Singlet Oxygen Modeling of PDT incorporating Local Vascular Oxygen Diffusion

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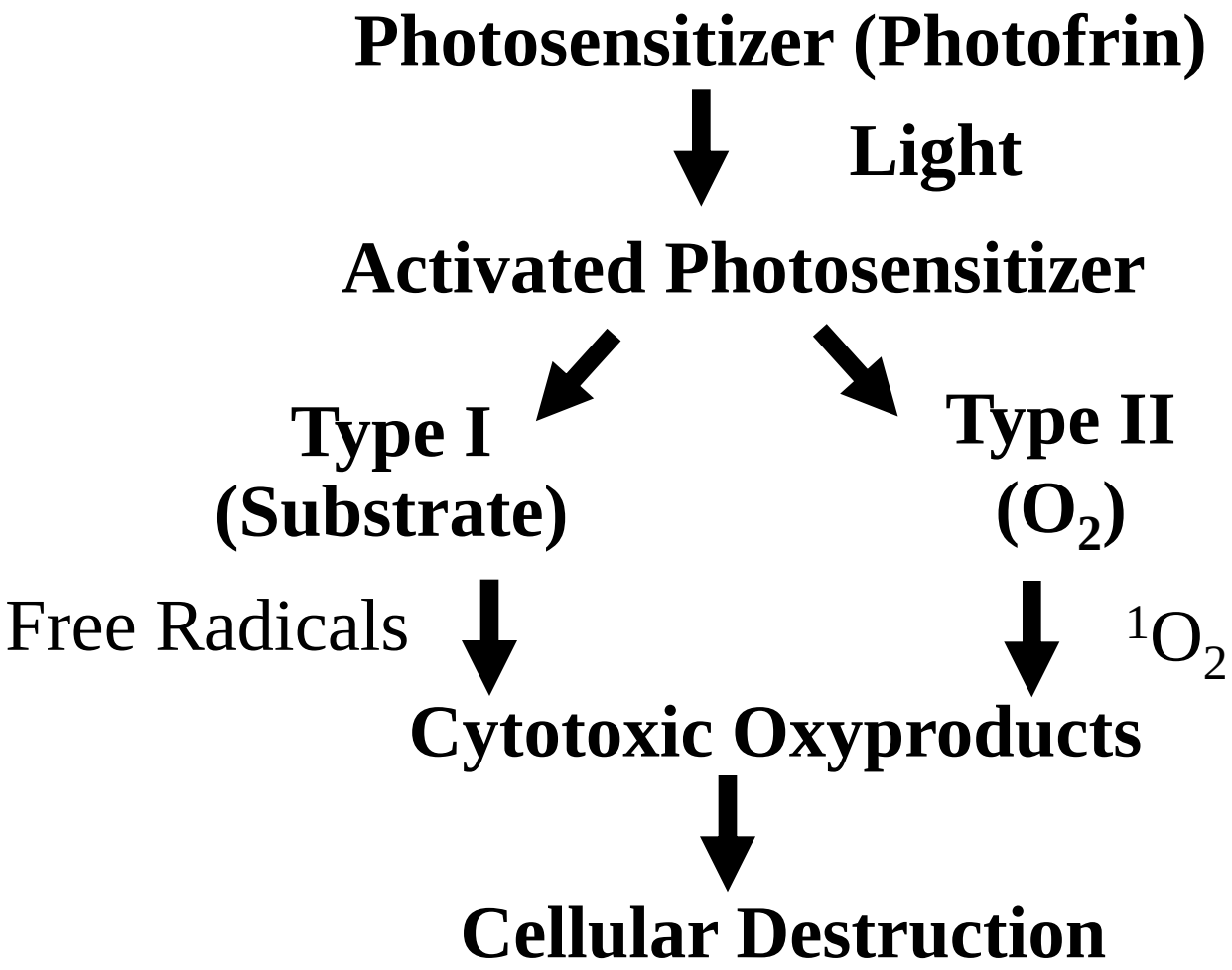
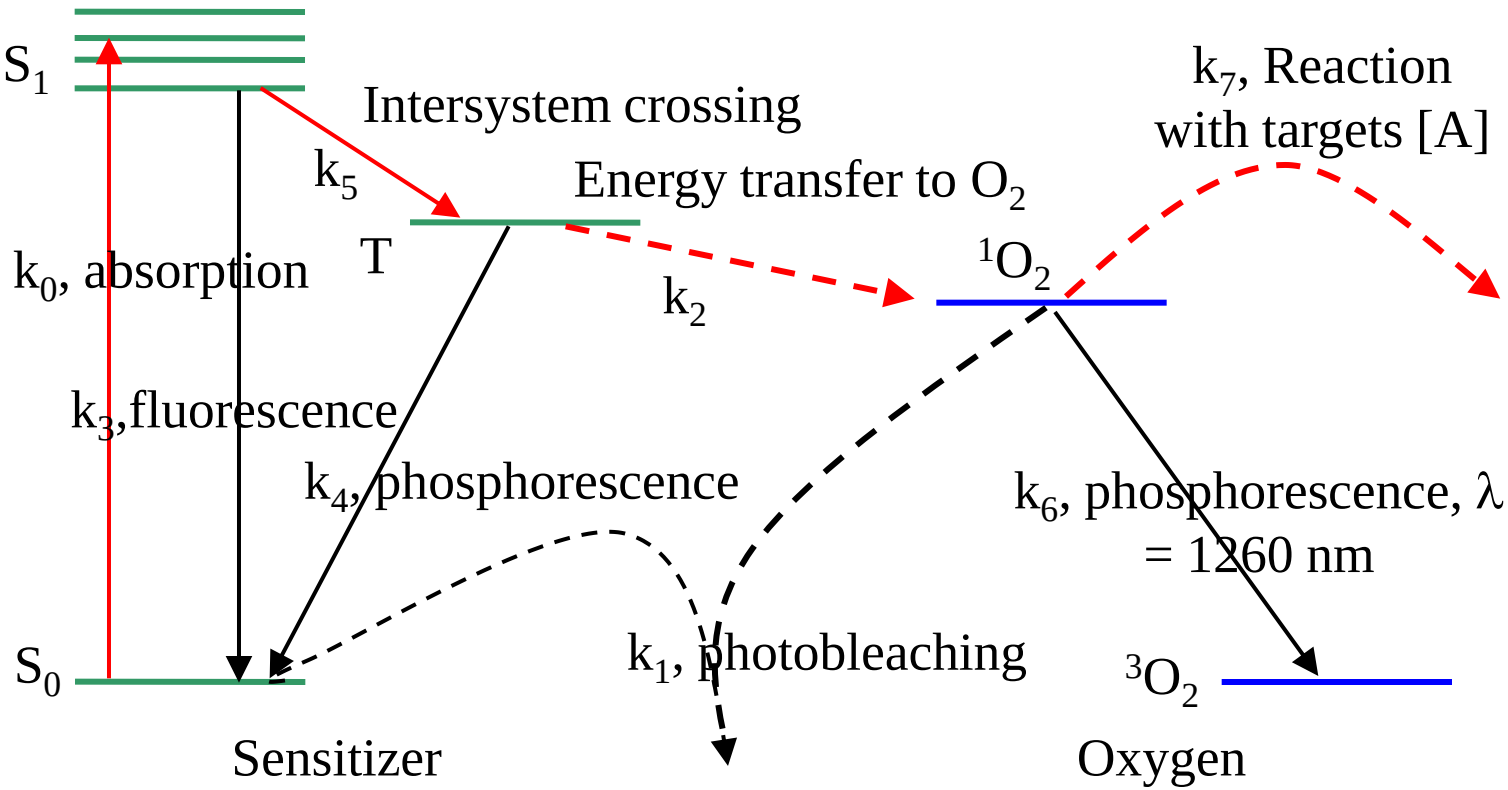
Mechanics of Action



