



A Model of Reoxygenation Kinetics of Chronically Hypoxic Tumor Regions

R.A. Popple and I.A. Brezovich

Department of Radiation Oncology, The University of Alabama at Birmingham, Birmingham, Alabama

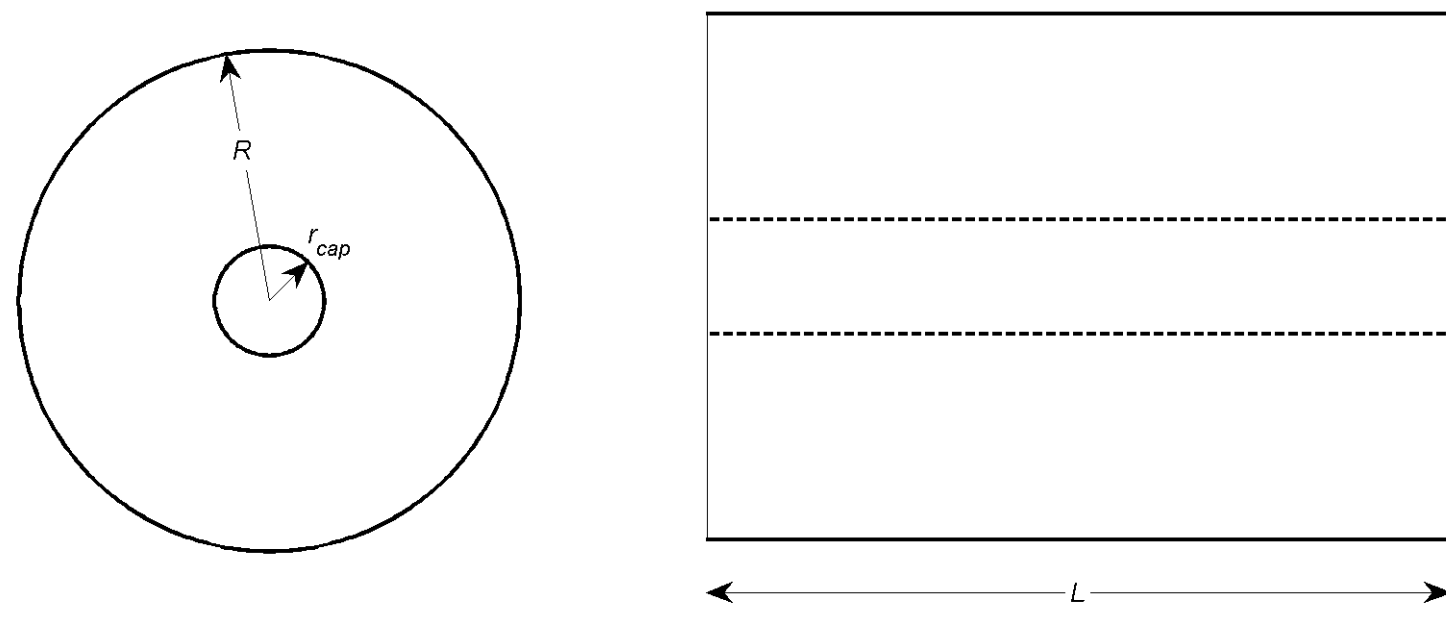
PURPOSE/OBJECTIVE

Chronic hypoxia arises from tumor regions with an insufficient number of microcapillaries, causing an oxygen deficiency in cells distant from a capillary. Fractionated radiation reduces the population of cells, and thus oxygen consumption, allowing reoxygenation of initially hypoxic cells. We developed a model for investigation of reoxygenation kinetics, based on a model of oxygen distribution developed by Krogh (1), in which a central capillary supplies oxygen to a concentric cylinder of tissue. We extended this model to include the changes in oxygen consumption in the cylinder resulting from radiation induced cell death.

MATERIALS AND METHODS

A. Model

The model is comprised of a capillary of radius r_{cap} surrounded by a coaxial cylinder of length L and radius R .



