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Mathematical modelling of oxygen transport to tissue

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Abstract. The equations governing oxygen transport from blood to tissue are presented for a cylindrical tissue compartment, with blood flowing along a co–axial cylindrical capillary inside the tissue. These governing equations take account of: (i) the non–linear reactions between oxygen and haemoglobin in blood and between oxygen and myoglobin in tissue; (ii) diffusion of oxygen in both the axial and radial directions; and (iii) convection of haemoglobin and plasma in the capillary. A non–dimensional analysis is carried out to assess some assumptions made in previous studies. It is predicted that: (i) there is a boundary layer for oxygen partial pressure but not for haemoglobin or myoglobin oxygen saturation close to the inflow boundary in the capillary; (ii) axial diffusion may not be neglected everywhere in the model; (iii) the reaction between oxygen and both haemoglobin and myoglobin may be assumed to be instantaneous in nearly all cases; and (iv) the effect of myoglobin is only significant for tissue with a low oxygen partial pressure. These predictions are validated by solving the full equations numerically and are then interpreted physically.

1. Introduction

Oxygen is transported to the body tissues by the systemic circulation. Most of the oxygen stored in the blood flowing into the capillaries is chemically bound to haemoglobin, although a small fraction is dissolved in plasma. The transport of oxygen into the tissue is driven by partial pressure gradients. Typically, oxygen stored in blood has to free itself from the haemoglobin molecule which is flowing through the capillary before it diffuses into tissue. Similarly, oxygen stored in tissue may be dissolved or chemically bound to myoglobin. The transport of oxygen from blood to tissue therefore involves convection, diffusion and reaction processes. An accurate description of the oxygen partial pressure within tissue is physiologically important - there is evidence that the oxygen consumption of cells within the tissue falls dramatically when the oxygen partial pressure falls below a critical threshold, [17]. In addition, some clinical techniques (see, for example, [4] and some models predicting the collapse of regions of the lungs, [5]) use calculations based on mathe-

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matical models of oxygen transport to tissue. If these techniques are to be successful, it is therefore essential that oxygen transport to tissue is modelled realistically.

Many authors have investigated the solution of the governing equations using various simplifications. Murray, [7], considered the one dimensional transport of oxygen through a solution containing either haemoglobin or myoglobin. This model considered diffusion in one dimension and the reaction between oxygen and either the haemoglobin or myoglobin molecule. A singular perturbation method was used to solve the governing equations. This was later extended, [8], to the problem of oxygen transport in a circular region with radial symmetry.

Rather than consider each capillary separately, Salathe and co–workers [11, 13–15] considered a group of several capillaries to investigate the effect of inhomogeneities in oxygen supply in capillaries. Oxygen concentration was calculated by combining the governing equations inside the capillaries and in tissue using a suitable weighting. This work has assumed that free oxygen and chemically bound oxygen are in equilibrium in both blood and tissue and neglects diffusion in the direction of the blood flow. Initial work, [11, 13] ignored the non–linear effects of myoglobin and haemoglobin. Later work, [14, 15], used asymptotic methods to investigate the solution of these non–linear equations.

Sharan, [18], considered a single capillary surrounded by a co–axial cylindrical tissue compartment. In the capillary there was diffusion in both the axial and radial directions, together with consideration of the non–linear oxy-haemoglobin dissociation curve. An instantaneous reaction was assumed between the oxygen and haemoglobin molecules. Only radial diffusion was considered in the tissue, and the effect of myoglobin was neglected completely. A finite–element solution to the governing equations was used to show the importance of using a non–linear oxyhaemoglobin dissociation curve.

Despite the common assumption of neglecting diffusion in the direction of blood flow, Schubert and Zhang, [16], report the importance of axial diffusion in experimental data.

In this paper we use a model consisting of a single cylindrical capillary with blood flowing through it surrounded by a co–axial cylindrical tissue compartment. We take account of the non–linear reaction terms between oxygen and haemoglobin in blood and between oxygen and myoglobin in the tissue. We consider diffusion of oxygen, haemoglobin and myoglobin in both the radial and axial directions. The aim of this paper is to use the non–dimensional form of the governing equations to investigate the effect of the various simplifying assumptions described above, namely: (i) neglecting axial diffusion; (ii) assuming an instantaneous reaction between oxygen and both haemoglobin and myoglobin: and (iii) neglecting the effect of facilitated myoglobin diffusion. In particular, we show that there is a boundary layer for oxygen partial pressure in the region of the inflow boundary of blood into the capillary, but not for either haemoglobin or myoglobin saturation near this boundary. Due to this boundary layer, we may not neglect axial diffusion. In most cases, we may assume an instantaneous reaction between oxygen and the haemoglobin and myoglobin molecules. The effect of myoglobin only becomes significant when oxygen partial pressure in tissue is low. These predictions are validated numerically, and interpreted physically.

