α_c	1.527^8	$^3\text{O}_2$ solubility in plasma ($\mu\text{M mmHg}^{-1}$)
v_z	100^1	Blood flow velocity ($\mu\text{m}/\text{s}$)
P_{50}	26^3	Half maximum hemoglobin saturation pressure (mmHg)
C_H	2500	Total hemoglobin concentration in capillary (μM)
q_0	0.9	$^3\text{O}_2$ maximum metabolic consumption rate ($\mu\text{M}/\text{s}$)
n	2.46^1	Hill constant
P_m	0.386	PO_2 at half maximum oxygen consumption concentration (mmHg)
P_{ts}	100	$^3\text{O}_2$ partial pressure artery (mmHg)
D_H	14^8	Hemoglobin diffusion coefficient in capillary ($\mu\text{m}^2/\text{s}$)
M	0.08	(s^{-1})
B	0.2/0.3	Ratio of final to initial of blood flow velocities at 150/75 mW/cm ²

Table 4

PDT parameters for HPPH.

Parameter	Value
$\xi(\text{cm}^2\text{mW}^{-1}\text{s}^{-1})$	94×10^{-3}
$\sigma(\mu\text{M}^{-1})$	1×10^{-5}
$g(\mu\text{M}/\text{s})$	0.21
$\mu_s'(\text{cm}^{-1})$	5 ± 1
$\mu_a(\text{cm}^{-1})$	0.52 ± 0.09