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Mathematical and Computer Modelling 42 (2005) 1113–1122
MATHEMATICAL AND COMPUTER MODELLING
www.elsevier.com/locate/mcm

Oxygen Transport to Muscle Tissue where Regions of Low Oxygen Tension Exist

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(Received and accepted September 2004)

Abstract—Most studies devoted to mathematical modelling of oxygen transport to tissue have assumed a constant oxygen consumption, independent of oxygen tension, whilst oxygen concentration remains positive. However, it is more physiologically realistic to allow the oxygen consumption to fall continuously to zero as the oxygen tension falls towards zero for low oxygen tensions. We show that using this more physiologically realistic oxygen consumption in a mathematical model of oxygen transport to tissue gives a significantly different solution to the governing equations when areas of low oxygen tension exist. We then use this method of modelling oxygen consumption to compare the location of regions of low tissue oxygen tension predicted by two previously published mathematical models of oxygen transport. The two models are a partial differential equation (PDE) model, and an ordinary differential equation (ODE) model that is a simplification of the PDE model. We show that most of the predictions of the ODE model are almost identical to those of the PDE model, but there are some significant differences.

Keywords—Oxygen transport, Myoglobin, Low oxygen.

1. INTRODUCTION

When oxygen levels in tissue are sufficiently high, the oxygen consumption of individual cells (the quantity of oxygen that tissue actually manages to consume) is equal to the oxygen demand of these cells (the quantity of oxygen that the tissue wishes to consume). However, when the oxygen concentration within the tissue approaches zero, the oxygen consumption of tissue falls significantly [1–4]. At these low oxygen tensions, the demand of cells is not met even when the oxygen tension is greater than zero, and oxygen consumption is a continuous function of oxygen concentration that reaches zero when oxygen concentration is zero. Many studies investigating low oxygen concentration within tissue [5–7] have modelled oxygen consumption using a step function instead of a continuous function of oxygen concentration. Using the step function approach, the

*Author to whom all correspondence should be addressed.
J. P. Whiteley is pleased to acknowledge Grant GR/M60705 from the Engineering and Physical Sciences Research Council of Great Britain which has allowed him to undertake this research.

0895-7177/05/$ - see front matter Typeset by AMS-TEX
doi:10.1016/j.mcm.2004.09.009

oxygen consumption is a positive constant where oxygen concentration is greater than zero, and oxygen consumption is zero where the oxygen concentration is zero. However, Taylor and Murray [8] have shown that using a step function instead of a continuous oxygen consumption affects the solution of the governing equations significantly. We note that oxygen consumption is only less than oxygen demand when oxygen concentration is exceptionally low (when the oxygen partial pressure is less than about 4 mm Hg), and so assuming a constant oxygen consumption is valid for most healthy subjects.

In this study, we apply a relationship between oxygen consumption and oxygen partial pressure in tissue that has been derived from first principles [1] to a general model of oxygen transport to tissue [9]. As stated above, this relationship will only differ from earlier models in situations where regions of low tissue oxygen tension exist. The first aim of this study is, therefore, to investigate the effect on oxygen transport to tissue of allowing oxygen consumption to vary with oxygen partial pressure at low oxygen partial pressures.

Studies on oxygen transport to tissue have often neglected diffusion of oxygen through tissue in the direction of the capillary bloodflow, commonly known as axial diffusion [7,10,11]. This is an attractive simplification as the governing equations then simplify to a system of ordinary differential equations. However, recent work by Whiteley [9] has shown that this assumption is not valid in all regions of tissue, and the full partial differential equation must be solved in these areas. The second aim of this study is to investigate the effect of neglecting axial diffusion on oxygen transport at low oxygen concentrations. This is assessed by solving both the PDE and the simplified ODEs that have been used to model oxygen transport to tissue.

2. THE MODELS

2.1. The PDE Model

This PDE model, we use is that described by Whiteley *et al.*, [9], modified to take account of oxygen consumption varying with oxygen partial pressure [1]. We model an individual capillary supplying oxygen to tissue using the model shown in Figure 1. This model consists of a cylindrical volume of tissue with radius R_T and length a. Within this cylinder is a concentric cylinder of radius R_C through which blood flows with speed u. This allows us to assume radial symmetry with the coordinate z in the direction of the axis of the cylinder, and the coordinate r being radial distance. We also assume an instantaneous reaction between oxygen and both the haemoglobin and myoglobin molecules, as has been justified previously, [9]. The governing equations for steady-state oxygen partial pressure P are

$$\nabla \cdot \left(\left(\alpha_c D_c + c_H D_H f'(P) \right) \nabla P \right) = u \left(\alpha_c + c_H f'(P) \right) \frac{\partial P}{\partial z}, \qquad \text{in the capillary,} \tag{1}$$

$$\nabla \cdot \left(\left(\alpha_T D_T + c_m D_m g'(P) \right) \nabla P \right) = q(P), \qquad \text{in tissue,} \tag{2}$$

where: α_c, α_T are the solubilities of oxygen in blood and tissue; D_c, D_T are the diffusion coefficients of free oxygen in blood and tissue; D_H, D_m are the diffusion coefficients of haemoglobin and