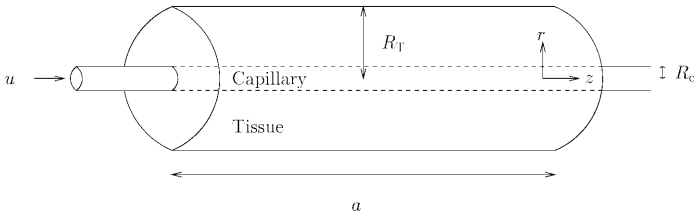

Fig. 1. The mathematical model used.

2. The mathematical model

We use a mathematical model consisting of a circular cylindrical capillary inside a coaxial circular cylindrical region of tissue, shown in Fig. 1. A glossary of terms used is given below.

r	Radial coordinate
z	Axial coordinate
R_c	Capillary radius
R_T	Tissue radius
a	Length of capillary
u	Blood velocity in capillary
P	Oxygen partial pressure
P_a	Arterial oxygen partial pressure
S	Fractional haemoglobin saturation
Y	Fractional myoglobin saturation
α_c	Oxygen solubility in plasma
α_T	Oxygen solubility in tissue
D_c	Diffusion coefficient of oxygen in plasma
D_T	Diffusion coefficient of oxygen in tissue
D_H	Diffusion coefficient of haemoglobin
D_M	Diffusion coefficient of myoglobin
c_H	Oxygen carrying capacity of haemoglobin
c_M	Oxygen carrying capacity of myoglobin
k_H	Backward reaction rate for oxyhaemoglobin reaction
k_M	Backward reaction rate for oxymyoglobin reaction
k'_M	Forward reaction rate for oxymyoglobin reaction
q	Oxygen consumption

We assume that blood flowing into the capillary from the artery, known as "arterial blood", has a constant partial pressure and that the oxy–haemoglobin reaction has reached equilibrium in arterial blood. Assuming a steady state and radial symmetry, we look for solutions of the form $P = P(r, z)$, $S = S(r, z)$ and $Y = Y(r, z)$.

2.1. Governing equations

2.1.1. Capillary

In the capillary, the equations governing oxygen transport are

$$\alpha_{\mathrm{c}} D_{\mathrm{c}} \nabla^2 P = u \alpha_{\mathrm{c}} \frac{\partial P}{\partial z} - \rho_{\mathrm{c}} \tag{1}$$

$$c_{\mathrm{H}} D_{\mathrm{H}} \nabla^2 S = u c_{\mathrm{H}} \frac{\partial S}{\partial z} + \rho_{\mathrm{c}} \tag{2}$$

where the reaction term, ρ_{c}, is given by

$$\rho_{\mathrm{c}} = k_{\mathrm{H}} c_{\mathrm{H}} \frac{S - f(P)}{1 - f(P)} \tag{3}$$

as derived by Clark *et al.,* [1], and Whiteley *et al.,* [19], where $S = f(P)$ is the equilibrium oxyhaemoglobin dissociation relationship. We use the dissociation curve given by Kelman, [6]:

$$f(P) = \begin{cases} \frac{a_1 P + a_2 P^2 + a_3 P^3 + P^4}{a_4 + a_5 P + a_6 P^2 + a_7 P^3 + P^4} & P \geq 12 mmHg \\ 0.003683 P + 0.000584 P^2 & P < 12 mmHg \end{cases} \tag{4}$$

where P is measured in mmHg, and

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

We note that when oxygen partial pressure and haemoglobin saturation are in equilibrium the reaction term, Eq. 3, is zero.

Some authors, [10, 12, 15], have negected radial diffusion of oxygen in the capillary. These authors justify this by claiming that the recirculating flow in the plasma reported by Aroesty and Gross, [3], leads to uniform radial mixing of oxygen within the capillary. However work by Whiteley *et al.,* [19], using a more realistic geometry has shown that there is no recirculating flow, and so we include radial diffusion of oxygen in the capillary in the mathematical model used in this study.

2.1.2. Tissue

The governing equations in tissue have a very similar form. They are given by

$$\alpha_{\mathrm{T}} D_{\mathrm{T}} \nabla^2 P = -\rho_{\mathrm{T}} + q \tag{5}$$

$$c_{\mathrm{M}} D_{\mathrm{M}} \nabla^2 Y = \rho_{\mathrm{T}} \tag{6}$$

where the reaction term, ρ_{T}, is given by, [8]:

$$\rho_{\mathrm{T}} = k_M c_{\mathrm{M}} Y - \alpha_{\mathrm{T}} k'_M c_{\mathrm{M}} (1 - Y) P \tag{7}$$

The dissociation curve for myoglobin saturation in equilibrium is given by

$$g(P) = \frac{k'_{\mathrm{M}} \alpha_{\mathrm{T}} P}{k'_{\mathrm{M}} \alpha_{\mathrm{T}} P + k_{\mathrm{M}}} \tag{8}$$

