Singlet Oxygen Modeling of BPD Mediated-PDT Using COMSOL

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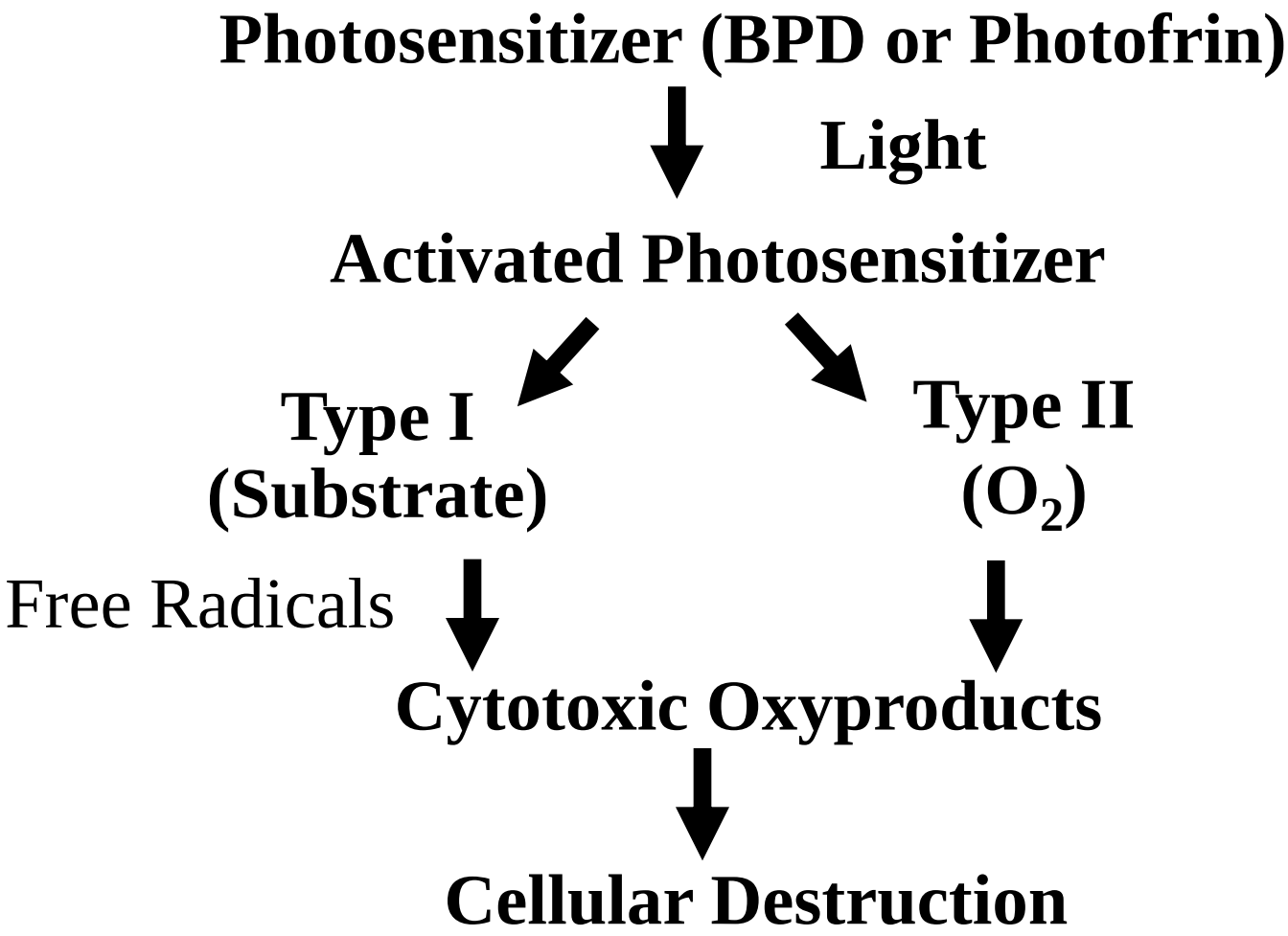
Outline

- Introduction
- Theory for PDT dosimetry model
- Experiments and Optimization results
- Comparison between Photochemical parameters between photofrin and BPD
- Conclusions