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.
- **A macroscopic singlet oxygen model has been developed to calculate, $[^1O_2]_{rx}$, from the all three components. However, one parameter, the oxygen supply rate, g, is not estimated based on the actual blood vasculature.**

Introduction



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

Formulation of the macroscopic problem

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

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

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

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

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

$$\frac{d[A]}{dt} = -k_7[A][{}^1O_2]$$

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

Sym.	Definition	Values
k_0	PS abs. rate at ϕ =100 mW/cm^2	18.8 1/s
k_1	Photobleaching rate	1.2×10^5 1/μM·s
k_2	Reaction rate of $^3O_2$ with T	100 1/μM·s
k_3	Rate of S_1 to S_0	2.0×10^7 1/s
k_4	Rate of T to S_0	1210 1/s
k_5	Rate of S_1 to T	8.0×10^7 1/s
k_6	Rate of $^1O_2$ to $^3O_2$	1×10^6 1/s
k_7	Reaction rate of $^1O_2$ with tissue	2.6×10^6 1/μM·s
S_Δ	Fraction [$^1O_2$] from reaction [T] and [$^3O_2$]	0.5
ε	Extinct. Coef.	0.036 cm^{-1}/μM
g	Max oxygen supply rate	0.7 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
$[A]_i$	Init. Con.	830 μM
$[T]_i$	Init. Con.	0 μM
$[^1O_2]_i$	Init. Con.	0 μM

Reference: J Biophotonics 3, 304-318, 2010

Macroscopic PDT model - current

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

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.