Combining Eqs. 7 and 8 allows us to write the reaction term in terms of this dissociation curve as

$$\rho_{\mathrm{T}} = c_{\mathrm{M}} k_{\mathrm{M}} \frac{Y - g(P)}{1 - g(P)} \tag{9}$$

2.2. Boundary conditions

1. Radial symmetry implies that

$$\frac{\partial P}{\partial r} = \frac{\partial S}{\partial r} = 0 \quad \text{at } r = 0, \quad 0 \le z \le a \tag{10}$$

2. P is initially in equilibrium with arterial blood, so

$$P = P_{\mathrm{a}} \quad z = 0, \quad 0 \le r \le R_{\mathrm{c}} \tag{11}$$

3. The flux of dissolved oxygen per unit area is given by $\alpha D \nabla P$, and is zero across closed boundaries. In addition, we assume a non–diffusional flux condition where blood flows out of the capillary, and so we have

$$\frac{\partial P}{\partial z} = 0 \quad z = 0, \quad R_{\mathrm{c}} \le r \le R_{\mathrm{T}} \tag{12}$$

$$\frac{\partial P}{\partial r} = 0 \quad r = R_{\mathrm{T}}, \quad 0 \le z \le a \tag{13}$$

$$\frac{\partial P}{\partial z} = 0 \quad z = a, \quad 0 \le r \le R_{\mathrm{T}} \tag{14}$$

4. Haemoglobin saturation is in equilibrium with partial pressure in blood entering the capillary and so

$$S = f(P_{\mathrm{a}}) \quad z = 0, \quad 0 \le r \le R_{\mathrm{c}} \tag{15}$$

where $f(P)$ is the oxyhaemoglobin equilibrium relationship given in Eq. 4.

5. No diffusive flux of haemoglobin out of capillary across any other boundary

$$\frac{\partial S}{\partial r} = 0 \quad r = R_{\mathrm{c}}, \quad 0 \le z \le a \tag{16}$$

$$\frac{\partial S}{\partial z} = 0 \quad z = a, \quad 0 \le r \le R_{\mathrm{c}} \tag{17}$$

6. No diffusive flux of myoglobin out of tissue

$$\frac{\partial Y}{\partial r} = 0 \qquad r = R_{\mathrm{c}}, R_{\mathrm{T}}, \qquad 0 \le z \le a \tag{18}$$

$$\frac{\partial Y}{\partial z} = 0 \qquad z = 0, a, \qquad R_{\mathrm{c}} \le r \le R_{\mathrm{T}} \tag{19}$$

7. For a unique solution for Y we must specify its value on some part of the tissue boundary. At a large distance from the capillary we assume it will be in equilibrium with partial pressure. We apply this by writing

$$Y(a, R_{\mathrm{T}}) = g(P(a, R_{\mathrm{T}})) \tag{20}$$

where $g(P)$ is the oxymyoglobin equilibrium relationship given in Eq. 8.

8. P and the flux of oxygen are continuous across the capillary–tissue interface. These conditions may be written

$$P\big|_{z=R_{\mathrm{c}}-} = P\big|_{z=R_{\mathrm{c}}+} \qquad 0 \le z \le a \tag{21}$$

$$\alpha_{\mathrm{C}} D_{\mathrm{C}} \frac{\partial P}{\partial r}\bigg|_{z=R_{\mathrm{c}}-} = \alpha_{\mathrm{T}} D_{\mathrm{T}} \frac{\partial P}{\partial r}\bigg|_{z=R_{\mathrm{c}}+} \qquad 0 \le z \le a \tag{22}$$

3. Non–dimensionalisation of the problem

In this section we non–dimensionalise the governing eqations, Eqs. 1-9. This will enable us to estimate the magnitude of each term in these equations and predict which terms, and therefore which physical processes, dominate the solution of these equations. It will also allow us to investigate some of the assumptions made by other authors, described in Section 1.

Before we non–dimensionalise the governing equations, we must obtain values for each of the parameters occuring. These are given in Table 1. In this table we have chosen a, the length of the capillary to be 50 times R_{c}.

3.1. Capillary

We first consider the reaction term between oxygen and haemoglobin, Eq. 3. This reaction unbinds oxygen from the haemoglobin model so that it can be transported to tissue, and so we assume that $S - f(P) \ge 0$. By noting further that $S < 1$ we may deduce that

$$0 \le \frac{S - f(P)}{1 - f(P)} < 1$$

We now non–dimensionalise the problem in the capillary in the region of the inflow boundary. All scalings are chosen so that the non–dimensional variables range from 0 to 1. We set

$$\begin{aligned} P &\to P_0 + (P_1 - P_0)\, P & \qquad S &\to S_0 + (S_1 - S_0)\, S \\ r &\to R_{\mathrm{c}} r & \qquad z &\to L z \end{aligned} \tag{23}$$

Table 1. The parameters used.

