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Parameter Optimization for FEM-based modeling of singlet oxygen during PDT

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Objective

- To determine the photochemical parameters necessary for singlet oxygen modeling during PDT using parameters obtained from a microscopic model.

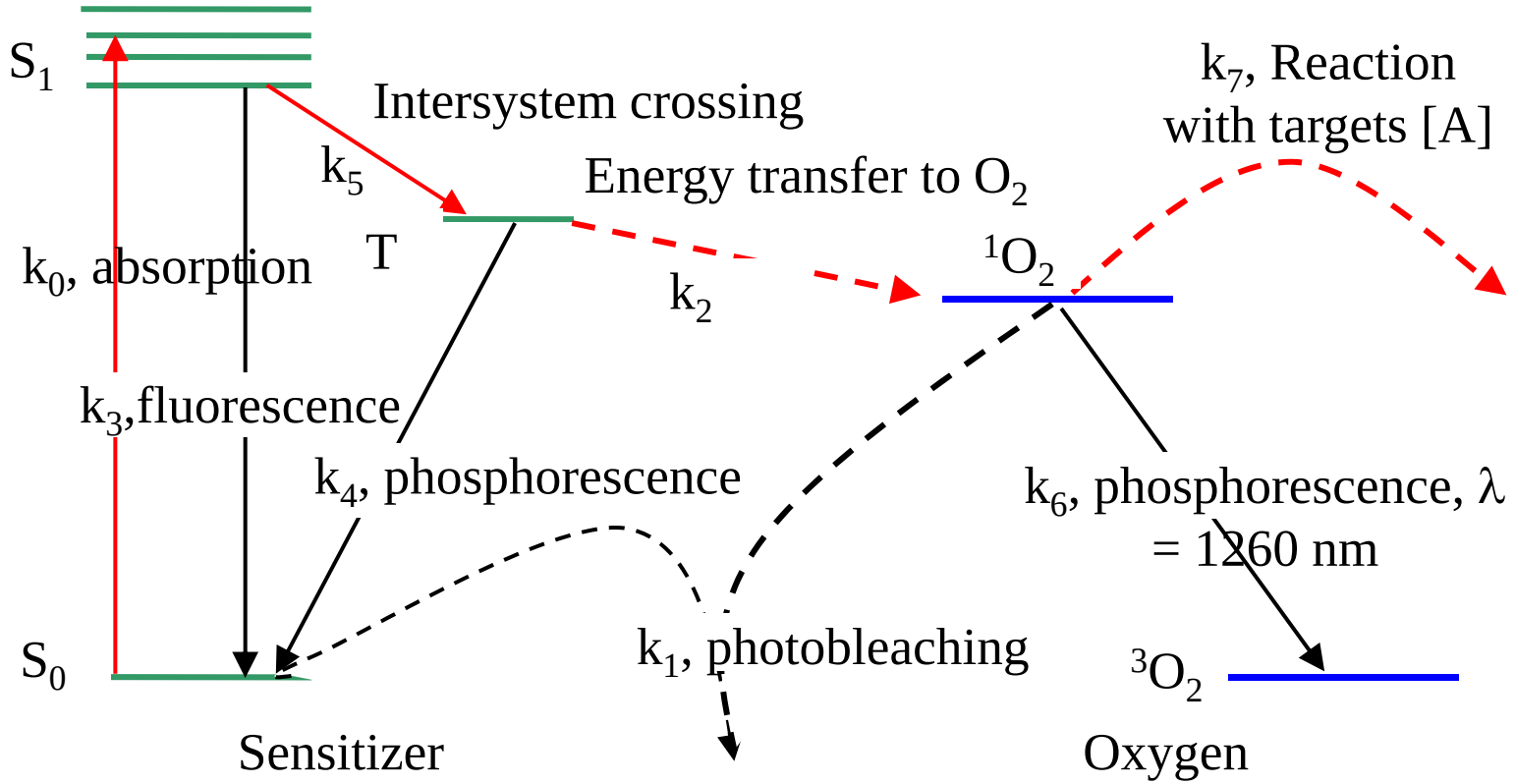
Introduction

- Photodynamic therapy is a new cancer treatment modality using the photochemical reaction of a photosensitizing drug (S), light (ϕ), and oxygen ($^1O_2$).
- Components of PDT
  - Photosensitizer
  - Light
  - Oxygen

Type II photodyanmic interaction

- Singlet oxygen ($^1O_2$) is believed to be the major cytotoxic agent during type II photodynamic therapy (PDT), and the reaction between $^1O_2$ and tumor cells define the treatment efficacy at the most fundamental level.

Jablonski Diagram – Type II



Formulation of the macroscopic problem

Assuming $d[S_1]/dt = 0$, $d[^1O_2]/dt = 0$, $d[T]/dt = 0$.

$$\frac{d[S_0]}{dt} + \gamma\left(\frac{[^3O_2]}{[^3O_2]+\beta}\right)\left(\frac{\kappa}{1+\alpha}\right)\eta\phi[S_0]^2 = 0$$

$$\frac{d[^3O_2]}{dt} + S_\Delta\gamma\frac{[^3O_2]}{[^3O_2]+\beta}\frac{\alpha}{1+\alpha}\eta\phi[S_0] = P$$

$$[^1O_2] = \gamma\frac{[^3O_2]}{[^3O_2]+\beta}\cdot\frac{\kappa}{1+\alpha}\cdot\eta\phi[S_0]$$

$$[S_1] = \frac{\gamma}{k_5}\eta\phi[S_0]$$

$$[T] = \frac{\gamma}{[^3O_2]+\beta}\eta\phi[S_0]$$

$$\nabla(1/3\mu_s')\nabla\phi - \mu_a\phi = S$$

Sym.	Definition	Values
k_5	Rate of S_1 to T	8.0×10^7 1/s
S_Δ	Fraction $[^1O_2]$ from reaction [T] and $[^3O_2]$	0.5
α	$k_7[A]/k_6$	2158
β	k_4/k_2	12.1 μM
γ	$k_5/(k_5+k_3)$	0.8 1/s
κ	k_1/k_6	0.12 1/μM
η	$\varepsilon/h\nu$	0.188 1/s·cm²/mW
P	Oxygen Perfusion rate	1.66×10^{-2} μM/s
$[S_0]_i$	PS concentration	17 μM (= 10mg/kg Photofrin *in-vivo*)
$[^3O_2]_i$	Init. Con.	83 μM
$[S_1]_i$	Init. Con.	0 μM
$[T]_i$	Init. Con.	0 μM
$[^1O_2]_i$	Init. Con.	0 μM