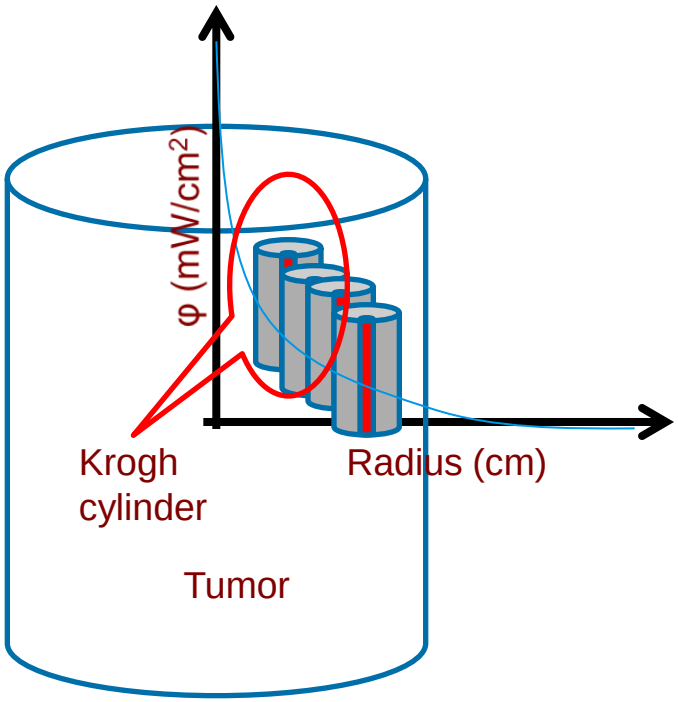
$\xi = S_\Delta k5/(k3+k5)\varepsilon/h\nu/(k6/k7[A]+1)$

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

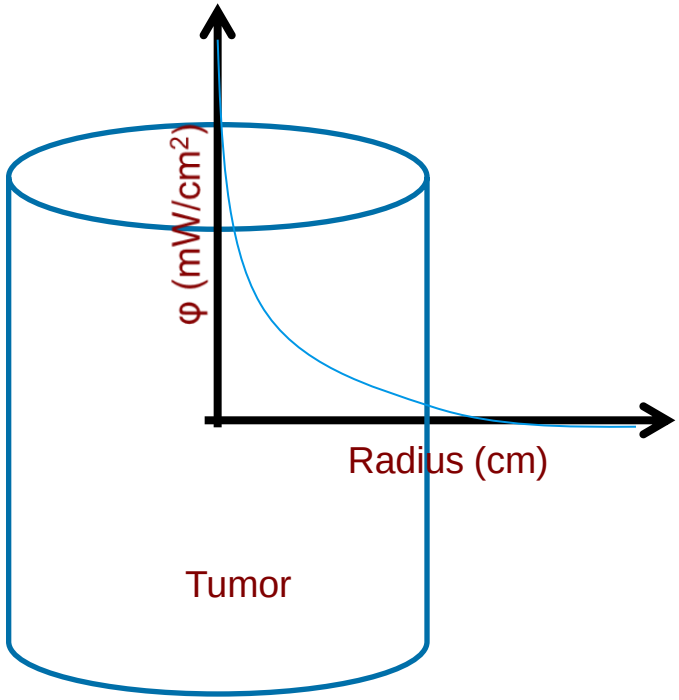
$[S_0](t)$, $[^3O_2](t)$, and $[^1O_2]_{rx}(t)$ Equs. are function of β, σ, ξ, and g, and initial conditions of $[^3O_2]$ and $[S_0]$.

Incorporation of vascular blood diffusion

- Cylinder **vascular model tissue model**:
  - Capillary – uniform distribution in tumor
  - Linear light source: radial-dependent fluence rate--diffusion
  - Krogh cylinder model: single capillary
    - Oxygen, hemoglobin: diffusion and convection
    - Oxy-hemoglobin saturation
    - Initial $[^3O_2]$: solution of steady state prior to PDT