The transport of oxygen is comprised of two components:

- Diffusion
- Mass transport along the axial direction due to blood flow

As described by Groebe and Vaupel (2), if we neglect the axial component of diffusion we can reduce the problem to that of a series of axial slabs of thickness Δz located at $z_i = (i-1)\Delta z$. Calculation of the oxygen distribution as a function of the distance r from the axis is then comprised of three steps:

1. Calculate the mean partial pressure of oxygen in the capillary $p_m(z_i)$ from the net outflow of the previous slab. For the first slab, $p_m(0) = p_{Arterial}$.
2. Calculate the partial pressure of oxygen at the tissue-capillary interface
3. Solve the diffusion equation in tissue

A. Oxygen mass transport due to blood flow

Oxygen is both dissolved in blood plasma and bound to hemoglobin. Using Hill's equation to model oxygen binding to hemoglobin, the mean partial pressure in the capillary at z is given by

$$p_m(z) = p_m(z - \Delta z) + \Delta z \frac{2\pi r_{cap} \phi(r_{cap}, z - \Delta z)}{Q} \left[a_b + \frac{C_s}{p_{50}} \frac{h \left(\frac{p_m}{p_{50}} \right)^{h-1}}{\left(1 + \left(\frac{p_m}{p_{50}} \right)^h \right)^2} \right]^{-1}$$

where

$\phi(r_{cap}, z - \Delta z)$ = oxygen flux through the capillary wall of the previous slab
 Q = blood volume flow rate

α_b = oxygen solubility

C_s = concentration of oxygen bound to hemoglobin at full saturation

p_{50} = oxygen pressure at which the concentration of oxygen bound to hemoglobin is 50% of full saturation.

$h = 2.55$

B. Oxygen diffusion in tissue

Neglecting axial diffusion, the differential equation for oxygen in tissue is

$$\frac{1}{r} \frac{d}{dr} \left(r \frac{dp}{dr} \right) = \frac{m(p, r)}{\alpha_r D_r}$$

where p is the partial pressure of oxygen, m is the rate of oxygen consumption by the tissue per unit volume per unit time, α_r is the solubility of oxygen in tissue, and D_r is the diffusion constant in tissue. The oxygen consumption is modeled using Michaelis-Menten kinetics, modified to account for reduction of respiring cells due to radiation, and is given by

$$m(p, r) = SF(r) \cdot m_0 \frac{\left(\frac{p}{p_M} \right)}{1 + \left(\frac{p}{p_M} \right)}$$

where m_0 is the rate of oxygen consumption when oxygen is not rate-limiting, p_M is the pressure at which consumption falls to $m_0/2$, and $SF(r)$ is the fraction of surviving cells at position r in the slab.

There are two boundary conditions. First, we assume no net oxygen flow out of the cylinder, which approximates an array of capillaries with inter-capillary distance $2R$. This condition requires that

$$\left. \frac{dp}{dr} \right|_{r=R} = 0$$

Second, the pressure and the flux of oxygen across the interface must be continuous at the capillary-tissue interface. If we solve for the radial distribution of oxygen pressure in the capillary, we obtain the boundary condition at the interface:

$$p(r_{cap}) = p_m + \frac{r_{cap} a_r D_r}{4 \alpha_b D_b} \left. \frac{dp}{dr} \right|_{r=r_{cap}}$$

We solve for p numerically using a 1-D partial differential equation solver in MatLab (The MathWorks, Inc., Natick, MA).

C. Cell survival

The number of cells surviving a fraction of radiation is modeled using the linear-quadratic (LQ) model. If the cells are not well-oxygenated, the fraction of clonogens surviving a radiation dose D , SF_D , is given by

$$SF_D = \exp(-OER \alpha D - OER^2 \beta D^2)$$

where α and β are the LQ parameters under well-oxygenated conditions, and the oxygen enhancement ratio (OER) is defined as the ratio of the dose to hypoxic cells relative to the dose to aerobic cells required to produce the same survival fraction. We model the OER as

$$OER(p) = \frac{cK + p}{K + p}$$

For each fraction of radiation, we calculated the survival fraction based on the oxygen distribution computed based on the survival fraction of the previous radiation fraction. From the survival fraction at each point, we calculated the probability of sterilizing the cylinder from

$$P_S = \prod (1 - SF(r, z))^{2\pi r \Delta r \rho}$$

where ρ is the clonogen density and Δr is the radial grid spacing.