Boundary Conditions

$$\begin{cases} u_1 + 2A\mathbf{n}\cdot\nabla\left(\frac{1}{3\mu_s'}\right)u_1 = 0 \\ \nabla[S_0] = 0 \\ \nabla[^3O_2] = 0 \end{cases}$$

$$[^1O_2]_{rx} = f\int k_7[A][^1O_2]dt = fS_\Delta\gamma\frac{\alpha}{1+\alpha}\int_0^t\frac{[^3O_2]}{[^3O_2]+\beta}\cdot\dot{D}dt$$

Physics Settings in COMSOL – macroscopic model

Governing Equations

$$\begin{cases} \nabla(1/3\mu_s')\nabla u_1 - (\mu_a + \varepsilon \cdot u_2)u_1 = 0 \\ \dfrac{du_2}{dt} + \left(\gamma\eta \cdot \dfrac{u_3}{u_3+\beta} \cdot u_1 \cdot u_2 \cdot \dfrac{\kappa}{1+\alpha}\right)u_2 = 0 \\ \dfrac{du_3}{dt} + \left(S_\Delta \gamma\eta \cdot \dfrac{u_1 \cdot u_2}{u_3+\beta} \cdot \dfrac{\alpha}{1+\alpha}\right)u_3 = P \\ \dfrac{du_4}{dt} = S_\Delta \gamma\eta \cdot \dfrac{u_1 \cdot u_2 \cdot u_3}{u_3+\beta} \cdot \dfrac{\alpha}{1+\alpha} \end{cases}$$

Boundary Conditions

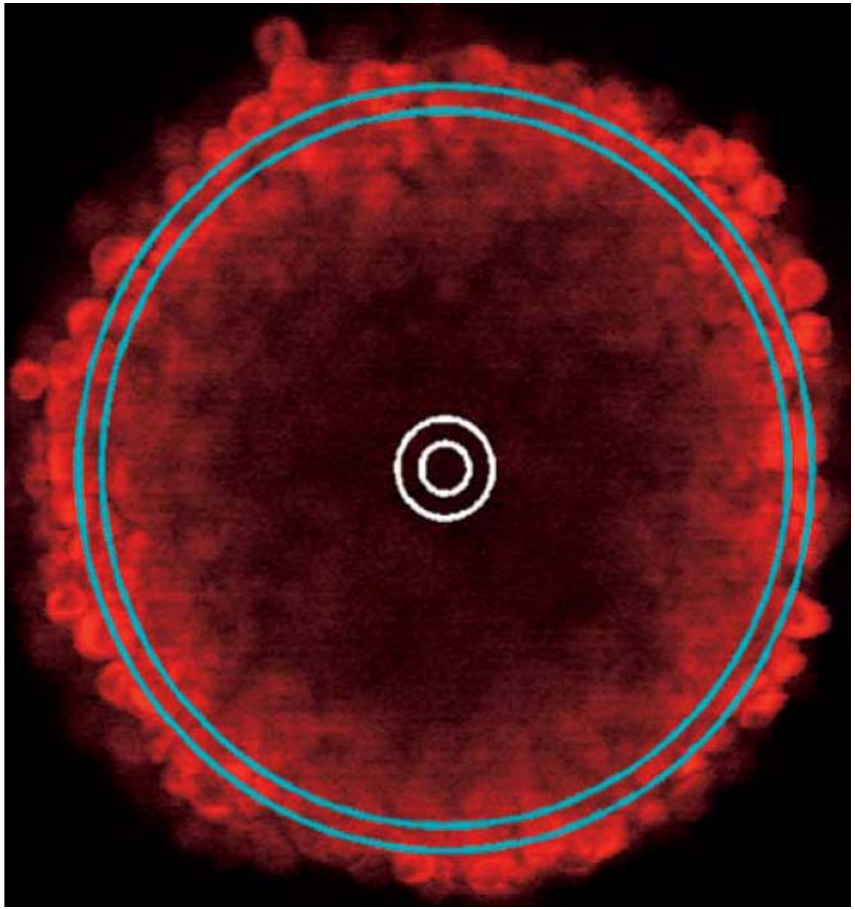
$$\begin{cases} u_1 + 2A\mathbf{n} \cdot \nabla\left(\dfrac{1}{3\mu_s'}\right)u_1 = 0 \\ \nabla u_2 = 0 \\ \nabla u_3 = 0 \end{cases}$$

The variables for ϕ, $[S_0]$, $[^3O_2]$, and $[^1O_2]_{rx}$ are named *u1*, *u2*, *u3*, *u4* . The parameters to be determined are α, β, γ, η, κ. ε can be independently measured. $P = g(1-u_3/u_3(t=0))$

Question?

- How to determine the photochemical parameters that can be used in in-vivo clinical application while most of constants was obtained from in-vitro conditions?
  - Applying the macroscopic model to an in-vivo microscopic model – the spheroid model to obtain photochemical parameters (present work)
  - Apply the macroscopic model to an in-vivo animal model - necrosis study of mouse (future work)

Photofrin-sensitized spheroid model



- Oxygen diffusion is well defined and measurable.
- Photosensitizer distribution is uniform.
- Light fluence distribution is uniform.
- Nichols and Foster, Phys. Med. Bio. 39 2161-2181 (1994)
- I. Georgakoudi, MG Nichols, TH Foster, Photochem. Photobiol. **65**, 135–144 (1997).

Physics Settings in COMSOL – microscopic model

Governing Equations

$$\nabla(1/3\mu_s')\nabla u_1 - (\mu_a + \varepsilon \cdot u_2)u_1 = 0$$

$$\frac{du_2}{dt} + \left(\gamma\eta \cdot \frac{u_3}{u_3+\beta} \cdot u_1 \cdot u_2 \cdot \frac{\kappa}{1+\alpha}\right)u_2 = 0$$

$$\frac{du_3}{dt} + \left(S_\Delta \gamma\eta \frac{\alpha}{1+\alpha}\frac{u_1 u_2}{u_3+\beta}\right) - D_{oxy}\nabla^2 u_3 = -\Gamma_{met}$$

$$\frac{du_4}{dt} = S_\Delta \gamma\eta \cdot \frac{u_1 \cdot u_2 \cdot u_3}{u_3+\beta} \cdot \frac{\alpha}{1+\alpha}$$