Parameter	Value	Reference
R_c	3.25×10^{-4} cm	[18]
R_T	3.25×10^{-3} cm	[18]
a	1.625×10^{-2} cm	
u	0.03 cm s^{-1}	[18]
α_c	1.527×10^{-9} mol cm^{-3} $(mmHg)^{-1}$	[18]
α_T	1.295×10^{-9} mol cm^{-3} $(mmHg)^{-1}$	[18]
D_c	1.12×10^{-5} cm^2 s^{-1}	[18]
D_T	1.7×10^{-5} cm^2 s^{-1}	[18]
D_H	1.4×10^{-7} cm^2 s^{-1}	[2]
D_M	5.0×10^{-7} cm^2 s^{-1}	[14]
c_H	9.1×10^{-6} mol cm^{-3}	[18]
c_M	2.8×10^{-7} mol cm^{-3}	[8]
k_H	40 s^{-1}	[7]
k_M	65 s^{-1}	[8]
k'_M	2.4×10^{10} mol^{-1} cm^3 s^{-1}	[8]
q	5×10^{-8} mol cm^{-3} s^{-1}	[8]

where L is a length scale to be chosen appropriately, and P_0, P_1, S_0 and S_1 are to be determined. We will use different scalings in different regions of the capillary. We may now write down the non–dimensional form of Eqs. 1-3:

$$A_1 \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial P}{\partial r}\right) + A_2\frac{\partial^2 P}{\partial z^2} = \frac{\partial P}{\partial z} + A_3\frac{S - f(P)}{(1-S_0)/(S_1-S_0) - f(P)} \quad (24)$$

$$B_1 \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial S}{\partial r}\right) + B_2\frac{\partial^2 S}{\partial z^2} = \frac{\partial S}{\partial z} - B_3\frac{S - f(P)}{(1-S_0)/(S_1-S_0) - f(P)} \quad (25)$$

where $f(P)$, has been non–dimensionalised using the same scaling as for S and the dimensionless parameters A_1, A_2, A_3, B_1, B_2, B_3 are given by

$$A_1 = \frac{D_c L}{R_c^2 u} = 3.5 \times 10^3 L$$

$$A_2 = \frac{D_c}{Lu} = \frac{3.7 \times 10^{-4}}{L}$$

$$A_3 = \frac{k_H c_H L}{u\alpha_c (P_1 - P_0)} = \frac{7.9 \times 10^6 L}{P_1 - P_0}$$

$$B_1 = \frac{D_H L}{R_c^2 u} = 4.4 \times 10^{-1} L$$

$$B_2 = \frac{D_H}{Lu} = \frac{4.7 \times 10^{-6}}{L}$$

$$B_3 = \frac{k_H L}{u(S_1 - S_0)} = \frac{1.3 \times 10^3 L}{S_1 - S_0}$$

and L is measured in cm.

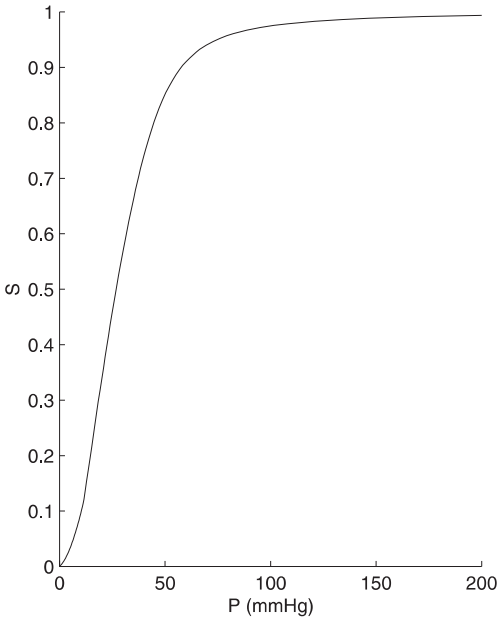

Fig. 2. The oxyhaemoglobin dissociation curve.

We begin by considering the region of the capillary near to the inflow boundary. The equilibrium oxyhaemoglobin dissociation relationship given by Eq. 4 is plotted in Fig. 2. We see that $f(P) > 0.95$ for $P > 75$ mmHg. Arterial blood entering the capillary typically has $P = 100$ mmHg and $S = 0.97$. As we have assumed that $S > f(P)$, we may use the non–dimensionalisation $P_0 = 75$ mmHg, $P_1 = P_a$, $S_0 = 0.95$ and $S_1 = 1$ in Eq. 23. To balance terms in Eq. 24 we set $L = R_c$. A_1 and A_2 are now approximately the same size in this region. Neglecting terms of $\mathcal{O}(10^{-2})$ the size of the largest terms the non–dimensional equations in this region are now:

$$A_1 \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial P}{\partial r}\right) + A_2\frac{\partial^2 P}{\partial z^2} = \frac{\partial P}{\partial z} + A_3\frac{S - f(P)}{1 - f(P)} \tag{26}$$

$$0 = \frac{\partial S}{\partial z} - B_3\frac{S - f(P)}{1 - f(P)} \tag{27}$$

The only terms that were included in the original equations, Eqs. 1 and 2 that are not included in these non–dimensional equations are the diffusion terms for oxygen bound to haemoglobin. In particular, as A_1 and A_2 are of the same order, we see that in this small region for P diffusion is equally important in both the axial and radial directions and so it is not valid to neglect axial diffusion. We see that, as the second derivatives are significant for P but not for S, we have a boundary layer for P but not S in the region of the inflow boundary into the capillary. As we have used the lengthscale $L = R_c$ to non–dimensionalise the axial coordinate, the thickness of the boundary layer is $\mathcal{O}(R_c)$.