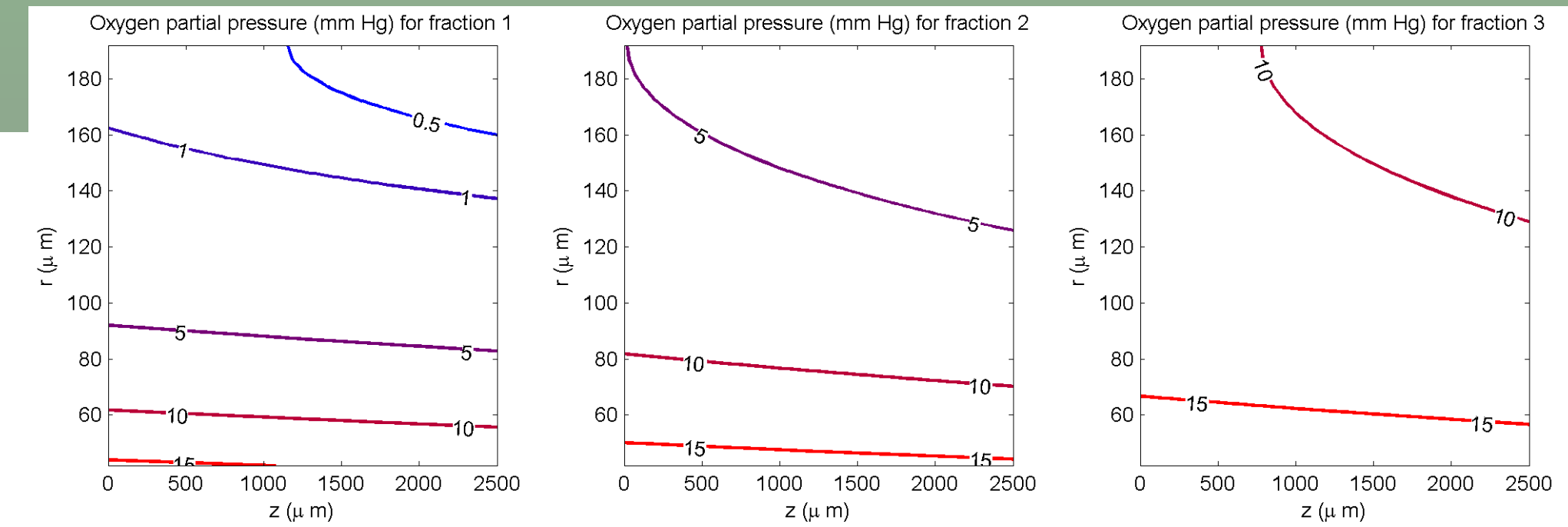
C. Model parameters

The parameters used were chosen to be typical of a poorly vascularized tumor region (3). The cylinder radius was chosen such that the initial fraction of hypoxic volume ($p < 1$ mm Hg) was approximately 50%.