- **Introduction**

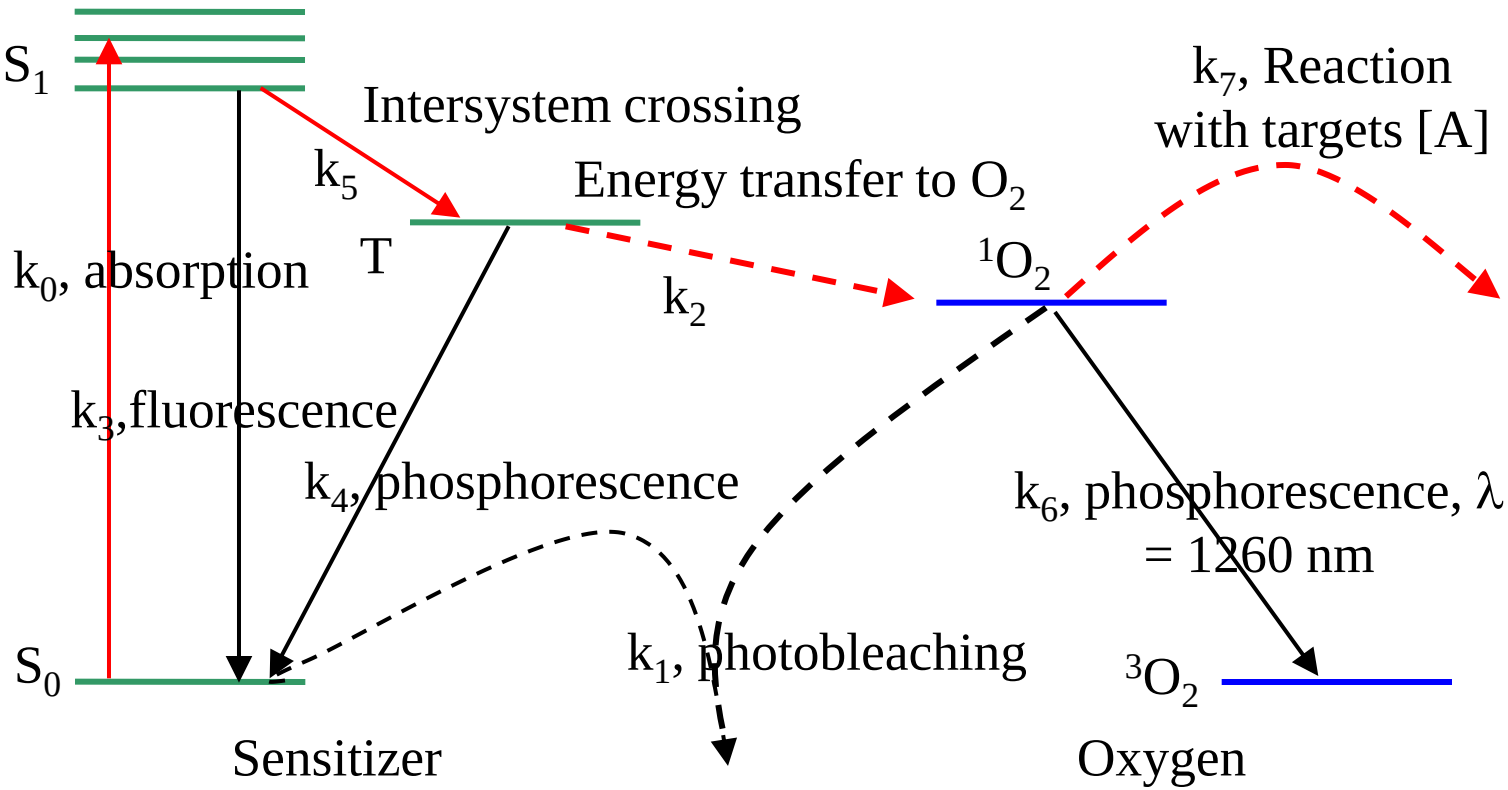
Mechanics of Action



Motivation – why?

- **PDT efficacy depends on three parameters: light, drug, and oxygen**
- **Current state of art for human PDT trial:**
  - PDT dose, the product of drug concentration and light fluence, is quantified.
  - The effect of light fluence rate is not accounted for.
- **Apparent reacted singlet oxygen, $[^1O_2]_{rx}$, can be introduced for clinical PDT to account for all three components including light fluence rate effect. However, sensitizer-specific photochemical parameters are unknown.**

Introduction



- **Jablonski Diagram – Type II PDT interaction**
- **Sensitizer (PS) + light + oxygen ($^3O_2$) → singlet oxygen ($^1O_2$)**

Introduction

Apparent reacted singlet oxygen $[^1O_2]_{rx}$ was introduced as a PDT dosimetry quantity to better predict the PDT treatment outcome than PDT dose