Boundary Conditions

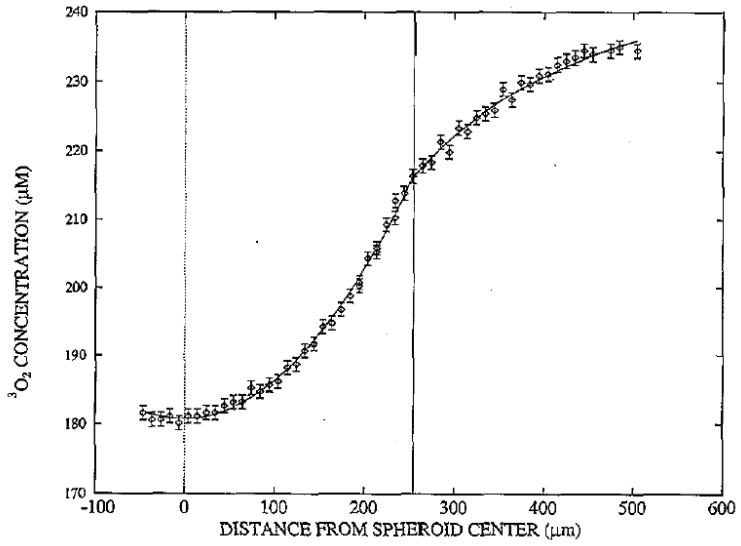
$$u_1 + 2A\mathbf{n} \cdot \nabla\left(\frac{1}{3\mu_s'}\right)u_1 = 0$$

$$\nabla u_2 = 0$$

$$\nabla u_3 = 0$$

The variables for ϕ, $[S_0]$, $[^3O_2]$, and $[^1O_2]_{rx}$ are named *u1*, *u2*, *u3*, *u4* . Same photochemical parameters α, β, γ, η, κ. ε and D_{oxy} can be independently measured. $\Gamma_{met} = \Gamma_{met}^{\max}\frac{u_3}{u_3 + k_{50}}$, k_{50} = 0.5 μM.

Boundary condition for oxygen in spheroid without PDT consumption



Phys Med Biol 39 (1994) 2161-2181

- Steady-state electrode measurement matches the boundary condition established for $^3O_2$:

$$0 \le r \le R_s$$

$$u_3(r, t=0) = C_m - \left(\frac{\Gamma_{met}^{\max} R_s^{\,3}}{3D_{oxy2}}\right)\left(\frac{1}{R_s} - \frac{1}{R_d}\right) - \left(\frac{\Gamma_{met}^{\max}}{6D_{oxy}}\right)\left(R_s^{\,2} - r^2\right)$$

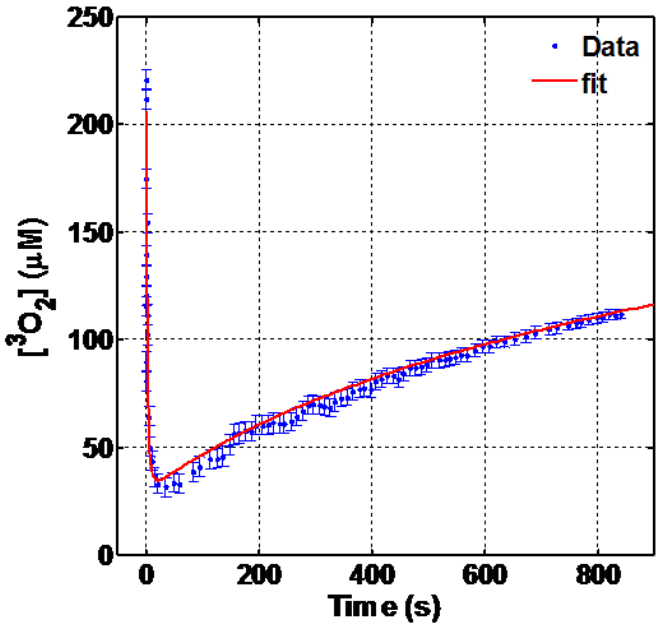
$$R_s \le r \le R_d$$

$$u_3(r, t=0) = C_m - \left(\frac{\Gamma_{met}^{\max} R_s^{\,3}}{3D_{oxy2}}\right)\left(\frac{1}{r} - \frac{1}{R_d}\right)$$

- Oxygen consumption follows a diffusion equation.

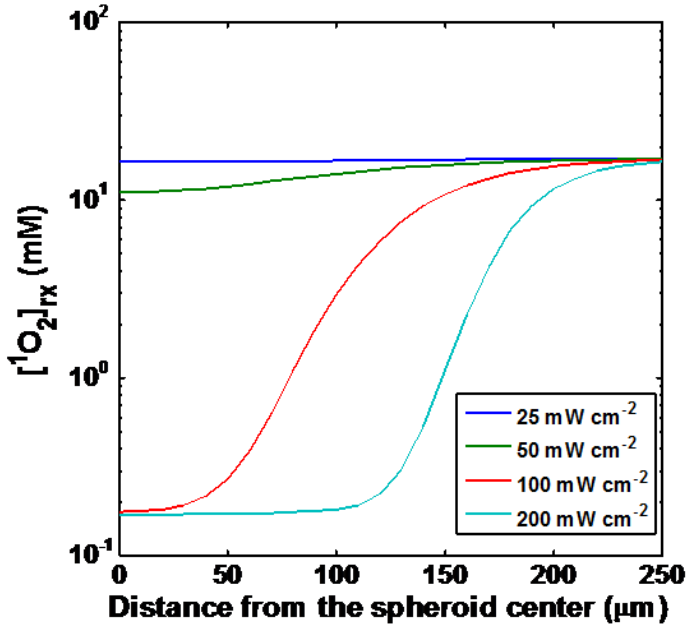
$$\frac{du_3}{dt} - D_{oxy2}\left(\frac{2}{r}\frac{\partial u_3}{\partial r} + \frac{\partial^2 u_3}{\partial r^2}\right) = 0$$

Fitting results – establishing microscopic model in COMSOL



- The comparison between the [$^3O_2$] (μM) calculated by microscopic model and experimentally measured oxygen data for Photofrin-PDT 514 nm and 50 mW/cm^2 irradiation at spheroid edge. The computed result was calculated at r = 230 μm.
- Original data obtained from I. Georgakoudi, et al, Photochem. Photobiol. **65**, 135–144 (1997).
- Same parameters as the above reference.