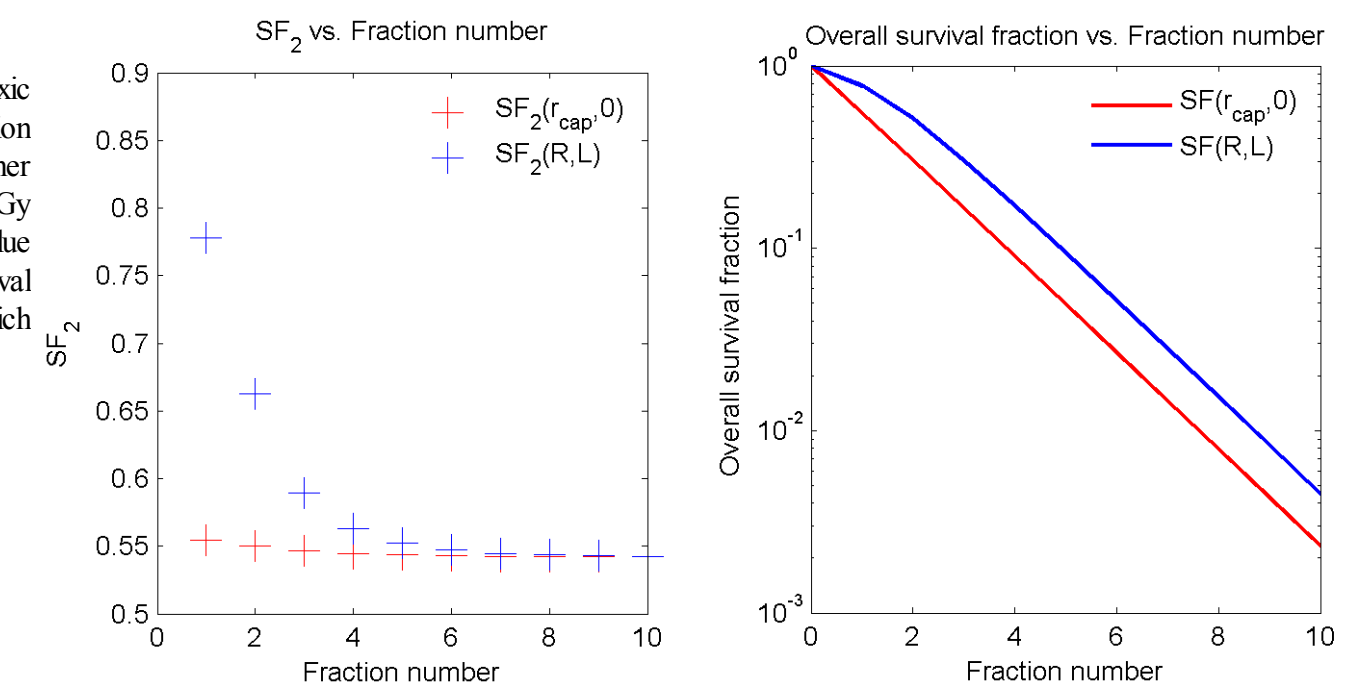
Parameter	Value	Parameter	Value
D	2 Gy	α_r	1.29×10^{-9} mol/cm ³ /mmHg
r_{cap}	42 μ m	D_b	1.12×10^{-5} cm ² /s
R	192 μ m	D_r	1.45×10^{-5} cm ² /s
L	2.5 mm	m_0	3.72×10^{-9} mol/cm ³ /s
$p_{Arterial}$	20 mm Hg	p_M	1 mm Hg
Q	2×10^{-6} cm ³ /s	α	0.273 Gy ⁻¹
C_s	0.1 cm ³ O ₂ /cm	β	0.045 Gy ⁻²
p_{50}	26 mm Hg	c	2.7
α_b	1.53×10^{-9} mol/cm ³ /mmHg	K	1.9 mm Hg

