

# Singlet Oxygen Modeling of BPD Mediated-PDT Using COMSOL

Baochang Liu<sup>1</sup>, Xing Liang<sup>1</sup>, and Timothy C. Zhu<sup>1\*</sup>

<sup>1</sup>Department of Radiation Oncology, School of Medicine, University of Pennsylvania, Philadelphia, PA 19104

\*Corresponding author: Radiation Oncology, University of Pennsylvania, 3400 Civic Blvd/TRC W4, Philadelphia, PA 19104, tzhu@mail.med.upenn.edu

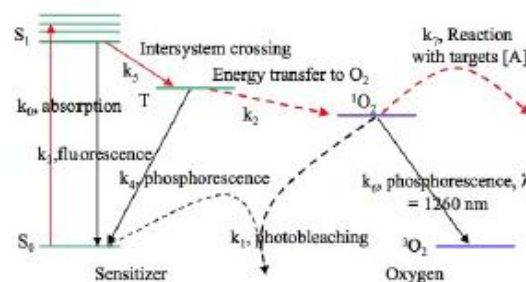
**Abstract:** Singlet oxygen ( $^1\text{O}_2$ ) is the major cytotoxic agent during photodynamic therapy (PDT). A previously developed model that incorporates the diffusion equation for the light transport in tissue and the macroscopic kinetic equations for the generation of the singlet oxygen, can be used to numerically calculate the distance-dependent reacted  $^1\text{O}_2$  using finite-element method (FEM). The formula of reacted  $^1\text{O}_2$  concentration involves 5 photophysiological parameters which can be determined explicitly to predict the generation of reacted  $^1\text{O}_2$ . We have improved an algorithm developed previously to solve the inverse problem to determine the 5 parameters. The optimization is performed using Matlab and dynamically linked with the COMSOL for the forward calculation. The sensitivity of the model parameters to the necrosis depths and treatment conditions are examined. We have shown the results of applying this algorithm on a new photosensitizer drug, BPD, which does not have any published results for these parameters in-vivo. The results are compared with in-vivo experiments performed in mice. In conclusion, our method can successfully extrapolate critical photochemical parameters in vivo for singlet oxygen based dosimetry of PDT.

**Keywords:** Singlet oxygen, BPD-PDT, finite element method, necrosis.

## 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 and molecular oxygen. 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 ( $^1\text{O}_2$ ). Singlet oxygen is considered as the major cytotoxic agent causing biological and therapeutic outcomes in type-II PDT. BPD-PDT uses benzoporphrin derivative monoacid ring A (BPD) which is one of the commonly studied second-generation photosensitizers.



Jablonski Diagram – Type II PDT interaction  
Sensitizer (PS) + light + oxygen ( $^3\text{O}_2$ )  $\rightarrow$  singlet oxygen ( $^1\text{O}_2$ )

**Figure 1.** Jablonski Diagram for type II PDT interaction.

A macroscopic theoretical model has been previously developed by our group to calculate the production of reacted singlet oxygen. The model incorporates the diffusion equation to calculate light fluence distribution in tissue and the macroscopic kinetic equations for updating ground- and singlet-state oxygen. The spatial distribution of reacted  $^1\text{O}_2$  can then be calculated using finite-element method (FEM). An algorithm is recently improved to inversely determine and optimize the five parameters in the equations using experimental results. The optimization is performed in Matlab linked with the COMSOL 4.3.

Additionally, this macroscopic model was modified to incorporate ground-state oxygen diffusion from blood vessel into and within tissue, so the effect of oxygen on the production of singlet oxygen can be investigated on the microscopic level, and the results are compared with these from the macroscopic model.

## 2. Material and Method

### 2.1 Macroscopic singlet oxygen model

The diffusion equation for light fluence rate ( $\phi$ ) in tissue and the differential equations for the concentration of ground-state sensitizer  $[S_0]$ , ground- and singlet-state oxygen ( $[^3O_2]$  and  $[^1O_2]$ , respectively) during PDT are described in equations (1) – (4):

$$\mu_a \phi - \nabla \cdot \left( \frac{1}{3\mu_s'} \nabla \phi \right) = S \quad (1)$$

$$\frac{d[S_0]}{dt} + \left( \xi \sigma \frac{\phi([S_0] + \delta)[^3O_2]}{[^3O_2] + \beta} \right) [S_0] = 0 \quad (2)$$

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

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

where  $\mu_a$ ,  $\mu_s'$ , and  $S$  are the absorption, reduced scattering coefficients at treatment excitation wavelength and source strength in mW/cm, respectively.  $\xi$  is the photochemical oxygen consumption rate per light fluence rate and photosensitizer concentration under the condition of infinite  $^3O_2$  supply and prior to photobleaching.  $\sigma$  is the probability ratio of a  $^1O_2$  molecule reacting with ground-state photosensitizer compared to the  $^1O_2$  molecule reacting with a cellular target.  $\beta$  represents the ratio of the monomolecular decay rate of the triplet state photosensitizer to the bimolecular rate of the triplet photosensitizer quenching by  $^3O_2$ . More details on the definition of these parameters can be found in [1].  $g$  is the maximum oxygen supply rate.