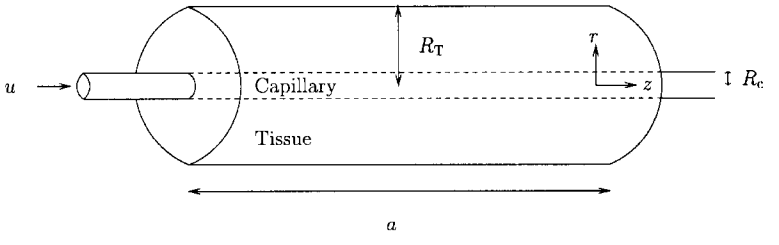


Figure 1. The model used.

myoglobin; c_H, c_m are the oxygen carrying capacities of haemoglobin and myoglobin; $f(P), g(P)$ are the oxygen dissociation curves for haemoglobin and myoglobin that have been used previously, [9], and are given in Appendix A; and $q(P)$ is the oxygen uptake, which we emphasise is a function of P, and is discussed below. The boundary conditions are

$$P = P_a, \qquad \text{for } 0 < r < R_C \qquad \text{and} \qquad z = 0, \tag{3}$$

$$\frac{\partial P}{\partial n} = 0, \qquad \text{on other boundaries,} \tag{4}$$

where $\frac{\partial P}{\partial n}$ denotes the normal derivative. The difference between this model and that described by Whiteley *et al.*, [9], is that we allow a more general oxygen uptake, $q(P)$, in this work.

2.2. The ODE Model

The ODE model that we use is that given by Salathe and Kolkka [7] modified to take account of an instantaneous reaction between the oxygen and myoglobin molecules, and also allowing a general oxygen uptake, $q(P)$. This model takes account only of convective transport in the capillary and neglects radial diffusion, and so we may write $P = P_c(z)$ in the capillary and $P = P_T(r, z)$ in tissue. The governing equations are

$$u\pi R_C^2 \left(\alpha_c + c_H f'(P_c)\right) \frac{dP_c}{dz} = -M(z), \qquad \text{in the capillary,} \tag{5}$$

$$\frac{1}{r}\frac{d}{dr}\left(r\left(\alpha_T D_T + c_m D_m g'(P_T)\right)\frac{dP_T}{dr}\right) = q(P_T), \qquad \text{in tissue,} \tag{6}$$

where $M(z)$ is the oxygen removed from the capillary and is given by

$$M(z) = \int_{R_C}^{R_T} 2\pi r q(P_T(r, z))\, dr.$$

The initial and boundary conditions for equations (5) and (6) are

$$P_c(0) = P_a, \tag{7}$$

$$P_T(R_C, z) = P_c(z), \tag{8}$$

$$P_T'(R_T, z) = 0. \tag{9}$$

2.3. The Oxygen Consumption Function $q(P)$

We investigate two functions that are used to describe $q(P)$. The first is the step function

$$q(P) = \begin{cases} q_0, & P > 0, \\ 0, & P = 0, \end{cases} \tag{10}$$

where q_0 is the oxygen demand, as has been used by many authors [5–7,9–11]. The second oxygen consumption function is the piecewise linear function

$$q(P) = \begin{cases} q_0, & P \geq P_{\text{crit}}, \\ \dfrac{q_0 P}{P_{\text{crit}}}, & 0 \leq P < P_{\text{crit}}, \end{cases} \tag{11}$$

where $P_{\text{crit}} = 74600000 q_0$ and the units of partial pressure are mm Hg and the units of oxygen demand are $\text{mol}\,\text{cm}^3\,\text{s}^{-1}$. This is the linearised form of the oxygen uptake function given by Farmery and Whiteley [1] and also described by Popel [2].