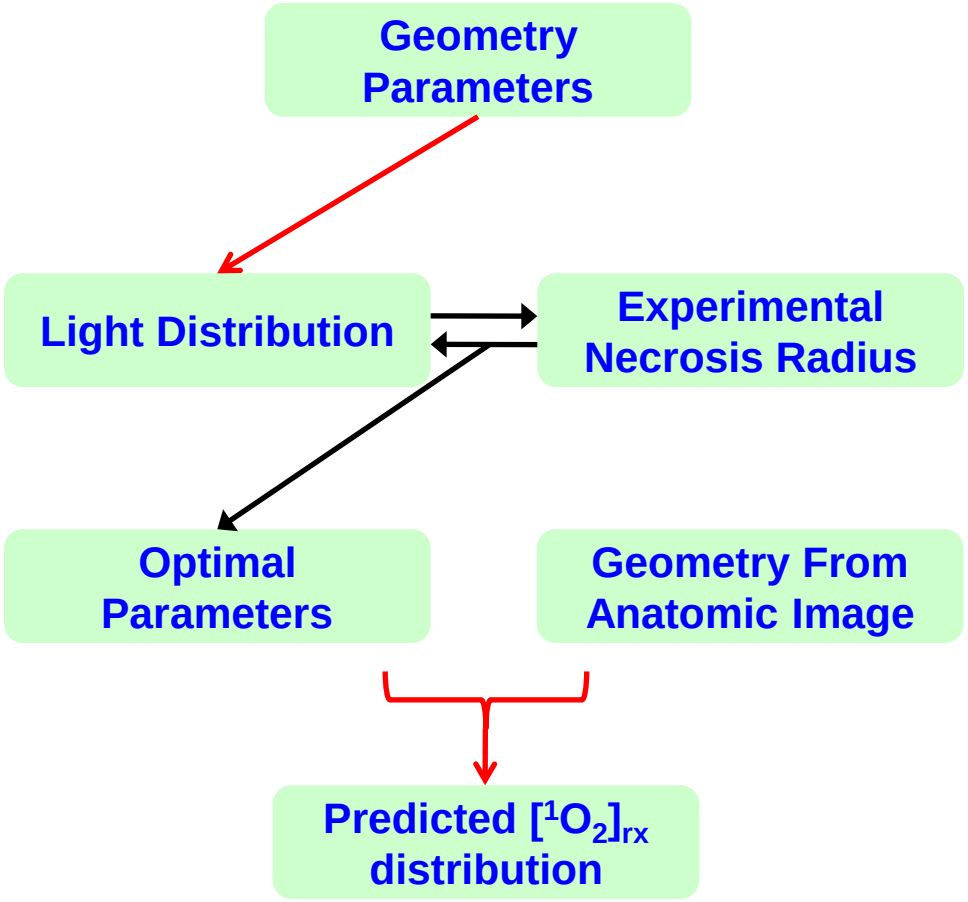
$$[^1O_2]_{rx} = \int_0^T \xi \frac{\phi[S_0][^3O_2]}{[^3O_2]+\beta} dt$$

Introduction

Apparent reacted singlet oxygen $[^1O_2]_{rx}$ was introduced as a PDT dosimetry quantity to better predict the PDT treatment outcome than PDT dose