Fitting results – establishing microscopic model in COMSOL



COMSOL result

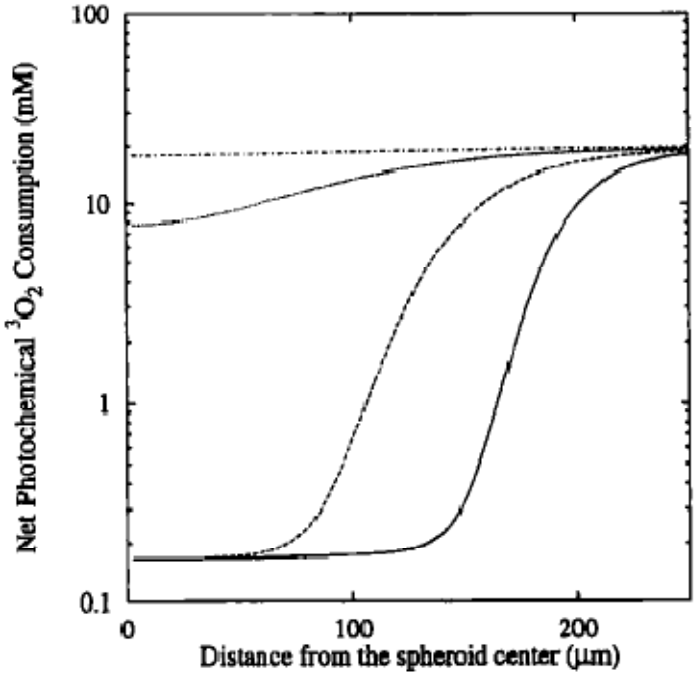
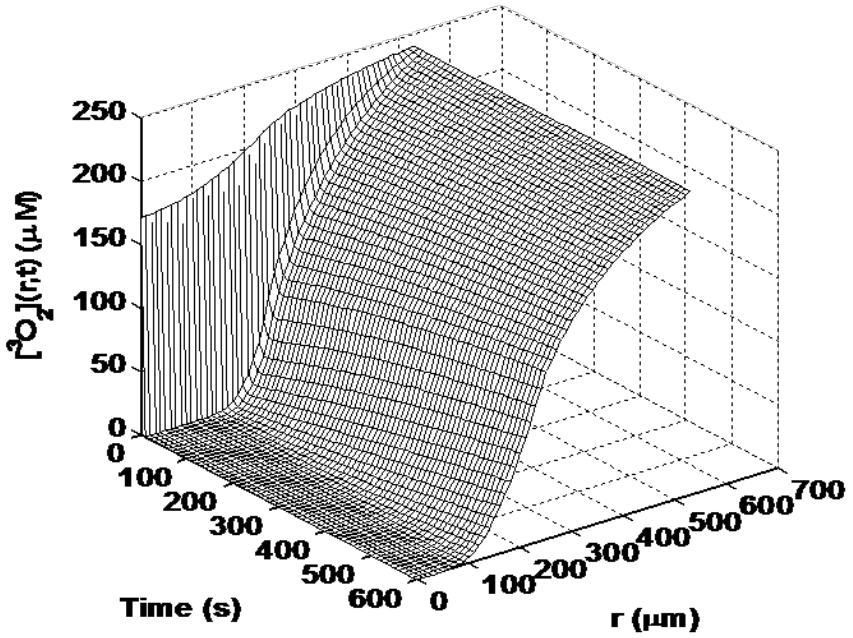


Fig. 5 from Ref. [1]

[1]. I. Georgakoudi, et al, Photochem. Photobiol. **65**, 135–144 (1997).

Fitting results – establishing microscopic model in COMSOL



COMSOL result

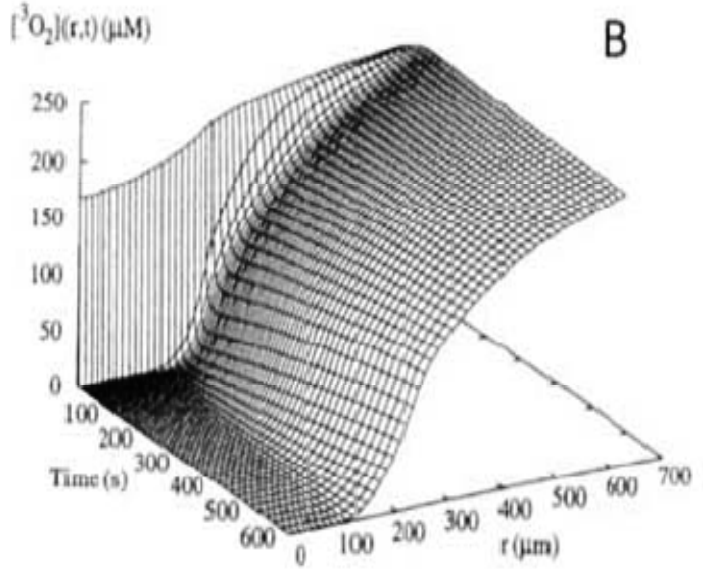
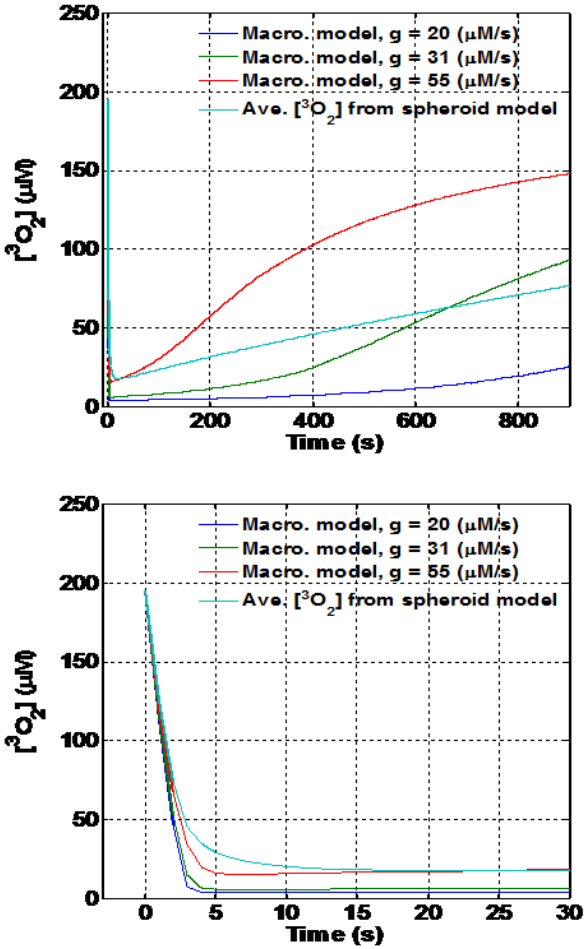


Fig. 3b from Ref. [1]

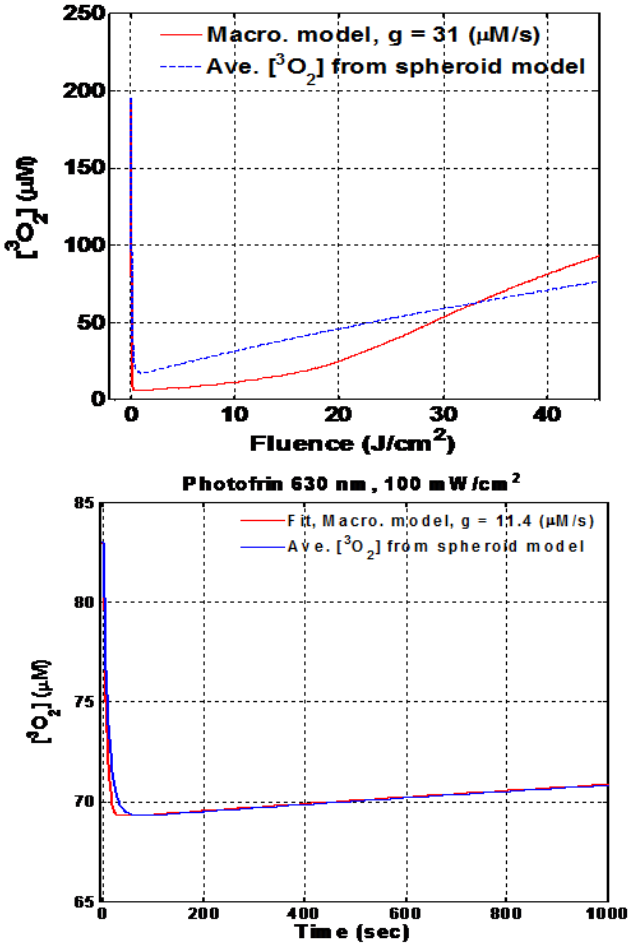
[1]. I. Georgakoudi, et al, Photochem. Photobiol. **65**, 135–144 (1997).