Salathe and Kolkka [7] have solved equations (5) and (6) using the step function equation (10) to model oxygen consumption. When the parameters were chosen suitably, regions existed where oxygen partial pressure was zero. We show in Appendix B that when equation (11) is used to model oxygen consumption, oxygen partial pressure may not fall to zero. This indicates that there will be significant differences between the solution of the governing equations in the cases highlighted by Salathe and Kolkka [7] depending on whether equations (10) or (11) is used to model oxygen consumption.

3. RESULTS

Unless otherwise stated, in the simulations in this section, we use the parameters that are used by Whiteley *et al.* [9]. These parameters are given in Table 1. As we need low oxygen tension in the tissue to investigate the differences between equations (10) and (11), we vary some of these parameters to give low oxygen concentrations, such as a relatively large tissue volume and high oxygen demand by the tissue.

Table 1. The parameters used.

Parameter	Value
R_c	3.25×10^{-4} cm
R_T	3.25×10^{-3} cm
a	1.625×10^{-2} cm
u	$0.03\,\mathrm{cm\,s^{-1}}$
α_c	$1.527 \times 10^{-9}\,\mathrm{mol\,cm^{-3}\,(mm\,Hg)^{-1}}$
α_T	$1.295 \times 10^{-9}\,\mathrm{mol\,cm^{-3}\,(mm\,Hg)^{-1}}$
D_c	$1.12 \times 10^{-5}\,\mathrm{cm^2\,s^{-1}}$
D_T	$1.7 \times 10^{-5}\,\mathrm{cm^2\,s^{-1}}$
D_H	$1.4 \times 10^{-7}\,\mathrm{cm^2\,s^{-1}}$
D_m	$5.0 \times 10^{-7}\,\mathrm{cm^2\,s^{-1}}$
c_H	$9.1 \times 10^{-6}\,\mathrm{mol\,cm^{-3}}$
c_m	$2.8 \times 10^{-7}\,\mathrm{mol\,cm^{-3}}$
k_M	$65\,\mathrm{s^{-1}}$
k'_M	$2.4 \times 10^{10}\,\mathrm{mol^{-1}\,cm^3\,s^{-1}}$
q_0	$5 \times 10^{-8}\,\mathrm{mol\,cm^{-3}\,s^{-1}}$

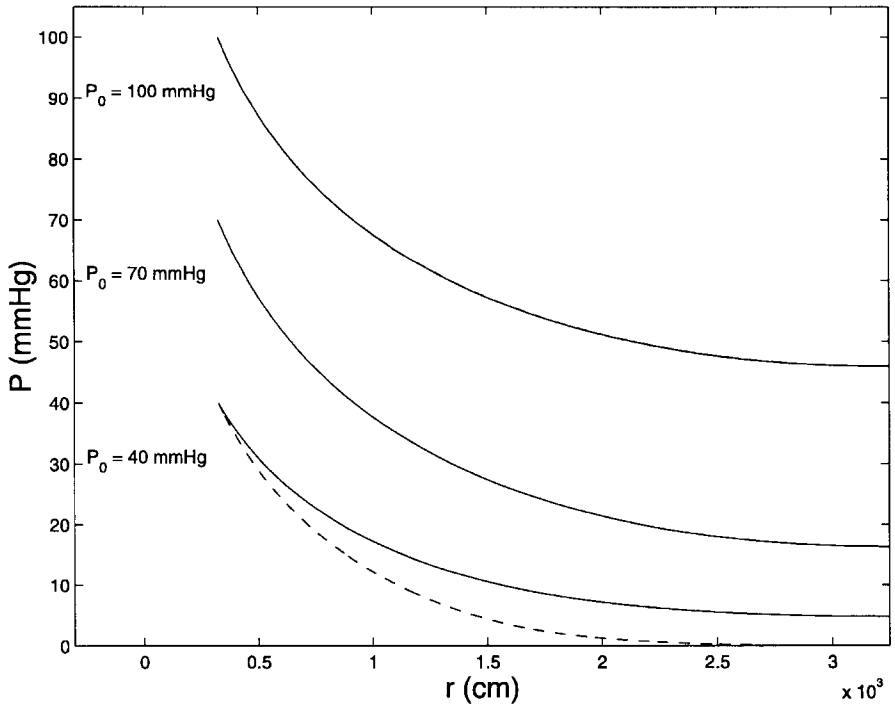
3.1. Oxygen Uptake for Low Oxygen Partial Pressure

We begin by investigating the differences in oxygen transport to tissue that are seen when using the different forms of the oxygen uptake function $q(P)$ given by equations (10) and (11).