We note that, using Eq. 27 and transforming back to dimensional parameters, we may deduce that

$$S - f(P) = \mathcal{O}(10^{-3})$$

and so, to a first approximation, we may write $S = f(P)$ in this boundary layer, i.e. assume an instantaneous reaction between oxygen and the haemoglobin molecule. We may then eliminate the reaction term from Eqs. 26 and 27 to give

$$A_1 \frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial P}{\partial r} \right) + A_2 \frac{\partial^2 P}{\partial z^2} = \left(1 + \frac{A_3}{B_3} f'(P) \right) \frac{\partial P}{\partial z} \tag{28}$$

and so we have now neglected the reaction term as well as diffusion of oxygen bound to haemoglobin from the original equations, Eqs. 1 and 2.

Whilst we have shown using the governing differential equations that we may write $S = f(P)$, we must use this with caution. We note that $\partial P/\partial r \neq 0$ on $r = R_c$, the boundary between blood and tissue. As a result, by writing $S = f(P)$ it is impossible to satisfy the boundary conditions of no flux of haemoglobin across the blood–tissue boundary, Eq. 16. This may be reconciled by a boundary layer for S along the blood–tissue boundary. In this boundary layer, the radial derivative of S changes rapidly to satisfy Eq. 16, and so the parameter B_1 must balance the parameter B_3 in Eq. 25. This may be achieved by using a scaling of $r \to L_r r$ in Eq. 23 where $L_r = 10^{-5}$ cm, and so there is a boundary layer of $\mathcal{O}(10^{-5}\text{cm})$ for S along this boundary.

Away from these boundary layers, we may now take $L = 0.01$ cm, (of order of the length of the capillary), $P_0 = 40$ mmHg (typical of P in blood leaving tissue) and $P_1 = 75$ mmHg in the non–dimensionalisation (Eq. 23). The corresponding values for S are $S_0 = 0.75$ and $S_1 = 0.95$. In this region, neglecting terms of size $\mathcal{O}(10^{-2})$ the magnitude of the largest term, the approximate non–dimensional equations are now

$$A_1 \frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial P}{\partial r} \right) = \frac{\partial P}{\partial z} + A_3 \frac{S - f(P)}{1.25 - f(P)} \tag{29}$$

$$0 = \frac{\partial S}{\partial z} - B_3 \frac{S - f(P)}{1.25 - f(P)} \tag{30}$$

and so diffusion of oxygen bound to haemoglobin and axial diffusion of free oxygen may be neglected in this region.

From Eq. 30 we may deduce that

$$\frac{S - f(P)}{1.25 - f(P)} = \mathcal{O}(10^{-2})$$

and so transforming Eq. 30 back to dimensional coordinates,

$$S - f(P) = \mathcal{O}(10^{-3})$$

and so we may again assume an instantaneous reaction, taking $S = f(P)$, except for the boundary layer for S on the capillary–tissue interface which we have discussed earlier. On combining Eqs. 29 and 30 this gives

$$A_1 \frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial P}{\partial r} \right) = \left(1 + \frac{A_3}{B_3} f'(P) \right) \frac{\partial P}{\partial z} \tag{31}$$

The only difference between Eq. 31 and Eq. 28 (the corresponding equation in the boundary) is that outside the boundary layer we may neglect diffusion in the axial direction.

3.2. Tissue

We first consider the reaction term between oxygen and myoglobin, Eq. 7. This reaction converts free oxygen to oxygen bound to the myoglobin molecule. The equilibrium relation between oxygen partial pressure and myoglobin saturation, Eq. 8, is shown in Fig. 3. We see that myoglobin is at least 90% saturated for $P > 20$ mmHg and at least 95% saturated for $P > 40$ mmHg.