By COMSOL

By COMSOL
+ MATLAB



Flow chart for PDT photophysiological parameter optimization and PDT dosimetry

- **Theory for PDT dosimetry model**

Theory for PDT dosimetry model

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

S: source term, Fluence rate: ϕ

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

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

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

g is the maximum oxygen perfusion rate where there is no oxygen gradient

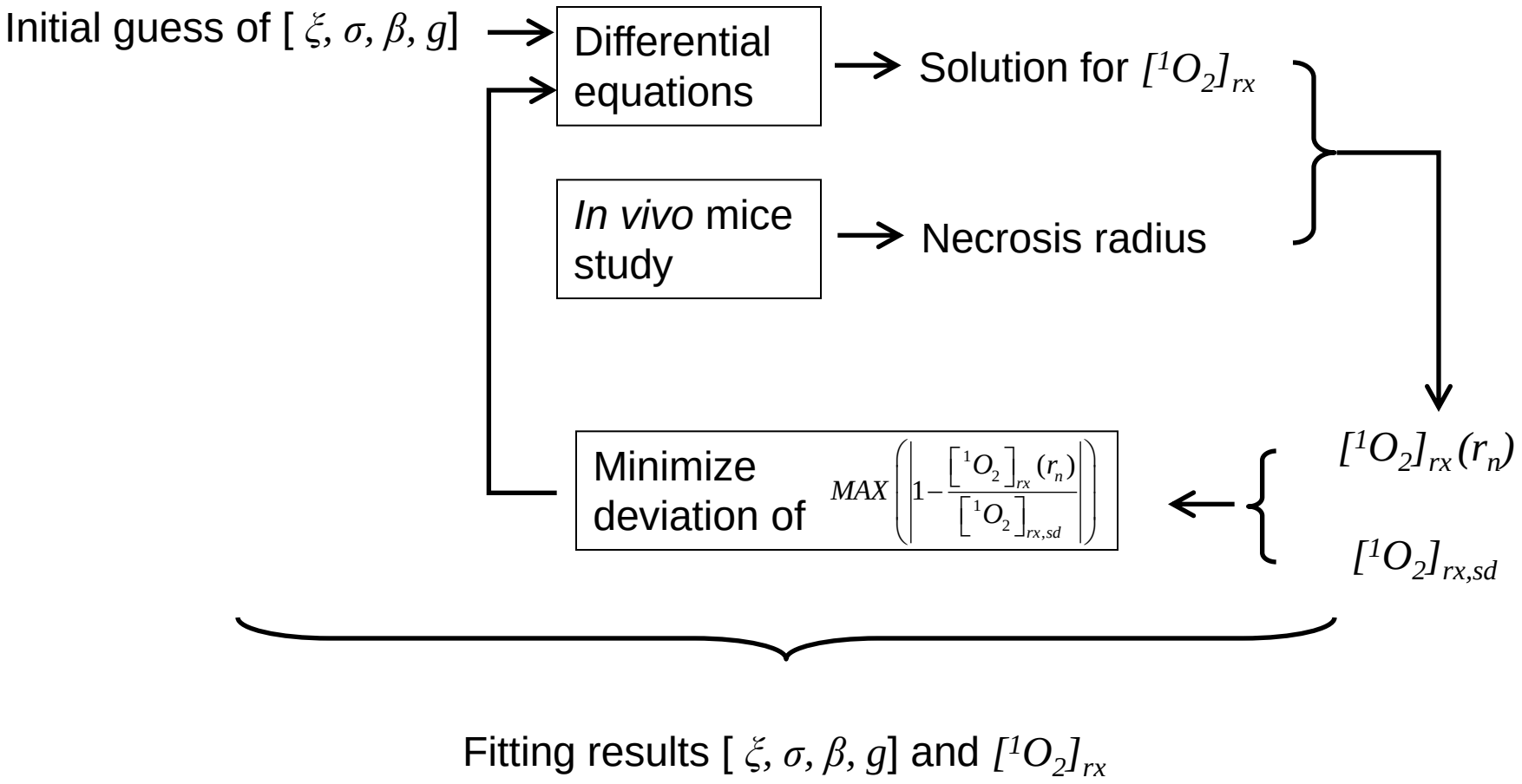
$\beta = k4/k2$ can be treated as constant.

$\xi = S_\Delta k5/(k3+k5)\varepsilon/h\nu/(k6/k7[A]+1)$

$\sigma = k1/(k7[A])$

$[S_0](t)$, $[^3O_2](t)$, and $[^1O_2]_{rx}(t)$ Equs. are function of β, σ, ξ, and g, and initial conditions of $[^3O_2]$ and $[S_0]$.

Theory for optimization model



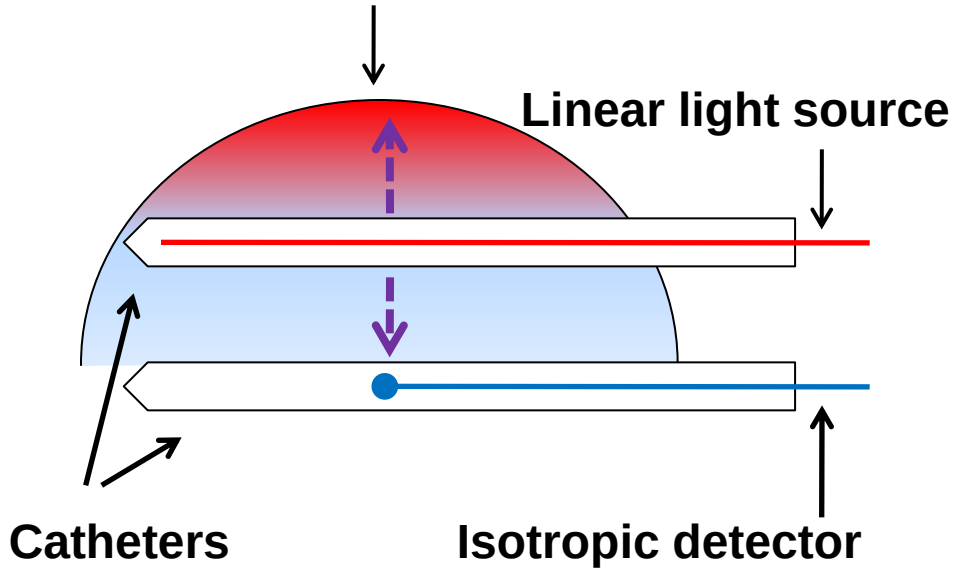
- **Experiments and Optimization Results**