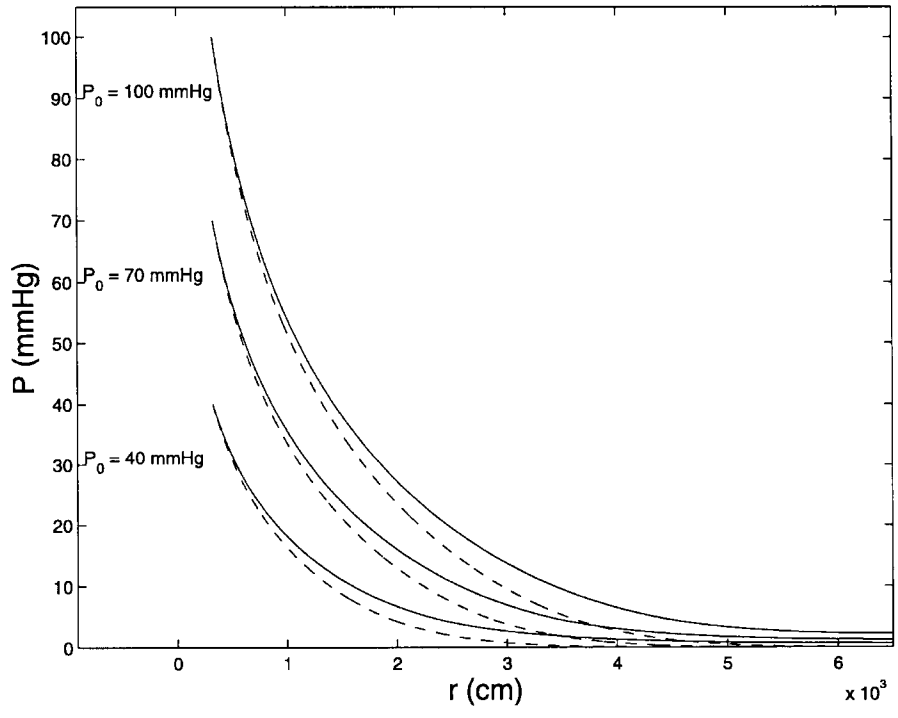
In Figure 2, we plot the results of simulations that investigate the effect on the solution of the ODE model, equation (6), on the choice of oxygen consumption function, $q(P)$. In Figure 2a, we use double the normal oxygen demand, so that $q_0 = 10^{-7}\,\mathrm{mol\,cm^3\,s^{-1}}$. In Figure 2b, we use double the normal tissue radius so that $R_T = 0.0065$ cm. In both graphs, we investigate the solution with boundary condition at the capillary for P_T being 100 mm Hg, 70 mm Hg, and 40 mm Hg. The solid lines are the solutions where equation (11) is used for the oxygen consumption, the broken lines are the solutions where equation (10) is used for the oxygen consumption.

We see in Figure 2a, (the simulation with a large oxygen demand) that, for the boundary condition at the capillary P_T being either 100 mm Hg or 70 mm Hg, there is no difference between the two models. This is because P_T is always greater than P_{crit}, and so the oxygen consumption given by equation (10) is identical to that given by equation (11). However, when we use the boundary condition $P_T = 40$ mm Hg at the capillary, the solutions from the two models are significantly different, with the model with a continuous $q(P)$ having a higher oxygen partial pressure (due to less oxygen being consumed). Note that all values of P_T in this solution are affected, and not just values of P_T that are less than P_{crit}.

We see in Figure 2b (the simulation with a large tissue radius) that the solutions are different for all of the boundary conditions used, with the model with a continuous $q(P)$ having a higher oxygen partial pressure. Again, note that all values of P_T are affected.