Using the non–dimensionalisation

$$\begin{aligned} P &\to P_0 + (P_1 - P_0)\, P & \qquad Y &\to Y_0 + (Y_1 - Y_0)\, Y \\ r &\to L_r r & \qquad z &\to L_z z \end{aligned} \tag{32}$$

Eqs. 5 and 6 become

$$\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial P}{\partial r} \right) + \frac{L_r^2}{L_z^2} \frac{\partial^2 P}{\partial z^2} = -C_1 \frac{Y - g(P)}{(1 - Y_0)/(Y_1 - Y_0) - g(P)} + C_2 \tag{33}$$

$$\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial Y}{\partial r} \right) + \frac{L_r^2}{L_z^2} \frac{\partial^2 Y}{\partial z^2} = D_1 \frac{Y - g(P)}{(1 - Y_0)/(Y_1 - Y_0) - g(P)} \tag{34}$$

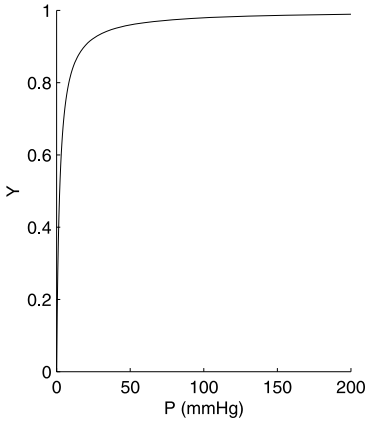

Fig. 3. The oxymyoglobin dissociation curve.

where we have used the same scaling for $g(P)$ as for Y, and

$$C_1 = \frac{c_{\mathrm{M}} k_{\mathrm{M}} L_r^2}{\alpha_{\mathrm{T}} D_{\mathrm{T}} (P_1 - P_0)} = \frac{8.2 \times 10^8 L_r^2}{(P_1 - P_0)}$$
$$C_2 = \frac{L_r^2}{\alpha_{\mathrm{T}} D_{\mathrm{T}} (P_1 - P_0)} q = \frac{2.3 \times 10^6 L_r^2}{(P_1 - P_0)}$$
$$D_1 = \frac{k_{\mathrm{M}} L_r^2}{D_{\mathrm{M}} (Y_1 - Y_0)} = \frac{1.3 \times 10^8 L_r^2}{Y_1 - Y_0}$$

In Section 3.1 we deduced that there is a boundary layer of order R_{c} in the z-direction in the region of $z = 0$. As P is continuous across the capillary–tissue boundary, Eq. 21, this boundary layer will apply in the tissue region as well. There is also a discontinuity in the boundary condition for P at $z = 0$, $r = R_{\mathrm{c}}$ where the boundary condition switches from a Dirichlet boundary condition to a Neumann boundary condition, and so we expect that diffusion in both the z and r directions to be significant in this region. A suitable scaling is therefore $L_r = L_z = R_{\mathrm{c}}$. Using $P_0 = 50$ mmHg and $P_1 = P_{\mathrm{a}}$ and the corresponding scalings $Y_0 = 0.96$ and $Y_1 = 1$ we see that, on neglecting terms of size $\mathcal{O}(10^{-2})$ the magnitude of the biggest term, Eq. 34 reduces to

$$0 = D_1 \frac{Y - g(P)}{1 - g(P)} \tag{35}$$

from which we deduce that we can assume an instantaneous reaction and write $Y = g(P)$. Eq. 33 then reduces to

$$\nabla^2 P = C_2 \tag{36}$$

We have already explained that as we have a boundary layer for P in the capillary, we will also have a boundary layer for P in the tissue. In this region we have justified writing $Y = g(P)$. From Fig. 3 we see that Y changes by only a small amount between the values of P_0 and P_1 in this region, and so there is not a boundary layer for Y in this region.

Outside this boundary layer, we use the scaling $L_r = R_{\mathrm{T}}$ and $L_z = 0.01$ (as was used in the capillary), $P_0 = 0$ mmHg, $P_1 = 75$ mmHg, $Y_0 = 0$ and $Y_1 = 1$. Using this scaling in Eqs. 33 and 34 we see that axial diffusion is of the order only ten times smaller than radial diffusion, and so may not be neglected. By using the same argument as that leading up to Eq. 35 we may deduce from the non–dimensional equations that we may write $Y = g(P)$, and so we may eliminate the reaction term to give

$$\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial}{\partial r}\left(P + \frac{C_1}{D_1} g(P)\right)\right) + \frac{L_r^2}{L_z^2}\frac{\partial^2}{\partial z^2}\left(P + \frac{C_1}{D_1} g(P)\right) = C_2 \tag{37}$$

The graph of $g'(P)$ is shown in Fig. 4. We see that, in dimensional coordinates, $g'(P) < 0.01$ for $P > 13$ mmHg. Noting that $C_1/D_1 = \mathcal{O}(10^{-1})$, we see that, for $P > 13$ mmHg we may neglect this term to give