Fitting results – determining oxygen perfusion coefficient, *g*.



- Fitting macroscopic model to the average oxygen from spheroid model.
- $P = g(1-u_3/u_3(t=0))$
- The best fit value is g = *31 μM/s.*
- The form for *P* may need further improvement.

Fitting results – determining oxygen perfusion coefficient, *g*.



- $P = g(1-u_3/u_3(t=0))$
- The best fit value of *g* changes with initial oxygenation conditions and oxygen consumption.
- Spheroid model: $u_3(t=0)$ = 240 μM, $u_2(t=0)$ = 170 μM.
- In-vivo human clinical case: $u_3(t=0)$ = 83 μM, $u_2(t=0)$ = 6 μM.

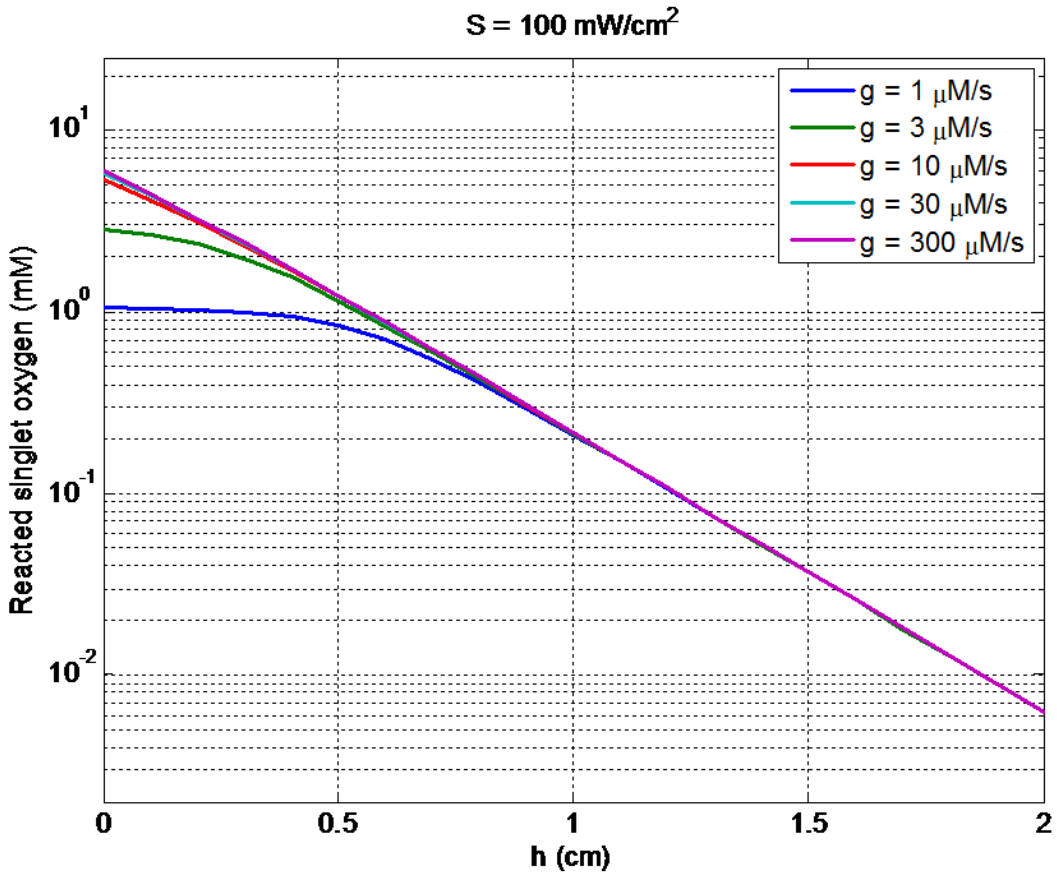
Comparison of fitting photochemical parameters for photofrin at 630 nm.

	Definition	New values	Old values
α	$k7[A]/k6$	**0.85**	**2158**
β	$k4/k2$	11.9 μM	12.1 μM
γ	$k5/(k5+k3)$	0.80	0.8
κ	$k1/k6$	**4.8×10^{-5}** 1/μM	**0.12** 1/μM
η	$\varepsilon/h\nu$	**0.0188** 1/s·cm^2/mW	**0.188** 1/s·cm^2/mW
$\beta_{PDT}/[S]_0$	$S_\Delta\gamma\eta\alpha/(1+\alpha)$	**0.0037** 1/s·cm^2/mW	**0.075** 1/s·cm^2/mW
g	Oxygen Perfusion rate	**31** μM/s	**1.66×10^{-2} μM/s**

In-vivo mice experiment to determine photochemical parameters

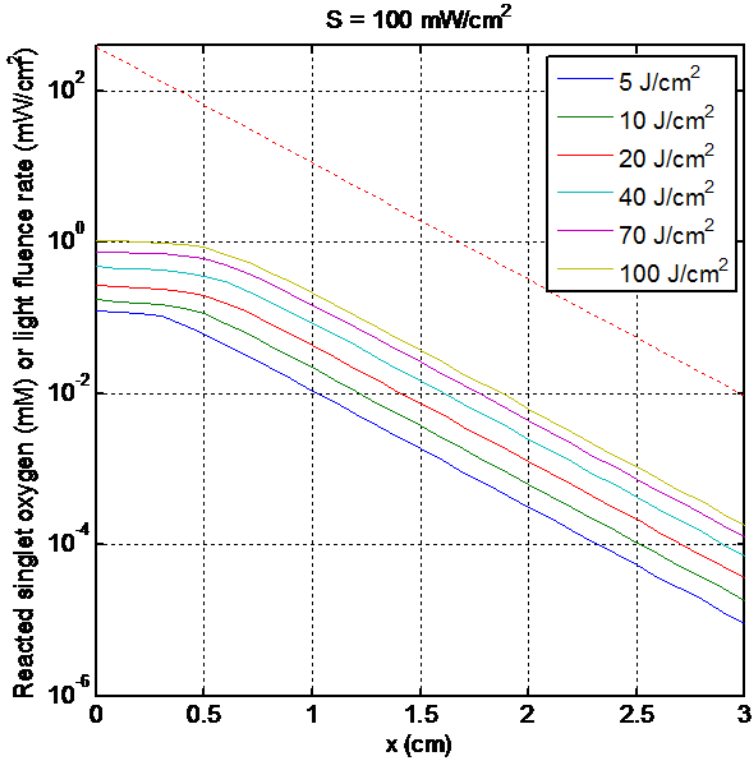
- Surface irradiation on mice with known optical properties
- Photofrin 5 mg/kg, fluence rate 5 – 100 mW/cm^2.
- Necrosis depth examination