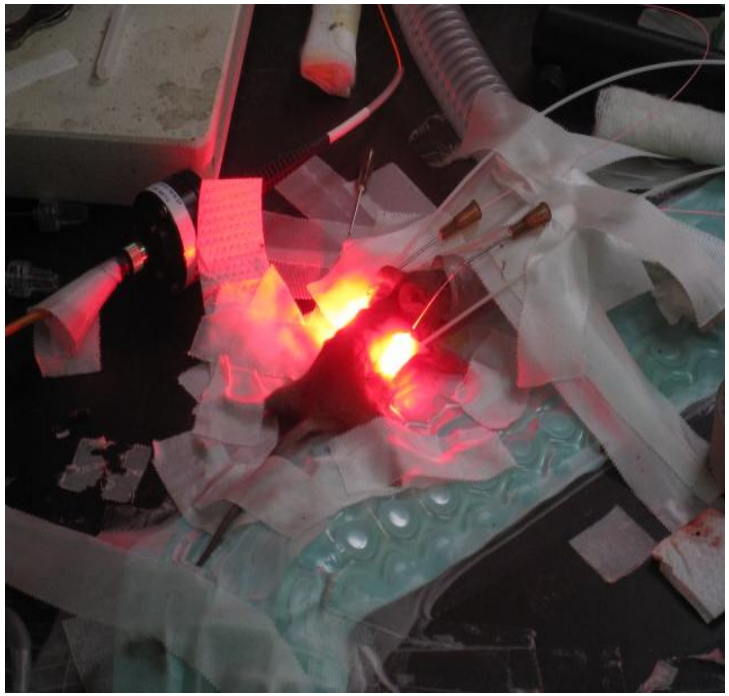
Experimental details

Interstitial treatment is designed to induce the necrosis distance which is expected to be related with the computed $[^1O_2]_{rx}$ profile.