$$\nabla^2 P = C_2 \tag{38}$$

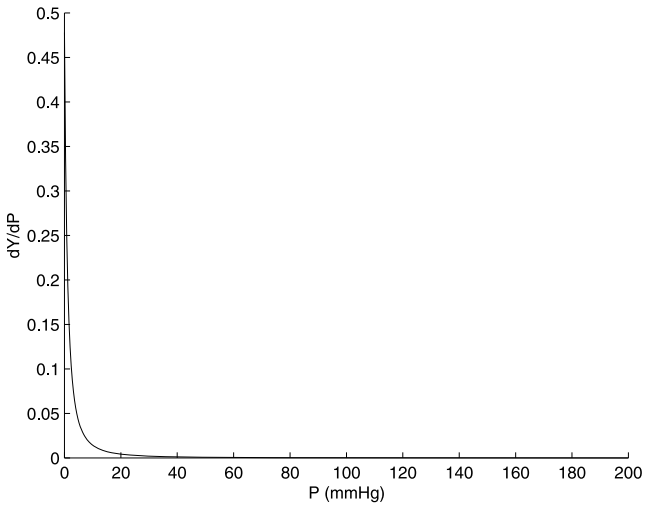

Fig. 4. The derivative of the myoglobin dissociation curve.

and so the contribution of myoglobin diffusion to total oxygen diffusion may be neglected provided that $P > 13$ mmHg.

In Section 3.1 we predicted the existence of a boundary layer for the haemoglobin saturation along the capillary–tissue interface, which may affect the assumption of an instantaneous reaction between oxygen and haemoglobin. A similar situation exists for myoglobin along this boundary. However, assuming an instantaneous reaction between oxygen and myoglobin allows us to write

$$\frac{\partial Y}{\partial r} = g'(P)\frac{\partial P}{\partial r}$$

At the capillary–tissue interface, in a physically realistic situation we will have $P > 30$ mmHg, and we can see from Fig. 4 that $g'(P)$ will be tiny giving $\partial Y/\partial r \approx 0$, and so the boundary condition Eq. 18 is satisfied even if we assume an instantaneous reaction.

4. Numerical results

In this section we solve the full conservation of mass equations, Eqs. 1-9 to investigate the phenonema predicted in Section 3. We solve these equations using the finite element method (see, for example, Reddy [9]). The mesh used was generated by the PDE toolbox provided by Matlab (The MathWorks Inc., Natick, MA) and is shown in Fig. 5. A finer mesh was tested, but did not improve the accuracy of the computed solution.

4.1. Boundary Layers

Our analysis above has predicted a boundary layer for P of $\mathcal{O}(R_c)$ inside the capillary on $z = 0$ and of $\mathcal{O}(R_c)$ inside the tissue on $z = 0$ and $r = R_c$. No

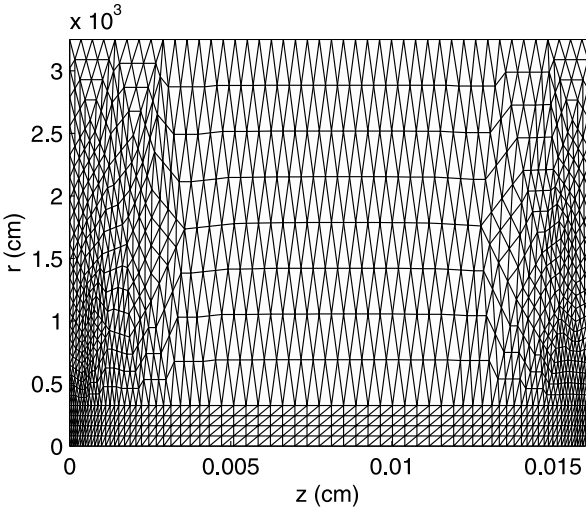

Fig. 5. The mesh used.

boundary layers were predicted for either S or Y. We begin by investigating this boundary layer for normal arterial oxygen partial pressure, $P_a = 100$ mmHg. In Fig. 6 we plot: (a) a surface plot for P; (b) a contour plot for P; (c) a surface plot for S; and (d) a surface plot for Y. Note the different scale on the r-axis in (c). In graph (b) we have added the boundary between the blood and tissue, and have drawn a square at the origin with sides $2R_c$ to show more clearly the boundary layer. In this graph, by considering the relative density of contour lines (corresponding to equally spaced values of P), we may see the presence of a boundary layer for P. Graphs (c) and (d) show no boundary layer for S or Y and so our predictions on boundary layers are correct in this case.

In Fig. 7 we repeat the simulation carried out in Fig. 6, but with $P_a = 600$ mmHg. We see the same boundary layer behaviour as in Fig. 6 for P, although, by considering the density of contour lines within the square at the origin, this boundary layer is more promenent due to the high value of P_a, as within this layer, P is reduced from P_a to approximately 75 mmHg. We note that there is still no boundary layer for S or Y.