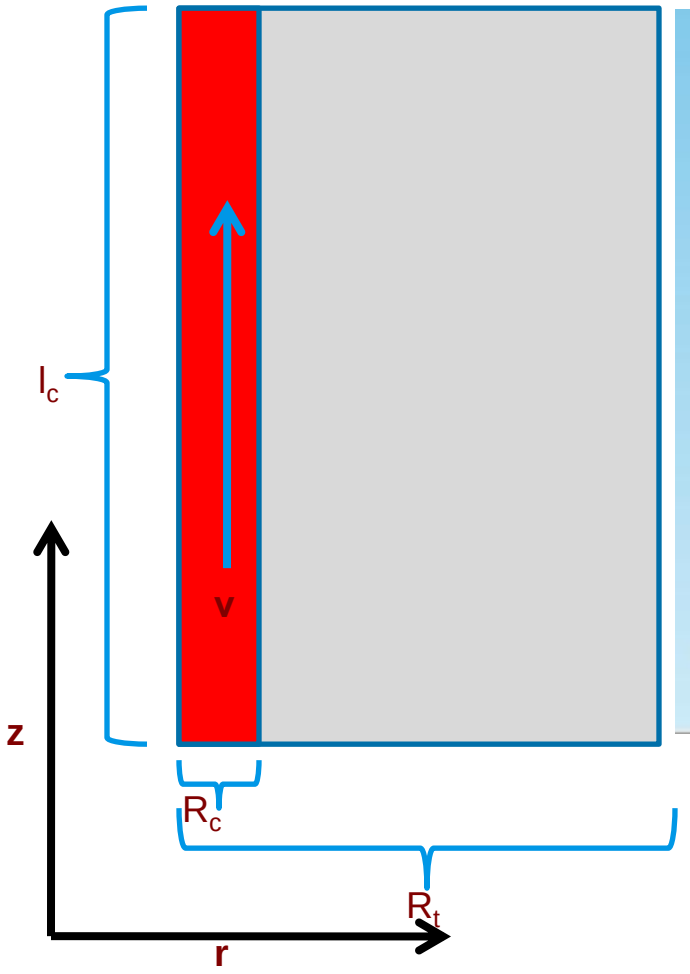
Microscopic model –oxygen supply via diffusion through capillary

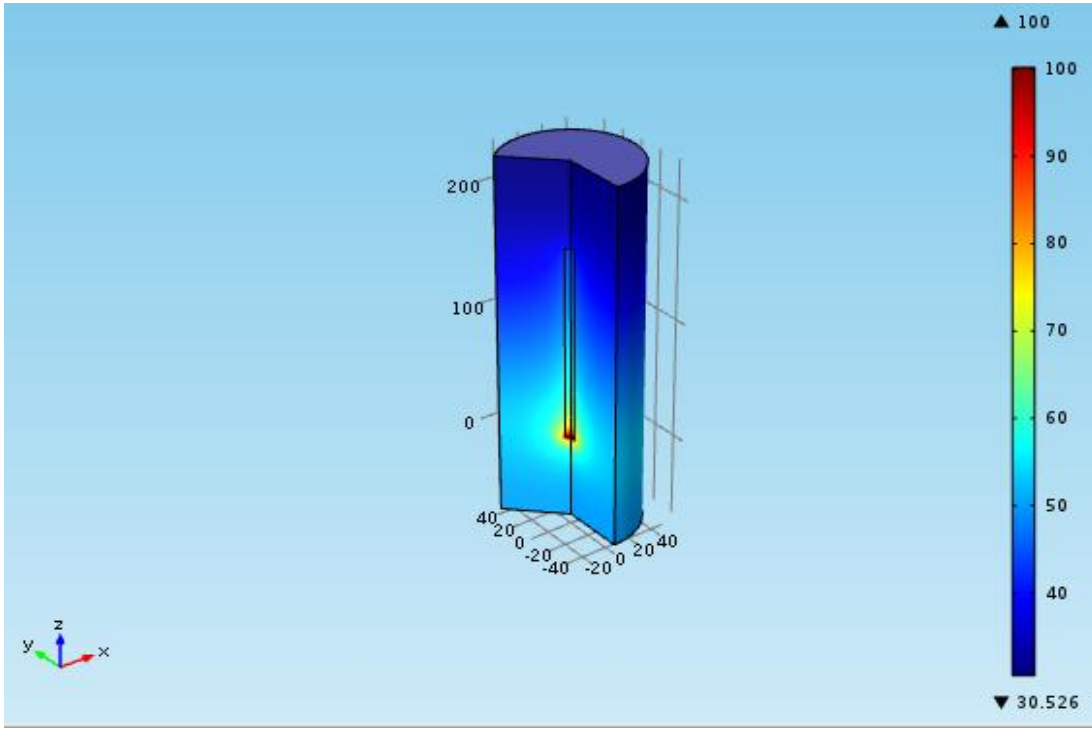


Macroscopic model – uniform oxygen supplies

Vascular model

- **Krogh's Model** - 3D cylindrical single blood vessel is modeled in 2D by taking advantage of cylindrical symmetry.





Equations describing vascular diffusion

- **Prior to PDT –Steady state solution**

Ground-state Oxygen in Tissue & capillary

$$\text{Tissue:}\quad \frac{d[^3O_2]}{dt} = D_t \nabla^2 [^3O_2] - q_0 \frac{[^3O_2]}{[^3O_2] + [^3O_2]_m}$$

$$\text{Capillary:}\begin{cases} \dfrac{d[^3O_2]}{dt} = D_c \nabla^2 [^3O_2] - \vec{v} \cdot \nabla [^3O_2] + \Gamma_{rec} \Rightarrow \text{Free oxygen} \\ C_H \dfrac{dS}{dt} = C_H D_H \nabla^2 S - \vec{v} \cdot C_H \nabla S - \Gamma_{rec} \Rightarrow \text{Bound oxygen} \end{cases}$$

$$S: \text{oxygen saturation},\ S = \frac{[^3O_2]^n}{[^3O_2]^n + [^3O_2]_{50}^n}$$