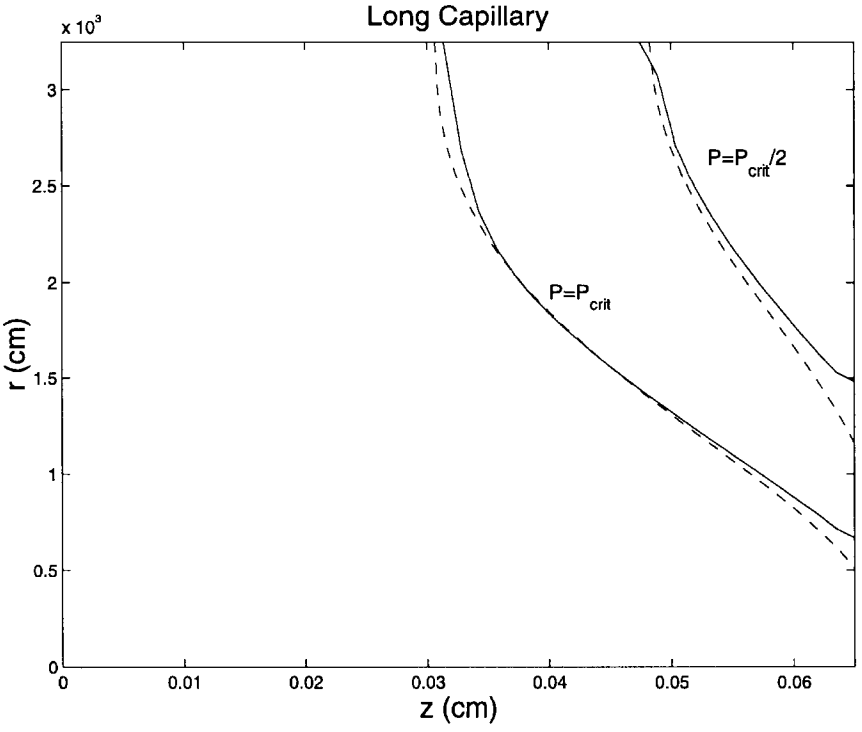


(a)

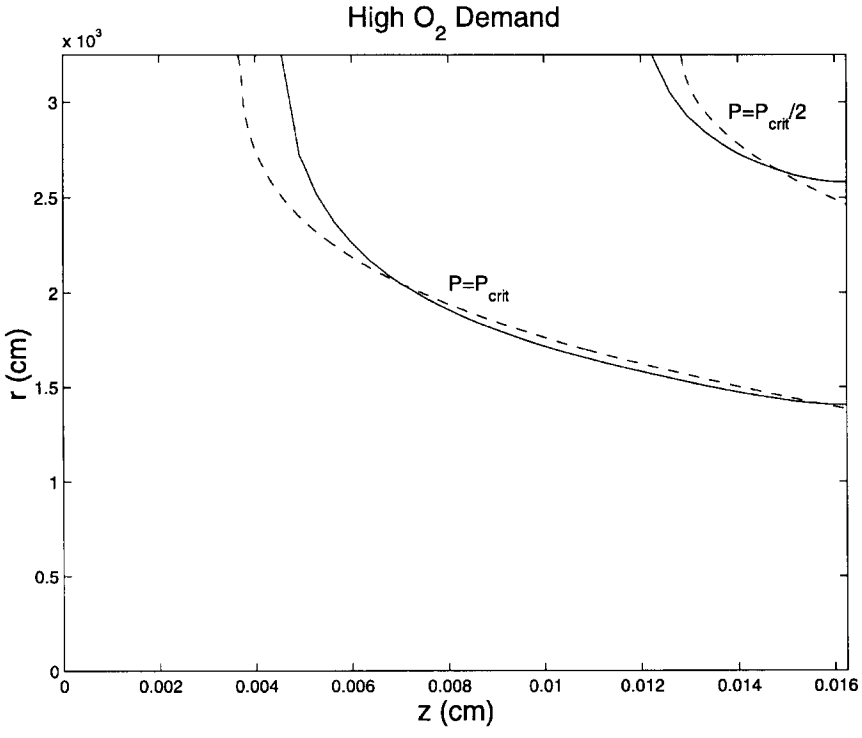


(b)

Figure 2. The effect of different forms of oxygen consumption $q(P)$ for tissue with regions of low oxygen partial pressure. The ODE model that neglects axial symmetry is used. Graph (a) simulates a high oxygen demand, graph (b) simulates a large tissue radius. In both graphs, the solid line represents the simulation with the continuous function $q(P)$ given by equation (11) and the broken line represents the simulation with the discontinuous function $q(P)$ given by equation (10).