BPD, 1 mg/kg, 3 hours, 690 nm light

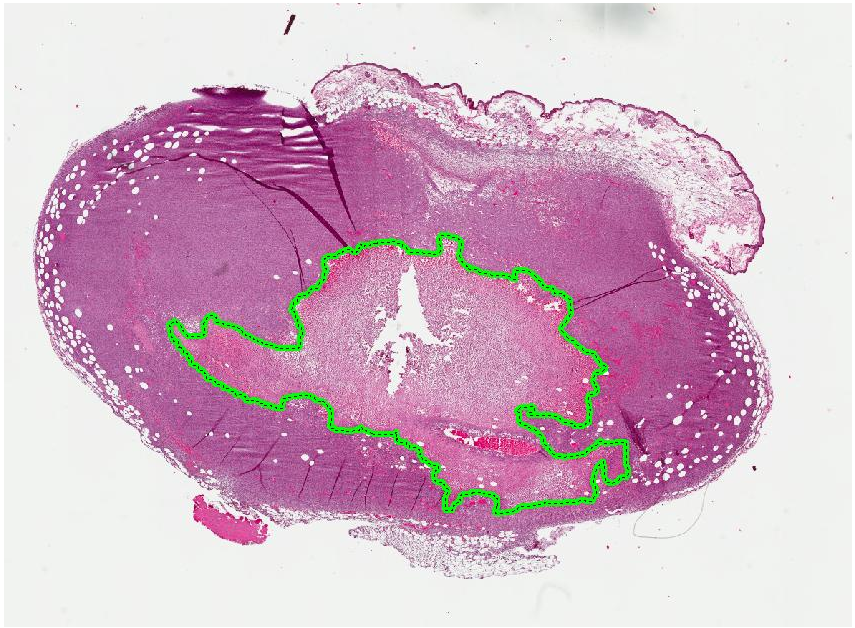
RIF tumor grown on mouse shoulder



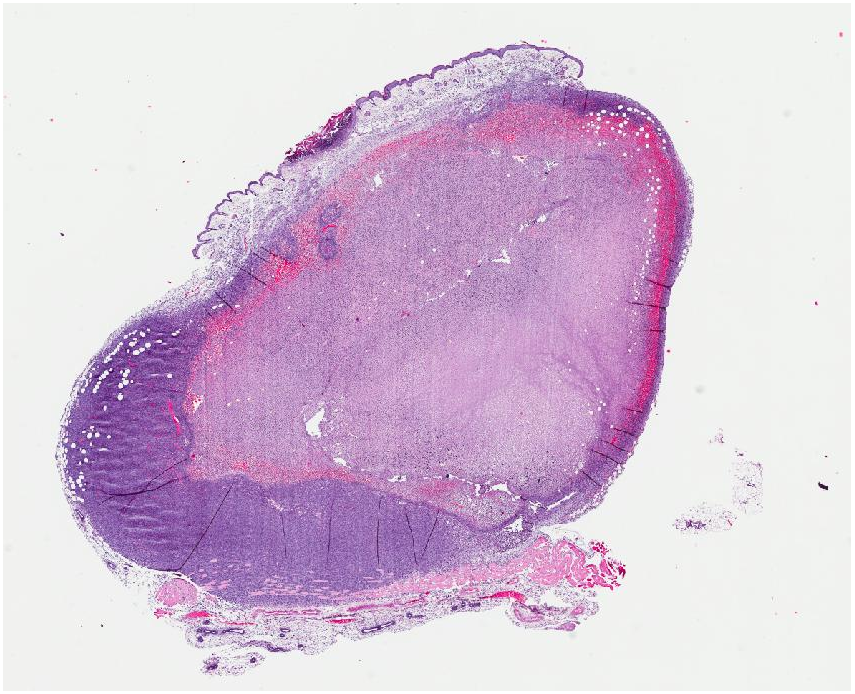


Necrosis distance can be detected by H&E staining

Results on BPD data



Necrosis not approaching boundary



(Necrosis approaching boundary)