- **During PDT --Tissue**

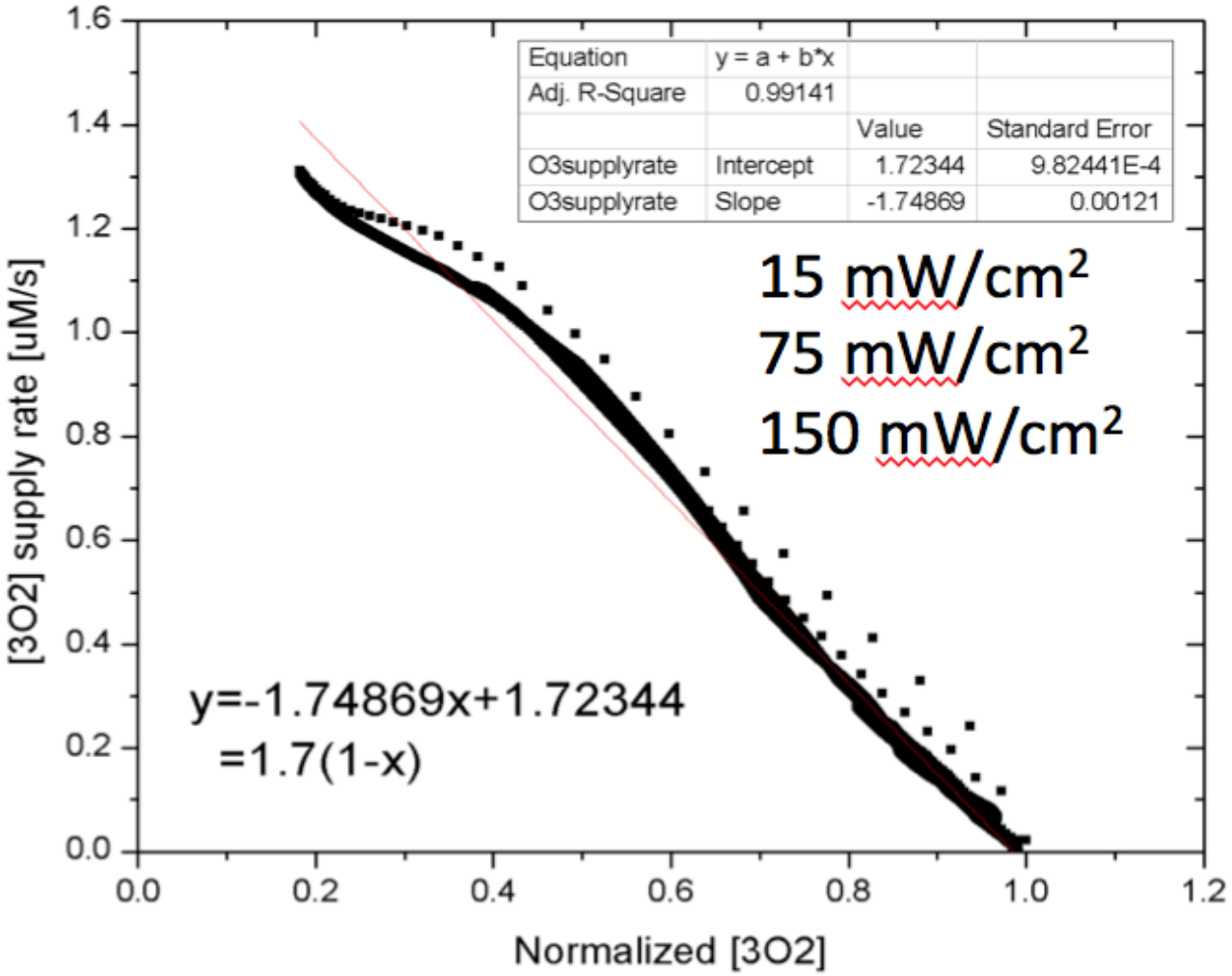
$$\frac{d[^3O_2]}{dt} + \left(\xi \frac{\phi [S_0][^3O_2](1 + \sigma([S_0] + \delta))}{[^3O_2] + \beta} \right) = \begin{cases} D_t \nabla^2 [^3O_2] - q_0 \dfrac{[^3O_2]}{[^3O_2] + [^3O_2]_m} \Rightarrow \text{Microscopic} \\ g\left(1 - \dfrac{[^3O_2]}{[^3O_2]_{t=0}}\right) \Rightarrow \text{Macroscopic} \end{cases}$$

Vascular Parameters (Zhu, et al, SPIE 2007,Wang, et al J Biophoton, 2010)