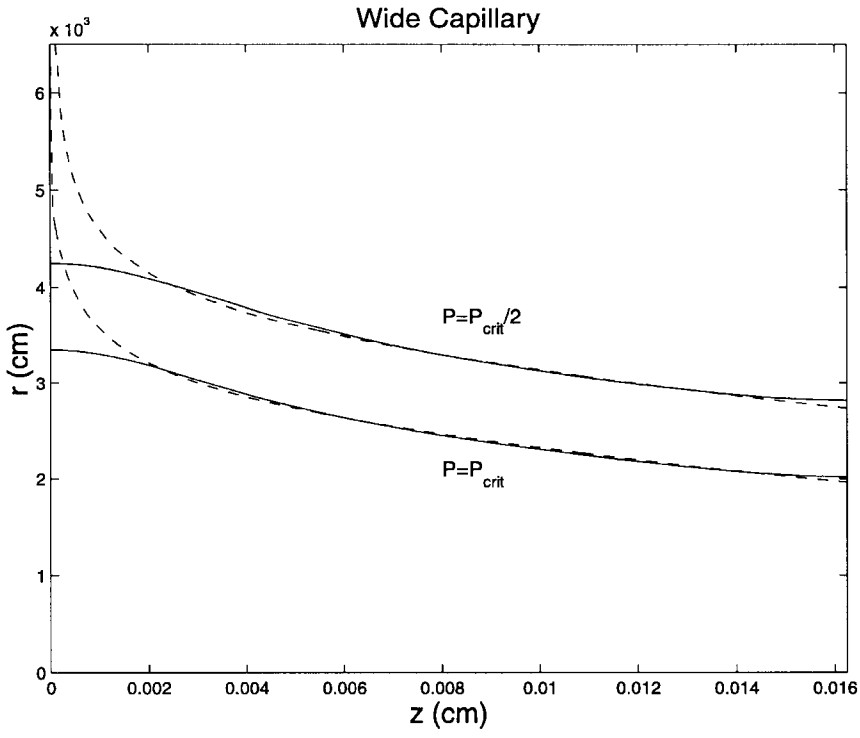


(a)



(b)

Figure 3. Regions of tissue where oxygen demand is not met: (a) a long cylinder; (b) a high oxygen demand; (c) a tissue region with a large radius. The solid lines correspond to the PDE model (equations (1) and (2)), the broken lines to the ODE model (equations (5) and (6)). In all graphs, the lower set of lines are where $P = P_{\text{crit}}$ and the higher set of lines are where $P = P_{\text{crit}}/2$.



(c)

Figure 3. (cont.)

3.2. Regions of Tissue where Oxygen Demand is Not Met

We have seen that it is necessary to use the more physiologically realistic oxygen consumption function given in equation (11) when areas of low oxygen tension exist. We now use this oxygen consumption function to compare the locations of regions of tissue where $q(P) < q_0$ that are predicted by both the ODE model and the PDE model.

The simulations chosen are shown in Figure 3. In Figure 3a, we simulate a long cylinder with $a = 0.065\,\text{cm}$, four times the normal length. In Figure 3b, we simulate a high oxygen demand, $q_0 = 10^{-7}\ \text{mol cm}^{-3}\ \text{s}^{-1}$, double the normal value. In Figure 3c, we simulate a high tissue radius, $R_T = 0.0065\,\text{cm}$, double the normal value. We plot the curves where $P = P_{\text{crit}}$ (where oxygen consumption will first fall below oxygen demand) and where $P = P_{\text{crit}}/2$. The solid lines refer to the PDE model, the broken lines to the ODE model. In Figures 3a and 3b, the curves predicted by the two models are very similar and so the ODE model is clearly a good approximation to the PDE model. However, in Figure 3c, we see that there is a significant difference between the curves predicted by the two models for small values of z. Away from this region, the curves predicted by the two models are very similar.

4. DISCUSSION

The two aims of this study were to investigate

(i) the effect of different oxygen consumption functions and

(ii) the effect of different mathematical models on the location of regions of low oxygen partial pressure in tissue.

We have found, in common with Taylor and Murray [8] (who used a different domain for the solution of the governing equations) that the choice of oxygen consumption function affects the solution significantly where regions of low tissue oxygen concentration exist. In these cases, a physiologically realistic relationship between oxygen consumption and partial pressure must be

used, such as that given by Farmery and Whiteley [1]. Using this oxygen consumption function we have shown that with this formulation of the problem, oxygen tension cannot fall to zero. Importantly, the solution is affected in all regions of tissue that oxygen diffuses through en route to areas of low oxygen tension and not just the areas of low tissue oxygen tension.

In Figure 3, we saw that when regions of low tissue oxygen tension existed in the region of $z = 0$, the ODE model predicted a very different region of low oxygen tension to that given by the PDE model. This is due to neglecting axial diffusion. Whiteley *et al.* [9], have shown that this is not a valid assumption in this region of the tissue. Away from this region, both the PDE model and ODE model predicted very similar regions of low oxygen tensions. In these situations, the assumptions made in deriving the ODE model do not affect the predictions of the PDE model, and so the (much more computationally efficient) ODE model may be used.