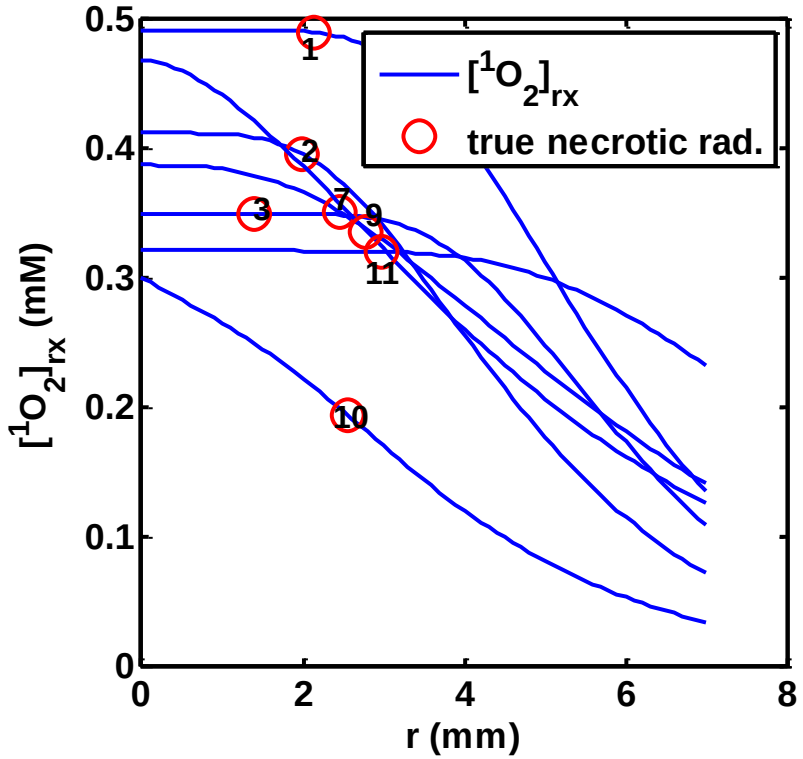
Results on BPD data

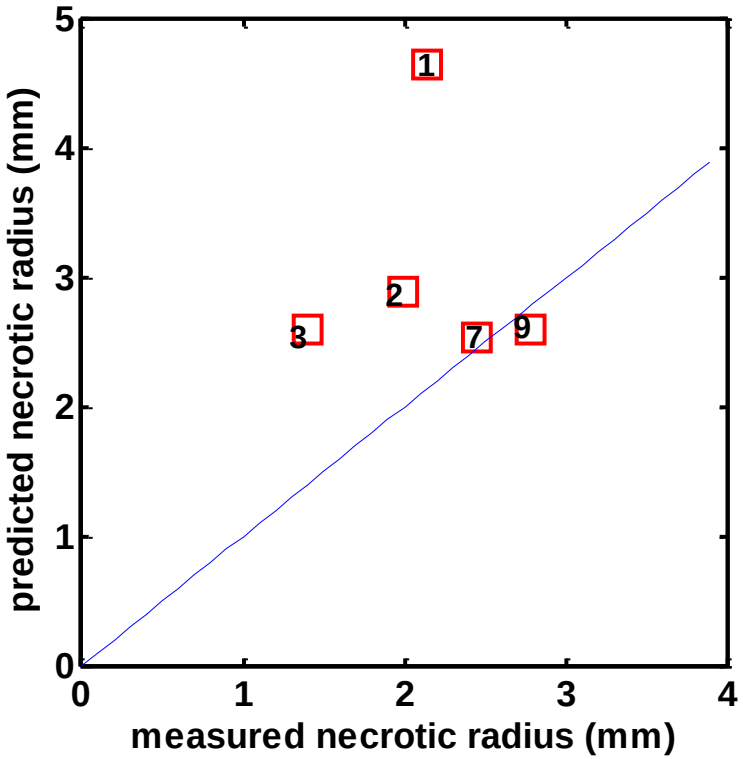
Mouse #	BPD concentration (uM)	LS strength (mW/cm)	Treatment time (s)	μ_a (cm^{-1})	μ_s' (cm^{-1})	Φ at necrosis radius (mW/cm^2)	Necrosis radius (mm)
1	0.414	75	1800	0.661	10.44	152.75	2.14
2	0.347	30	1980	0.549	10.78	76.79	1.99
3	0.294	30	4500	0.533	14.28	135.93	1.40
4	0.139	150	660	0.396	18.852	567.41	2.030
(5)	0.174	150	180	0.529	9.75	231.33	2.786
(6)	0.165	12	6000	0.142	11.163	34.12	3.112
7	0.326	12	4000	0.226	6.54	27.03	2.454
(8)	0.181	12	3000	0.207	15.5	46.64	2.445
(9)	0.394	12	2000	0.152	7.41	29.31	2.789
(10)	0.254	75	300	0.376	12.18	178.21	2.550
11	0.270	20	4000	0.138	15.153	72.39	2.978
(12)	0.172	20	3000	0.283	13.45	63.78	2.386
13	0.183	75	660	0.352	9.013	181.51	2.325

Results on selected BPD data

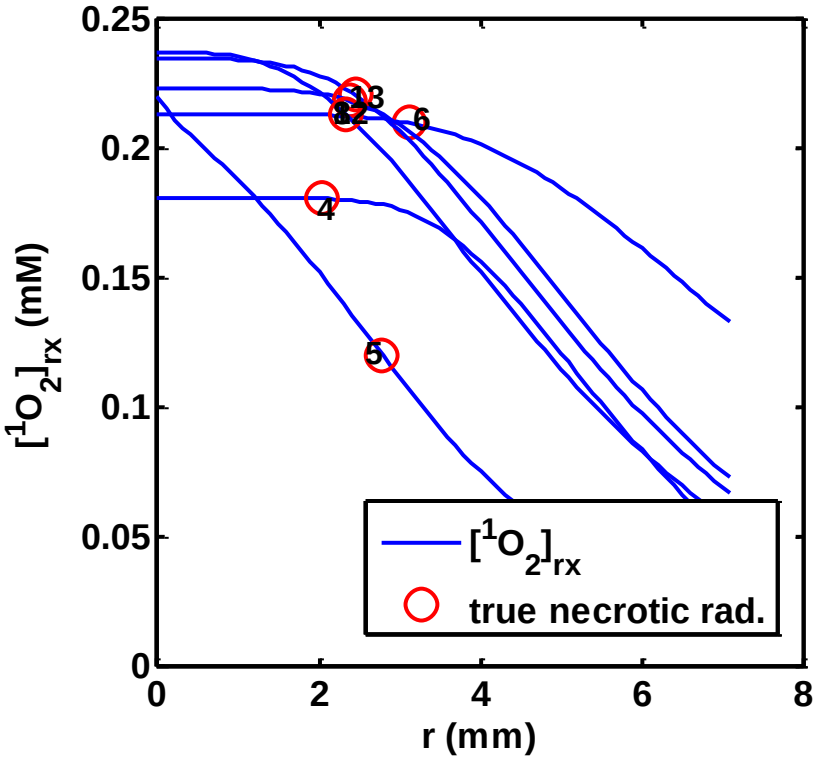
Parameters	BPD (A)	BPD (B)	BPD (All)	Photofrin
ξ ($cm^2/s/mW$)	30.26×10^{-3}	30.26×10^{-3}	30.26×10^{-3}	2.9×10^{-3}
σ ($1/\mu M$)	2.53×10^{-5}	2.33×10^{-5}	2.33×10^{-5}	8.41×10^{-5}
β (μM)	11.9	11.9	11.9	11.9
g ($\mu M/s$)	0.93	0.93	0.93	0.71
$[^1O_2]_{rx,sh}$(mM)	0.35±0.09	0.19±0.04	0.29±0.12	0.56±0.26