Parameter	Description	Value
R_c	Capillary radius	4~10 μm
R_t	Tissue radius	18~65 μm
z	Length of capillary	220 μm
u	Blood velocity in capillary	50~750 μm/s
C_H	Plasma oxygen carrying capacity	9000 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}	Tumor supply pO_2	20~40 mmHg
n	Hill constant	2.7
D_c	Oxygen capillary diffusion coefficient	1120 μm2/s
D_t	Oxygen tissue diffusion coefficient	1700 μm2/s
q_0	Oxygen consumption	2~16 μM/s

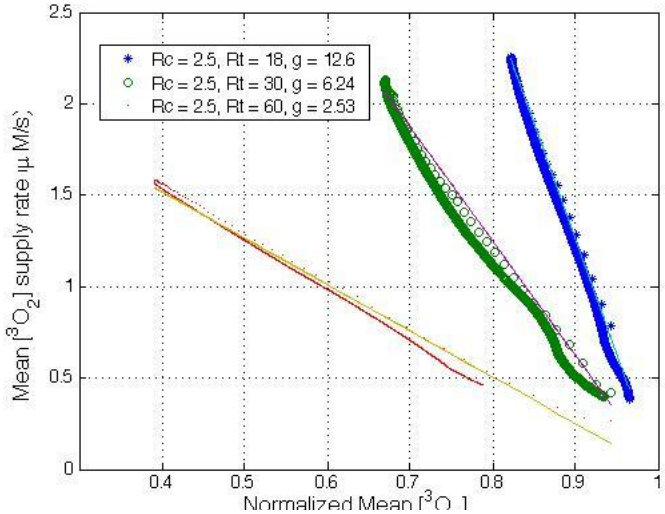
Parameter	Value	Definition
ξ ($cm^2mW^{-1}s^{-1}$)	3.7×10^{-3}	$\xi = S_\Delta k5/(k3+k5)\varepsilon/h\nu/(k6/k7[A]+1)$
σ (μM^{-1})	2.97×10^{-5}	$\sigma = k1/(k7[A])$
δ (μM)	33	
β (μM)	8.7	$\beta = k4/k2$

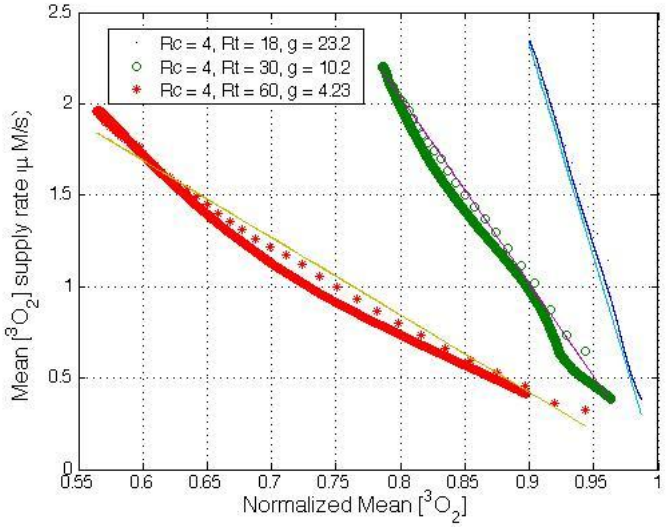
Microscopic model predicts $F = g^*(1 - [^3O_2]/[^3O_2]_0)$, independent of light fluence rate

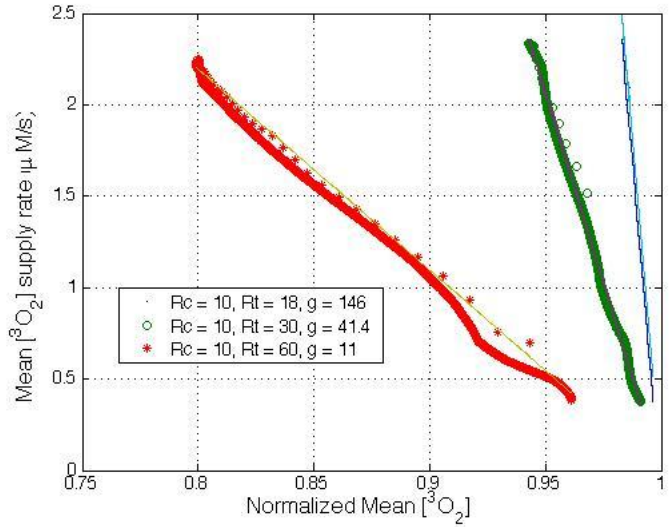


- C_H = 2500 μM
- R_c = 2.5 μm.
- R_t = 60 μm.
- l_c = 300 μm.

g values vs. R_c and R_t (l_c = 220 μm)