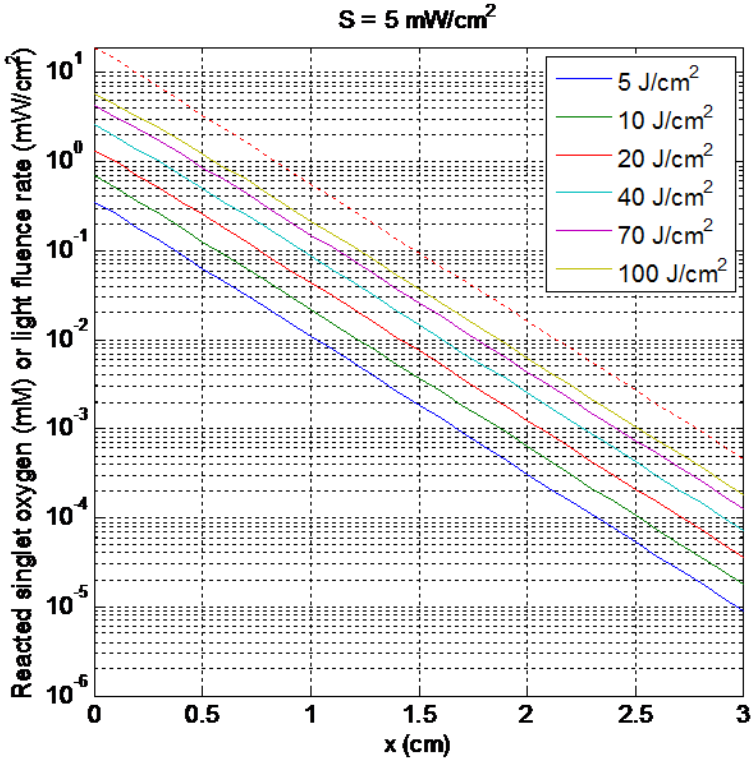
Surface irradiation predictions: $[^1O_2]_{rx}$ *vs.* depth for different oxygen perfusion coefficient *g*



Photofrin-PDT 630 nm,
Source strength 100 mW/cm^2
$[S_0](t = 0) = 6$ μM,
$[^3O_2](t = 0) = 83$ μM

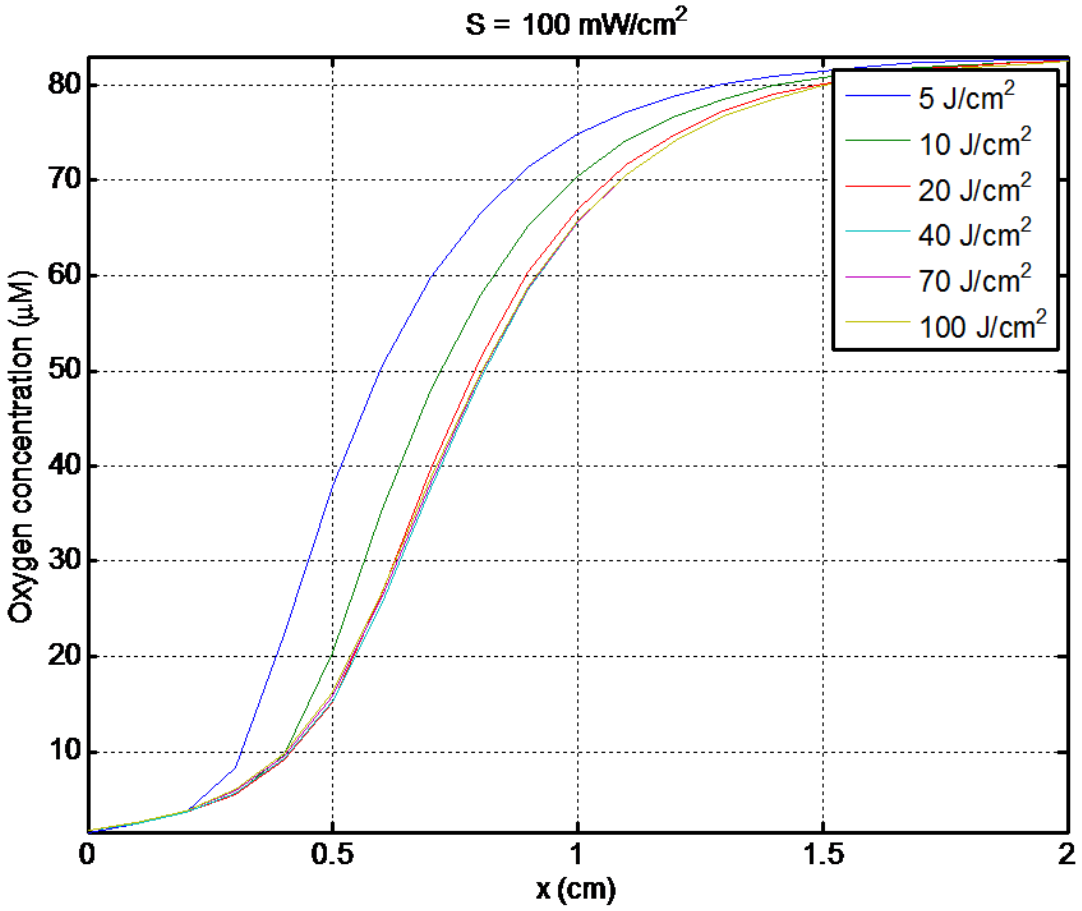
Surface irradiation predictions: $[^1O_2]_{rx}$ *vs.* depth for different total fluence and fluence rate.