### 2.1 Microscopic singlet oxygen model

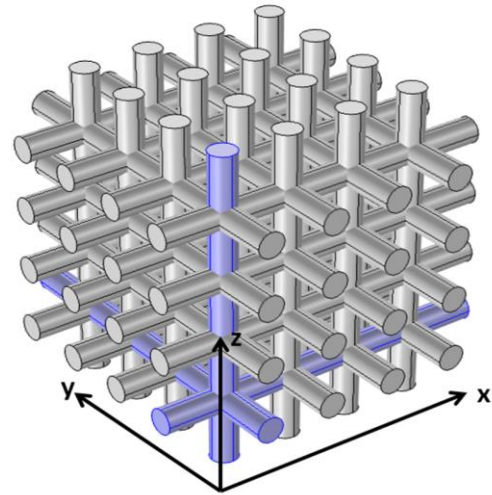
Ground-state tissue oxygen in the macroscopic model is assumed uniform prior to PDT and has spatially invariant perfusion supply with the maximum rate  $g$  from uniformly distributed blood vessels during PDT. In contrast to that, microscopic model incorporates both oxygen diffusion in the capillary and within tissue. Hence, the governing equation for ground-state oxygen in tissue is given by equation (5), and the oxygen transport in the capillary is described by equation (6). These two

equations combined with equations (1), (2) and (4) are used for the calculation.

$$\frac{d[^3O_2]}{dt} + \left( \xi \frac{\phi[S_0]}{[^3O_2] + \beta} \right) [^3O_2] - D\nabla^2[^3O_2] = 0 \quad (5)$$

$$D_c \nabla^2[^3O_2] = \bar{u} \cdot \nabla[^3O_2] \quad (6)$$

A three-dimensional blood vessel network is constructed using uniformly spaced Krogh cylinders representing capillaries. A cubical block consisting of 4 x 4 x 4 cylinders is designed in COMSOL as shown in figure 1, which demonstrates the blood vessel network distribution in the microscopic model.



**Figure 2.** Three-dimensional blood vessel network in the microscopic model.

### 2.3 Experimental procedures

The total number of 13 C3H mice with radiation-induced fibrosarcoma (RIF) tumors were used for animal experiments. Tumors were implanted to 6 – 8 weeks old mice. PDT was performed when tumor diameters were about 8 mm. Mice were euthanized 24 hours post PDT. Tumors were excised for the measurement of the radius of the necrosis area. PDT was performed using linear light source at 690 nm at 3 hours after the application of sensitizer BPD (1 mg/kg). Sectioning and hematoxylin and eosin (H&E) staining was performed post PDT to determine

necrotic depths. The detailed experimental procedure can be found in [1].

The treatments were conducted at different light irradiance ranging from 12 to 150 mW/cm<sup>2</sup>, different exposure time period ranging from 180 to 6000 seconds. In-vivo optical properties of the sample at 690 nm were first measured interstitially with two catheters inserted parallelly into the tumor. The one going through the center was used to deliver excitation light from a 2 mm light point source. The other one contained an isotropic detector measuring the local light fluence rate. Hence, the optical properties could be obtained prior to PDT using a fitting algorithm from the recorded light profiles. [2]

Photosensitizer concentrations were determined from in-vivo fluorescence measurements using 405 nm excitation light. Light was delivered through a side-emitting fiber in the center catheter. The in-vivo BPD fluorescence spectra were obtained using singular value decomposition (SVD) analysis [3], and then compared to the ones measured from phantom with known concentration of sensitizer. Then, optical properties, initial BPD concentration and measured necrotic depths were used for the fitting algorithm to calculate the photophysiological parameters using COMSOL.

### 3. Results and discussions

As mentioned in the previous section, the measured optical properties, necrotic depth and initial BPD concentrations from 13 mice (results not shown) were used to calculate photophysiological parameters in the differential equations (1) – (4).