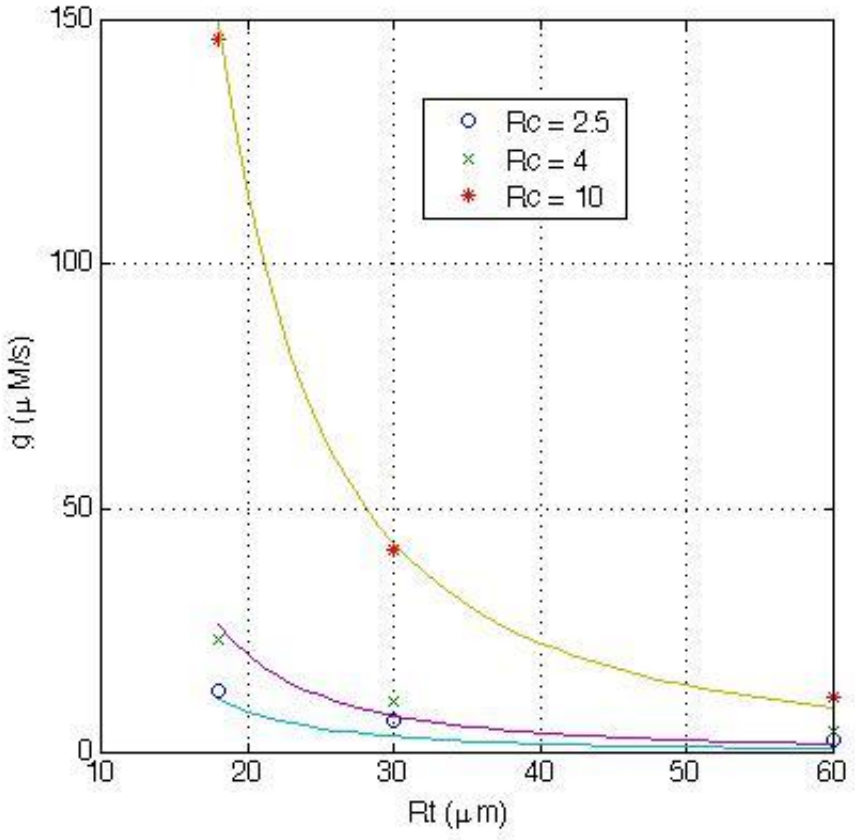


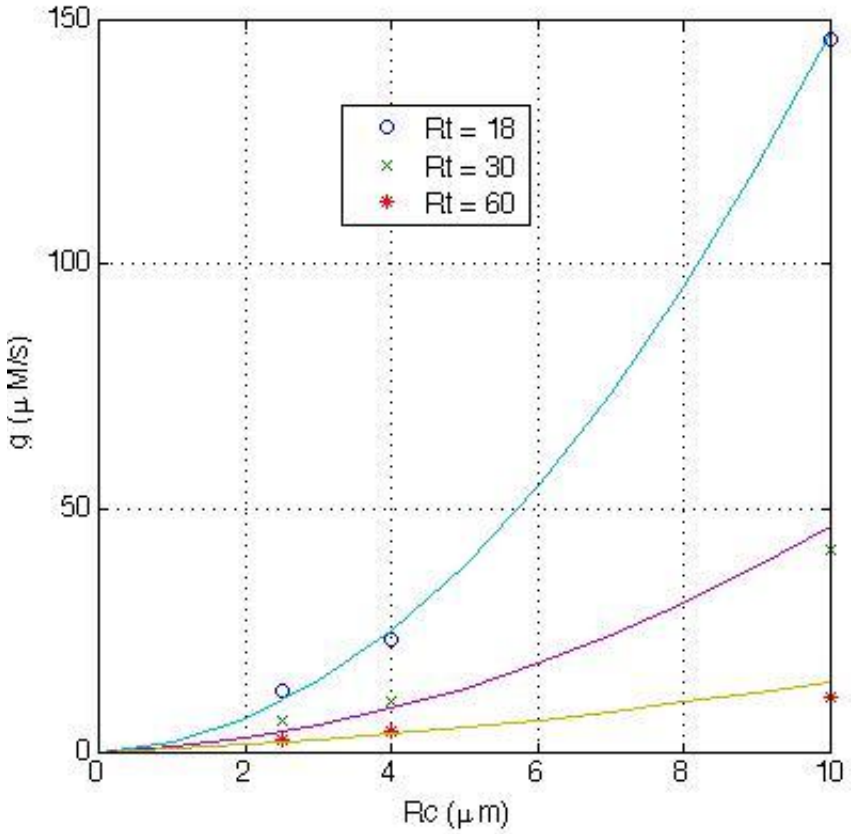


Rt \ Rc (μm)	2.5	4	10
18	12.6	23.2	146
30	6.24	10.2	41.4
60	2.53	4.23	11

g values vs. R_c, R_t, and l_c

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

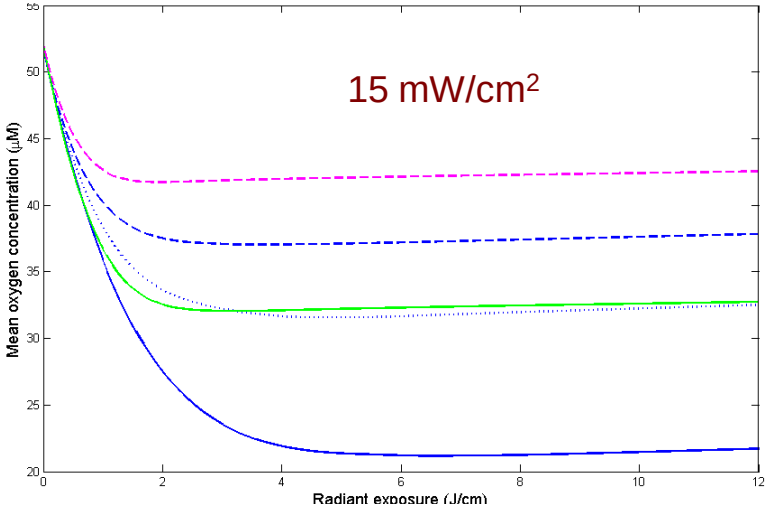


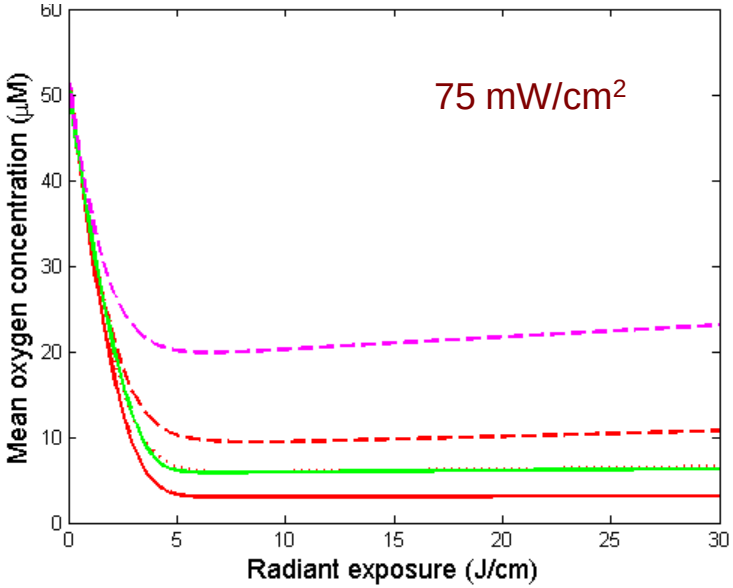


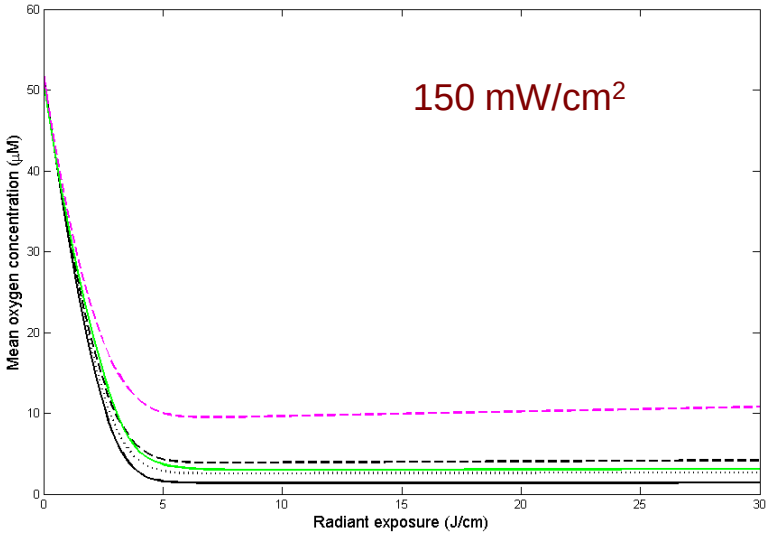
g on mean oxygen concentration

- Fluence rate at 15, 75 and 150 mW/cm^2

Micro no flow red (g= 1.7 μM/s)
Macro g=1 μM/s
Macro g=0.7 μM/s
Macro g=0.4 μM/s
Micro w flow red (g = 1.7 μM/s)







Conclusions

- **Incorporation of vascular blood vessel provides a good validity of macroscopic model.**
- **An estimation of the blood perfusion value, g, is established based on the known parameters of vasculature in normal tissue.**
- **The calculated g based on microvascular is too high, additional mechanism needs to be identified to explain the results (blood flow reduction?, longer capilary?).**

Acknowledgements

Thank you – any questions?

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