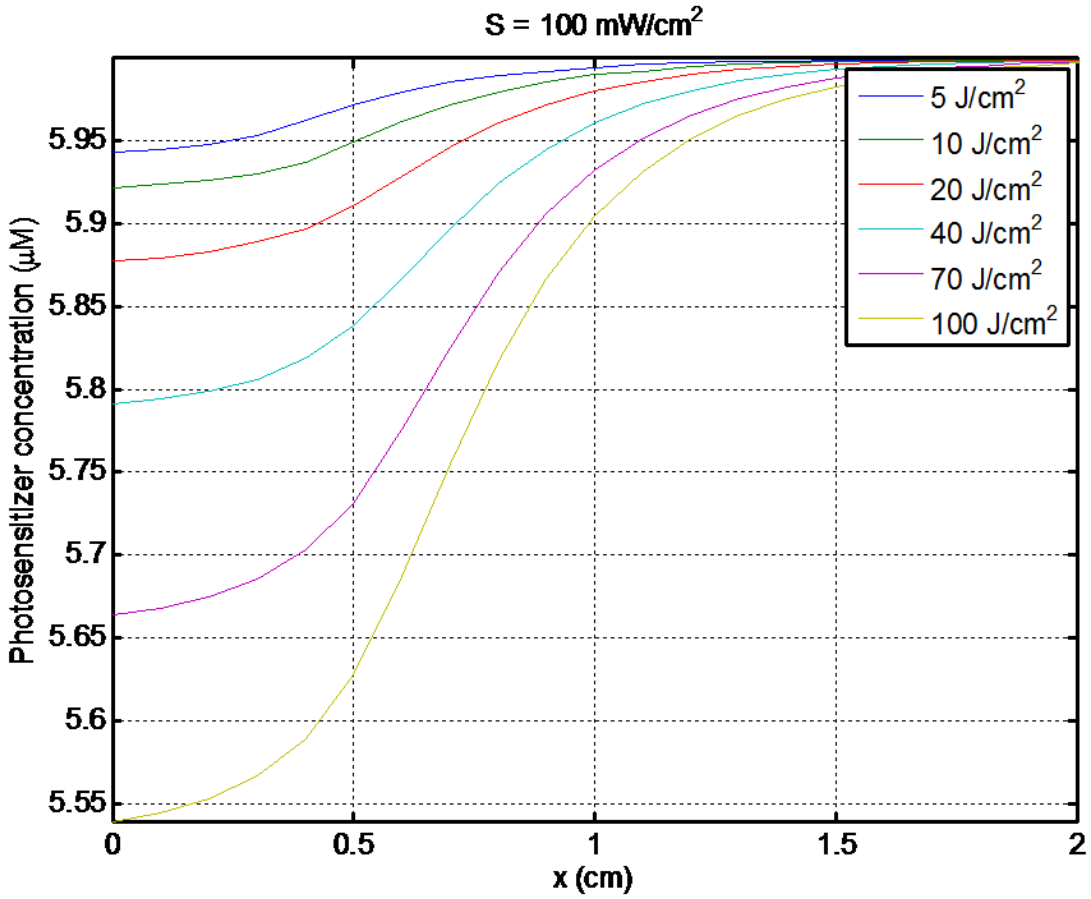
Photofrin-PDT 630 nm, g = 1 μM/s
$[S_0](t = 0) = 6$ μM, $[^3O_2](t = 0) = 83$ μM

Surface irradiation predictions: $[^3O_2]$ *vs.* depth for different total fluence.



Photofrin-PDT 630 nm,
Source strength 100 mW/cm^2
$[S_0](t = 0) = 6$ μM,
$[^3O_2](t = 0) = 83$ μM

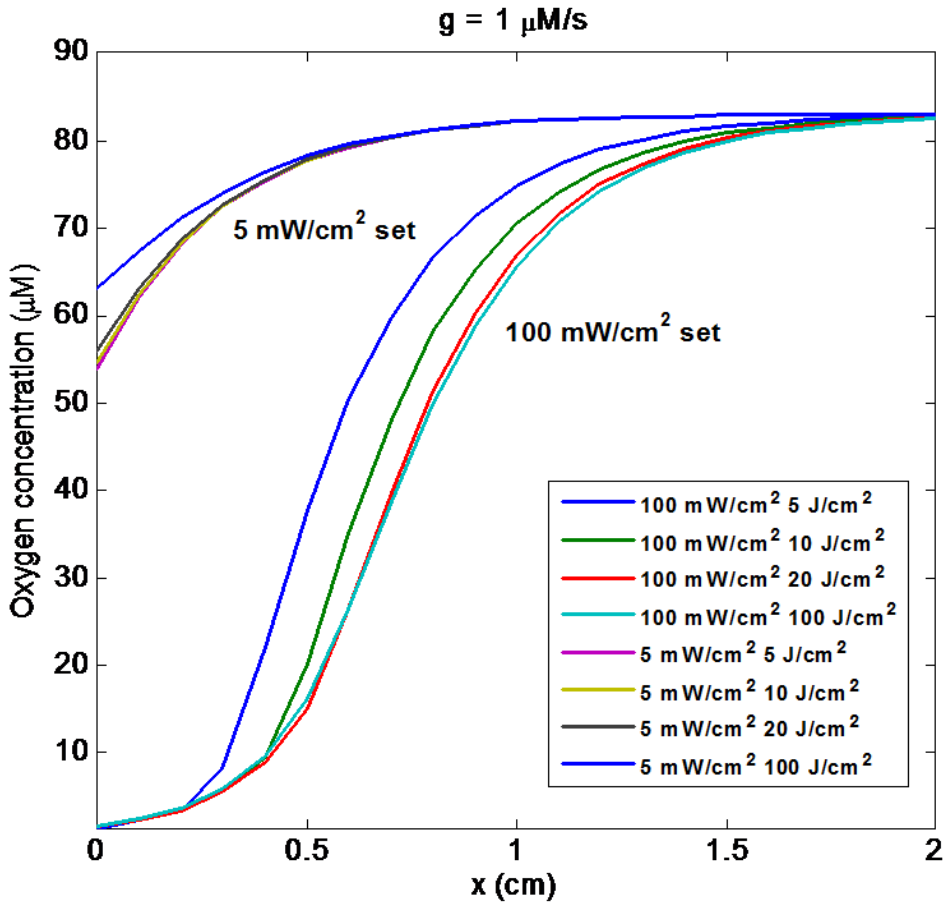
Surface irradiation predictions: [S] *vs.* depth for different total fluence.