Figure 3 shows the representative calculated spatial distribution of <sup>1</sup>O<sub>2</sub> and the corresponding necrotic radius measured post PDT. The <sup>1</sup>O<sub>2</sub> concentration near the light source (r=0) is greater than 0.3 mM, The discrepancy among lines is mainly due to the different initial sensitizer concentration among mice.

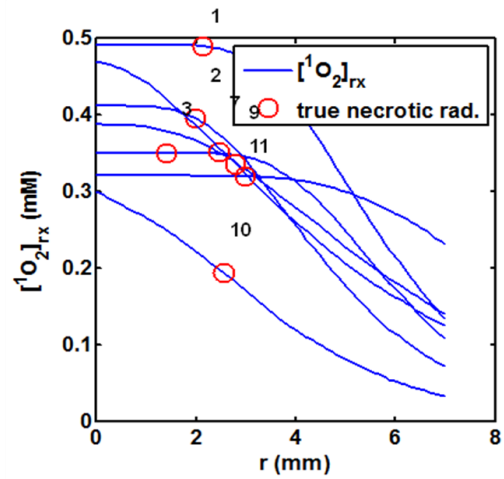


Figure 3. Simulated results of reacted <sup>1</sup>O<sub>2</sub> distribution fitted and measured necrotic radius for all 13 mice.

Figure 4 shows the predicted necrotic radius versus the measured ones. In general, the measured values are slightly less than the prediction. This may be due to the limitation of tumor size and/or the variation among animals. Figure 5 shows one example of tumor with necrosis approaching the boundary of the tumor.

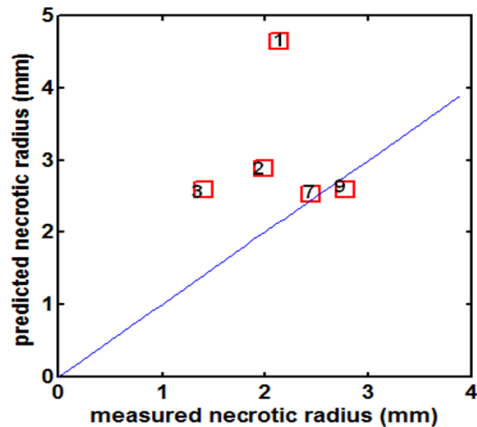
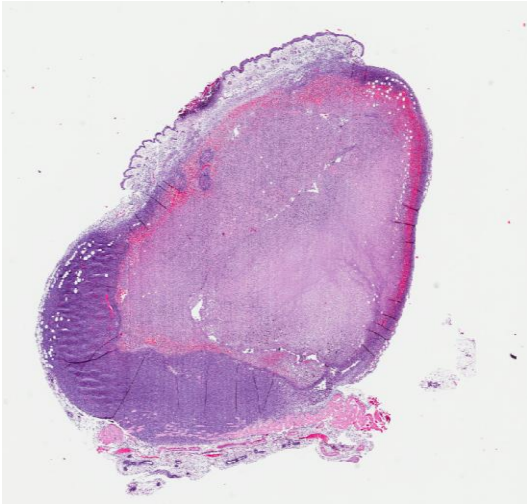


Figure 4. The comparison between predicted and measured necrotic radius.



**Figure 5.** H&E staining of a section from a tumor with necrosis approaching the edge of tumor.

The fitting results are summarized in Table 1. These parameters for BPD in vivo were reported for the first time. The  $\xi$  value for BPD is much greater than that for photofrin. The maximum oxygen supply rate  $g$  for BPD is in the range of that for photofrin. However, the apparent singlet oxygen threshold concentration  $[^1\text{O}_2]_{\text{rx,sh}}$  defined in [1] for BPD is little lower than that for Photofrin.

Parameters	BPD	Photofrin [1]
$\xi$ (cm <sup>2</sup> /s/mW)	$30.26 \times 10^{-3}$	$2.9 \times 10^{-3}$
$\sigma$ (1/ $\mu\text{M}$ )	$2.53 \times 10^{-5}$	$8.41 \times 10^{-5}$
$\beta$ ( $\mu\text{M}$ )	11.9	11.9
$g$ ( $\mu\text{M/s}$ )	0.93	0.71
$[^1\text{O}_2]_{\text{rx,sh}}$ (mM)	$0.35 \pm 0.09$	$0.56 \pm 0.26$

**Table 1.** The fitting results for BPD and comparison with the literature values for Photofrin.

#### 4. References

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#### 5. Acknowledgements

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