RESULTS

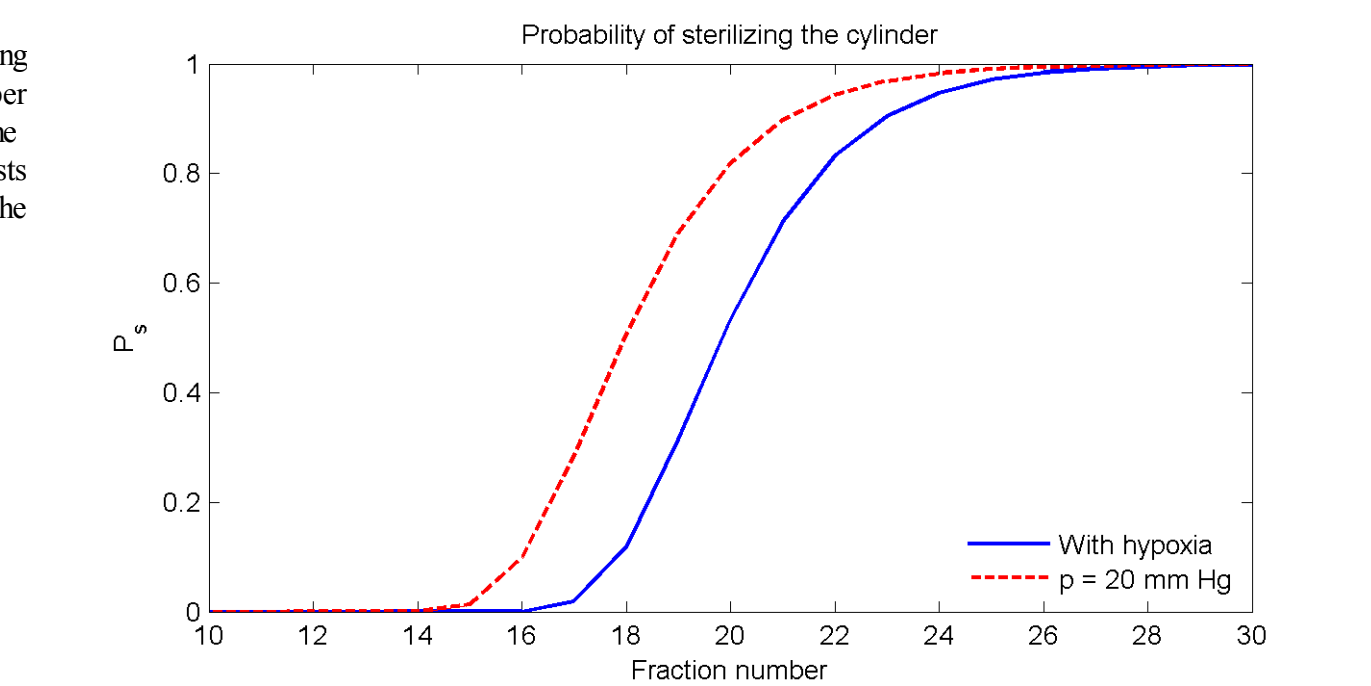
The oxygen distribution in the cylinder is shown in the figures below for the first 3 fractions. We see that the population reduction due to cell death results in reoxygenation of the hypoxic corner, located at $(r, z) = (R, L)$. The survival fractions for 0.5, 1, 5, 10, and 15 mm Hg are 0.77, 0.74, 0.63, 0.58, and 0.56, respectively.



The figure on the near right shows SF₂ at the hypoxic corner and adjacent to the capillary inlet as a function of radiation fraction number. As the hypoxic corner becomes oxygenated, the fraction surviving 2 Gy decreases, approaching that of the oxygenated value by fraction 3 to 4. On the far right is the total survival as a function of radiation fraction number, which shows the effect of the higher initial SF₂.



The figure on right shows the probability of sterilizing the cylinder as a function of radiation fraction number for the cylinder under consideration and for the same number of oxygenated clonogens. This figure suggests that the number of fractions required to overcome the initial hypoxia is approximately 2.



CONCLUSIONS

For the parameters used, almost complete reoxygenation occurs after 2 fractions. Different fractionation schemes for overcoming the initial hypoxia and the effect of delayed cell death on reoxygenation need to be investigated. This approach has the potential to design more effective fractionation schemes for control of hypoxic volumes.

REFERENCES

1. A. Krogh, "The number and distribution of capillaries in muscles with calculations of the oxygen pressure head necessary for supplying the tissue," J. Physiol. 52, 409-415 (1919)
2. K. Groebe and P. Vaupel, "Evaluation of oxygen diffusion distances in human breast cancer xenografts using tumor-specific in vivo data: role of various mechanisms in the development of tumor hypoxia," Int. J. Radiat. Oncol. Biol. Phys. 15, 691-697 (1988)
3. T.W. Secomb, R. Hsu, M.W. Dewhirst, B. Kitzman, and J.F. Gross., "Analysis of oxygen transport to tumor tissue by microvascular networks," Int. J. Radiat. Oncol. Biol. Phys. 25, 481-489 (1993)