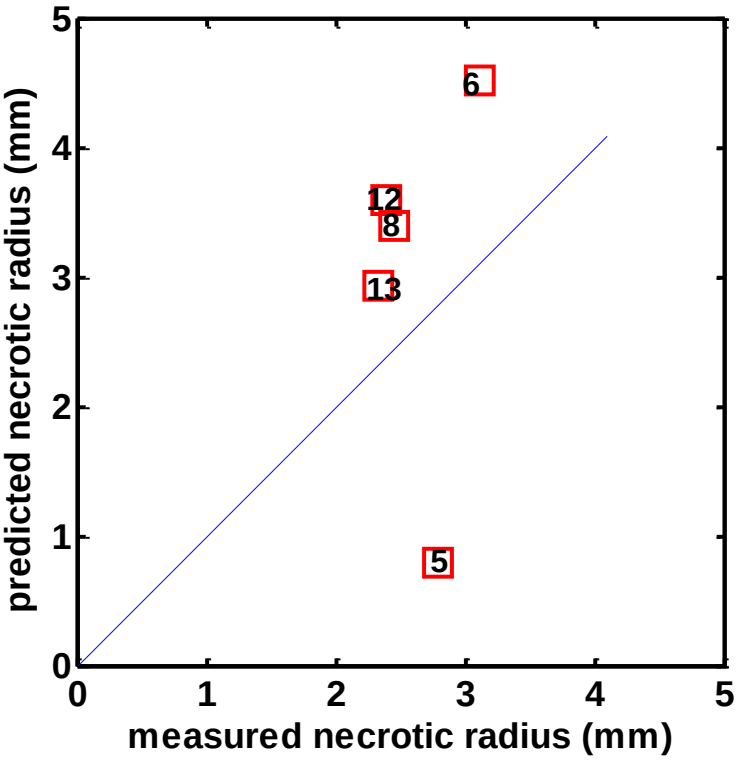
Results on selected BPD A





Results on selected BPD B





- **Comparison between photochemical parameters between Photofrin and BPD**

Results on BPD data

Photosensitizer	BPD	Photofrin
Incubation time	3 hr	24 hr
Drug concentration	1 mg/kg	5 mg/kg
Light wavelength	690 nm	630 nm

Comparison

ξ ($cm^2\ mW^{-1}\ s^{-1}$)	$S_\Delta \left(\frac{k_5}{k_5+k_3}\right) \frac{\varepsilon}{h\nu} \frac{k_7[A]/k_6}{k_7[A]/k_6+1}$ [1]	Photofrin: 3.7×10^{-3} Photofrin: $(2.1 \pm 0.3) \times 10^{-3}$ mTHPC: 0.03 ALA-PpIX[2]: 3.7×10^{-3}	[16, 38][1] fitted value [30]
σ (μM^{-1})	$k_1/k_7[A]$	Photofrin: 7.6×10^{-5} mTHPC: 2.97×10^{-5} ALA-PpIX: 9×10^{-5}	[16] [30] [39]

PS	ξ ($cm^2/s/mW$)	σ ($1/\mu M$)	$k_5/(k_3+k_5)$	ε ($M^{-1}cm^{-1}$)	$k_7[A]/k_6$
Photofrin (630nm)	2.9×10^{-3}	8.41×10^{-5}	0.80	3500	10^3-10^4
BPD (690nm)	30.26×10^{-3}	2.33×10^{-5}	0.76	33000	10^3- 10^4
References			[1],[3]	[1],[3]	[2]

1. Mitra and Foster, Photochem & Photobiol 81, 849-859 (2005). 2. Hu et al, Photochem & Photobiol, 81, 1460-1468 (2005). 3. Aveline B, Hasan T, et al, Photochem & Potobiol, 59, 328-335 (1994)

Comparison

	PS	Media	Threshold dose	Reference
1	Photofrin	spheroid	12.1±1.2 mM	I. Georgakoudi, M. G. Nichols, and T. H. Foster, Photochem. Photobiol. 65(1), 135–144 (1997).
2	mTHPC	Mice in vivo	0.4 mM	K. K. Wang, S. Mitra, and T. H. Foster, Med. Phys. 35(8), 3518–3526 (2008).
3	Photofrin	Mice in vivo	0.74 mM	Wang K et al, J Biophoton 3, 304-318 (2010),
4	mTHPC	spheroid	7.9 ±2.2 mM	S. Coutier, S. Mitra, L. N. Bezdetnaya, R. M. Parache, I. Georgakoudi, T. H. Foster, and F. Guillemin, Photochem. Photobiol. 73, 297–303 (2001).

Conclusions

- PDT model including light diffusion and PDT kinetics equations
- PS-specific photochemical parameters can be obtained in the in-vivo PDT model using COMSOL
- Photochemical parameters for BPD is reasonable based on previous results for Photofrin.
- Apparent singlet oxygen can be used directly for clinical PDT treatment to correlate better with efficacy than PDT dose.

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