APPENDIX A
OXYGEN DISSOCIATION CURVES

We use the same dissociation curves that are used by Whiteley *et al.*, [9]. These dissociation curves are given by

$$f(P) = \begin{cases} \dfrac{a_1 P + a_2 P^2 + a_3 P^3 + P^4}{a_4 + a_5 P + a_6 P^2 + a_7 P^3 + P^4}, & P \geq 12\,\text{mm Hg}, \\ 0.003683P + 0.000584P^2, & P < 12\,\text{mm Hg}, \end{cases}$$

$$g(P) = \frac{k'_M \alpha_T P}{k'_M \alpha_T P + k_M},$$

where P is measured in mm Hg, k_M is the backward reaction rate for the oxy-myoglobin reaction, k'_M is the forward reaction rate for the oxy-myoglobin reaction, and

$$\begin{aligned} a_1 &= -8.5322289 \times 10^3, & a_2 &= 2.1214010 \times 10^3, \\ a_3 &= -6.7073989 \times 10, & a_4 &= 9.3596087 \times 10^5, \\ a_5 &= -3.1346258 \times 10^4, & a_6 &= 2.3961674 \times 10^3, \\ & & a_7 &= -6.7104406 \times 10. \end{aligned}$$

The values of k_M and k'_M are given in Table 1. Graphs of $f(P)$ and $g(P)$ are shown in Figure 4.

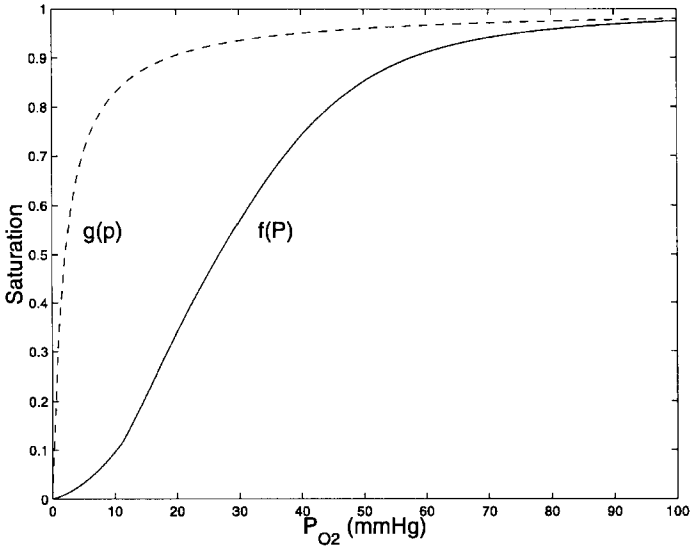


Figure 4. The oxy-haemoglobin dissociation curve $f(P)$ (solid line) and the oxy-myoglobin dissociation curve $g(P)$ (broken line).

APPENDIX B

PROOF THAT $P > 0$ FOR $q(P)$ GIVEN BY EQUATION (11)

We begin by proving the result for the ODE model that neglects axial symmetry (described by equations (5) and (6)) that tissue oxygen partial pressure is never zero. For the PDE model, there is extra diffusion and so if $P(r, z) > 0$ for the ODE model then $P(r, z) > 0$ for the PDE model as well.

Suppose the solution of equation (6) at $r = r_\epsilon$ is $P_T(r_\epsilon, z) = \epsilon$ for some ϵ where $0 < \epsilon \ll 1$. In this region, we may use the approximation $g'(P_T) \approx g'(0)$, which has error $\mathcal{O}(\epsilon)$, and write equation (6) as

$$\frac{\Gamma}{r}\frac{d}{dr}\left(r\frac{dP_T}{dr}\right) = P, \tag{B.1}$$

where

$$\Gamma = \frac{(\alpha_T D_T + c_m D_m g'(0))P_{\text{crit}}}{q_0}. \tag{B.2}$$

This may be written

$$\Gamma r^2\frac{d^2P_T}{dr^2} + \Gamma r\frac{dP_T}{dr} - r^2P = 0. \tag{B.3}$$