Photofrin-PDT 630 nm,
Source strength 100 mW/cm^2
$[S_0](t = 0) = 6\ \mu M$,
$[^3O_2](t = 0) = 83\ \mu M$

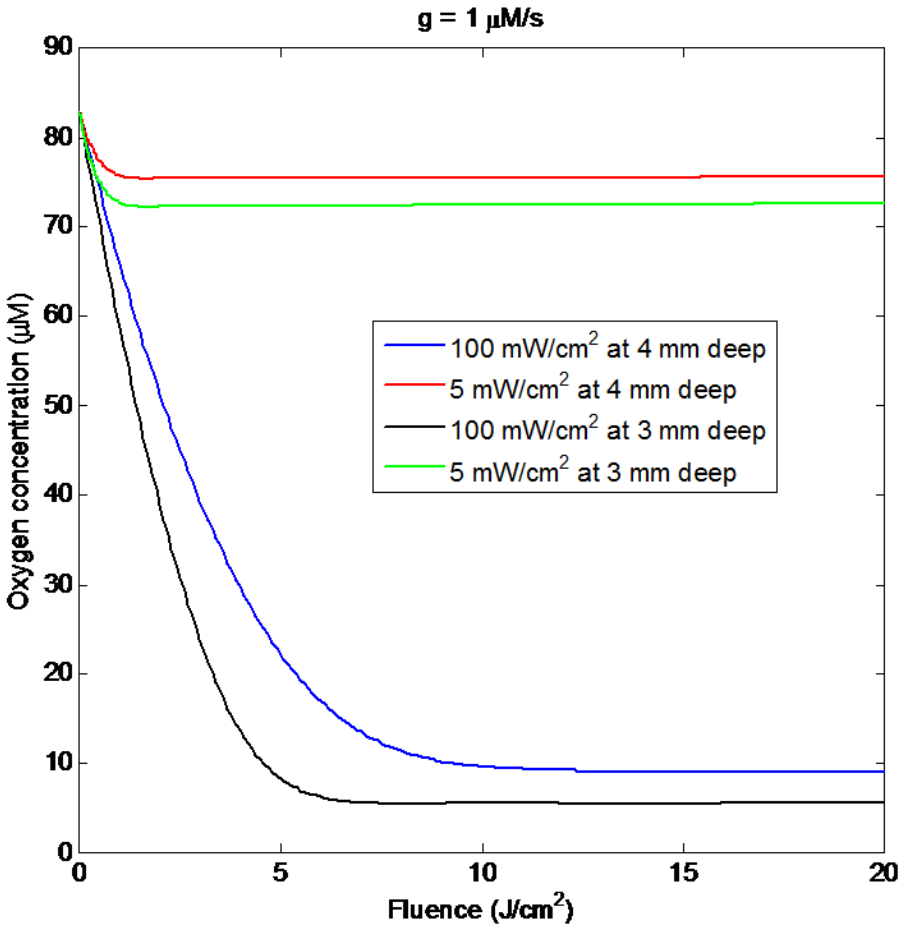
Planar source

Surface irradiation predictions: $[^3O_2]$ *vs.* depth for different incident fluence rates.



Photofrin-PDT 630 nm,
$[S_0](t = 0) = 6$ μM,
$[^3O_2](t = 0) = 83$ μM

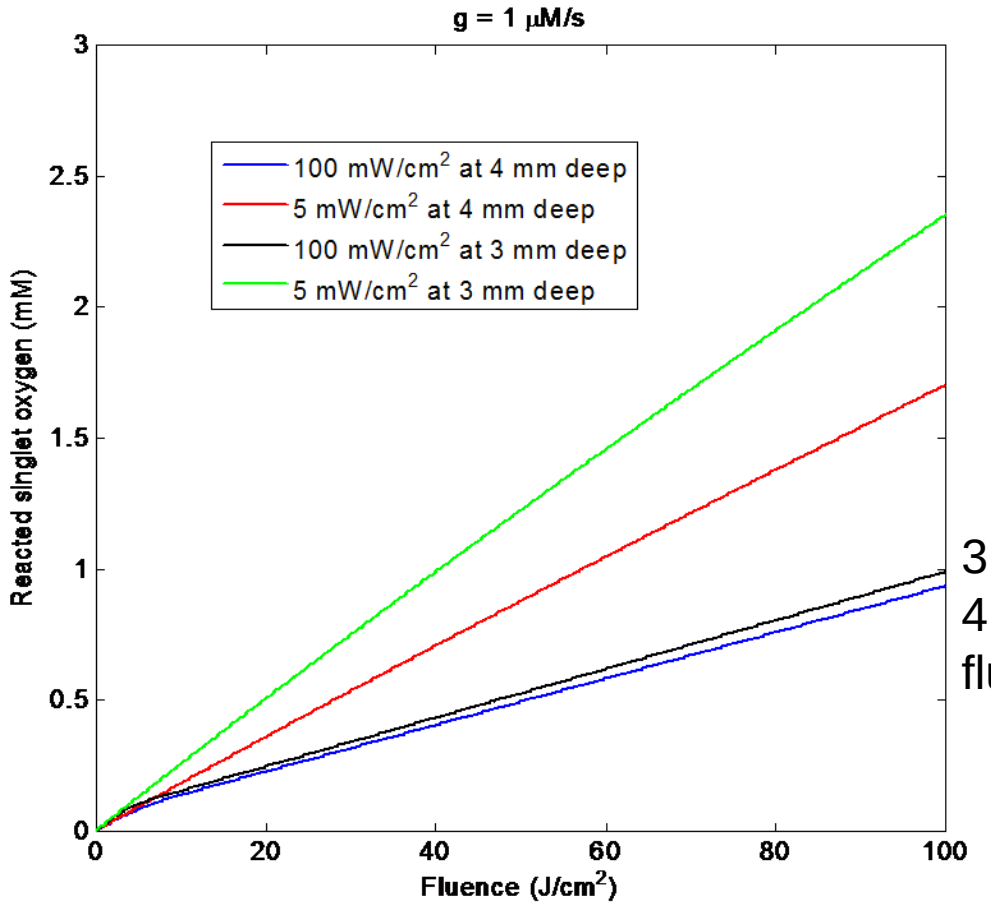
Surface irradiation predictions: $[^3O_2]$ *vs.* fluence for different fluence rate.



Photofrin-PDT 630 nm,
$[S_0](t = 0) = 6$ µM,
$[^3O_2](t = 0) = 83$ µM

3 mm deep is the bottom of tumor
4 mm is the depth where
fluence rate equal to source strength

Surface irradiation predictions: [1O2] *vs.* fluence for different fluence rate.



Photofrin-PDT 630 nm,
$[S_0](t = 0) = 6\ \mu M$,
$[^3O_2](t = 0) = 83\ \mu M$

3 mm deep is the bottom of tumor
4 mm is the depth where
fluence rate equal to source strength

Conclusions

- We have developed a macroscopic model and compared the results with a microscopic model to determine the photochemical parameters to match the spheroid experimental results.
- The resulting parameters are substantially different from the photochemical parameters obtained from in-vitro experiments.
- The macroscopic model with the appropriate constants can predict variation of tissue necrosis as a function of light fluence rate for surface irradiation.

Future works

- Match the photochemical parameters from in-vivo mice study for the specific photosensitizer of interest and at the oxygen environment similar to clinical cases.
- Improve the oxygen perfusion function for the macroscopic model.
- Incorporation of photosensitizer distribution in the macroscopic model.

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