By using the change of variable $r \to i\sqrt{\Gamma}r$, equation (B.3) may be reduced to Bessel's equation

$$r^2\frac{d^2P_T}{dr^2} + r\frac{dP_T}{dr} + r^2P = 0 \tag{B.4}$$

and so we may write

$$P_T = K_1 J_0\left(i\sqrt{\Gamma}r\right) + K_2 Y_0\left(i\sqrt{\Gamma}r\right), \tag{B.5}$$

where K_1 and K_2 are complex constants, $J_0(x)$ and $Y_0(x)$ are linearly independent solutions of equation (B.4) given by

$$J_0(x) = \sum_{m=0}^{\infty}\frac{(-1)^m x^{2m}}{2^{2m}(m!)^2}, \qquad Y_0(x) = \frac{2}{\pi}\left(J_0(x)\left(\log\frac{x}{2} + \gamma\right) + \sum_{m=1}^{\infty}\frac{(-1)^{m-1}\nu_m x^{2m}}{2^{2m}(m!)^2}\right) \tag{B.6}$$

and

$$\nu_m = 1 + \frac{1}{2} + \frac{1}{3} + \cdots + \frac{1}{m}, \qquad \gamma = \lim_{m\to\infty}(\nu_m - \log m).$$

From equation (B.6) we see that, as the expansion for $J_0(x)$ contains only even powers of x, $J_0(ix)$ is a real-valued function. For the same reason, the infinite sum in the expression for $Y_0(ix)$ is real, and so the imaginary part of $Y_0(x)$ is proportional to $J_0(x)$ and we may write

$$J_0\left(i\sqrt{\Gamma}r\right) = h_1(r), \qquad Y_0\left(i\sqrt{\Gamma}r\right) = h_2(r) + ih_1(r), \tag{B.7}$$

where h_1 and h_2 are real-valued functions given by

$$h_1(r) = \text{Im}\left(Y_0\left(i\sqrt{\Gamma}r\right)\right), \qquad h_2(r) = \text{Re}\left(Y_0\left(i\sqrt{\Gamma}r\right)\right). \tag{B.8}$$

As a result, we may write equation (B.5) as

$$P_T(r) = Ah_1(r) + Bh_2(r), \tag{B.9}$$

where h_1 and h_2 are given by equation (B.8), and A and B are real constants. The boundary conditions for this problem are

$$P_T(r_C) = P_c, \qquad P_T'(r_T) = 0. \tag{B.10}$$

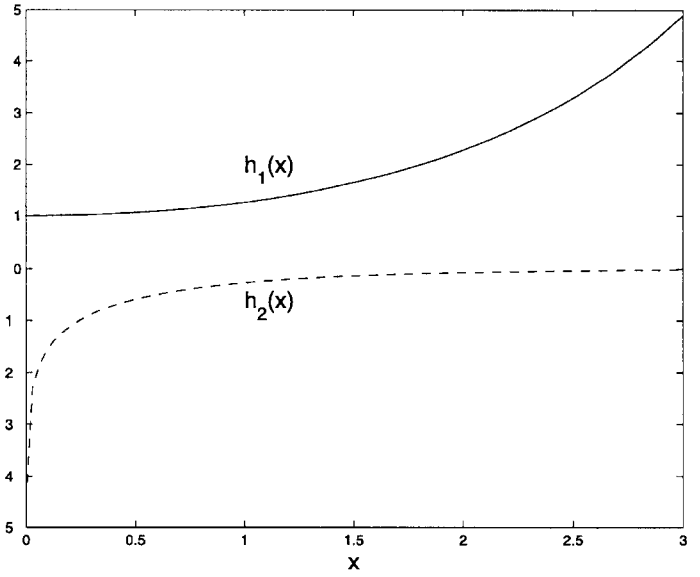


Figure 5. Functions $h_1(x)$ and $h_2(x)$ given by equation (B.8).

In Figure 5, we plot functions $h_1(x)$ and $h_2(x)$ given by equation (B.8). We note that

$$h_1(x) > 0; \qquad h_1'(x) > 0; \qquad h_2(x) < 0; \qquad h_2'(x) > 0. \tag{B.11}$$

Equations (B.9) and (B.10) give

$$Ah_1(r_C) + Bh_2(r_C) = P_c, \tag{B.12}$$

$$Ah_1'(r_T) + Bh_2'(r_T) = 0. \tag{B.13}$$

From equations (B.11) and (B.13), we may deduce that $A/B = -h_2'(r_T)/h_1'(r_T) < 0$ and so A and B have different signs. In addition, equations (B.12) and (B.13) give

$$A\left(h_1(r_C) - \frac{h_1'(r_T)h_2(r_C)}{h_2'(r_T)}\right) = P_c$$

from which we may use equation (B.11) to deduce that $A > 0$, implying that $B < 0$. Using these conditions on A and B, equation (B.11) and the general solution (equation (B.9)), we see that $P_T(r) > 0$ for all values of r.

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