4.2. Axial diffusion

Many authors have neglected axial diffusion in their solution of the governing equations. Our analysis in Section 3 and the plots for P in Fig. 6 and 7 indicate that the axial diffusion term, $\partial^2 P/\partial z^2$ should not be neglected. We demonstrate this numerically by solving the full governing equations, Eqs. 1-9, but neglecting the axial diffusion term. We take $P_a = 100$ mmHg as our boundary condition. This allows comparison with Fig. 6, the example in Section 4.1 where we solved the full governing equations (including the axial diffusion term). The solution to the equations neglecting axial diffusion is shown in Fig. 8, where the graphs are (a) a

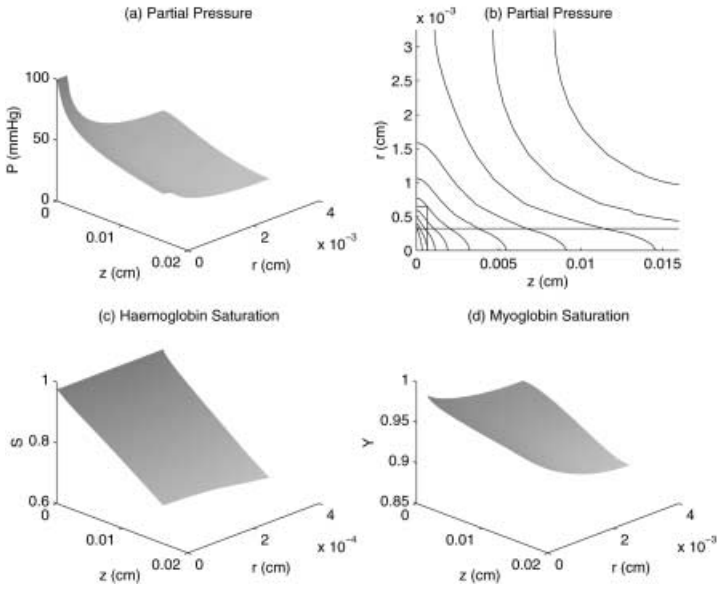

Fig. 6. The solution of the governing equations, Eqs. 1-6 and 9 with $P_a = 100$ mmHg.

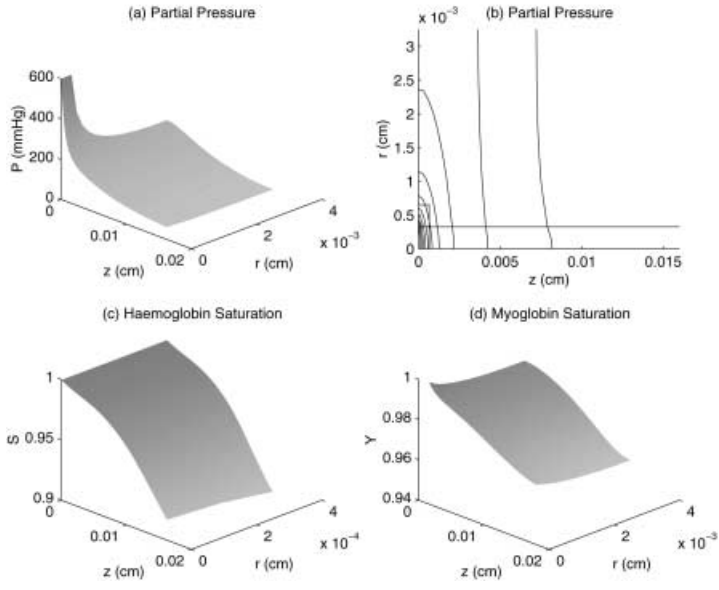

Fig. 7. The solution of the governing equations, Eqs. 1-6 and 9 with $P_a = 600$ mmHg.

surface plot for P; (b) a contour plot for P; (c) a surface plot for S; and (d) a surface plot for Y. By comparison with Fig 6, the solution including axial diffusion, we can see visually that neglecting axial diffusion has a significant effect on the solution. In this example, P differs by up to 30 mmHg, S differs by up to 0.02 and Y differs by up to 0.03.

In Fig 9 we plot the percentage error in P that is induced by neglecting axial diffusion. In Fig 9(a) $P_a = 100$ mmHg, in Fig 9(b) $P_a = 600$ mmHg. Note the difference in the scale of the vertical axis in these graphs. In both diagrams we see that the error is largest (almost 30% in (a) and over 40% in (b)) where $z = 0$ and $r = R_T$. In both diagrams as z increases, the error approaches zero. Note in (b) the negative value of the error for a small range of values of z.

4.3. Instantaneous reactions

The non–dimensionalisation analysis carried out in Section 3 demonstrated that we may assume an instantaneous reaction between oxygen and both haemoglobin and myoglobin. In the capillary region we may write $S = f(P)$ and eliminate the reaction terms from Eqs. 1 and 2 to give

$$\nabla \cdot \left(\left(\alpha_c D_c + c_H D_H f'(P) \right) \nabla P \right) = u \left(\alpha_c + c_H f'(P) \right) \frac{\partial P}{\partial z} \tag{39}$$

In the same way, in the tissue region we may write $Y = g(P)$ and eliminate the reaction term from Eqs. 5 and 6 to give

$$\nabla \cdot \left(\left(\alpha_T D_T + c_M D_M g'(P) \right) \nabla P \right) = q \tag{40}$$

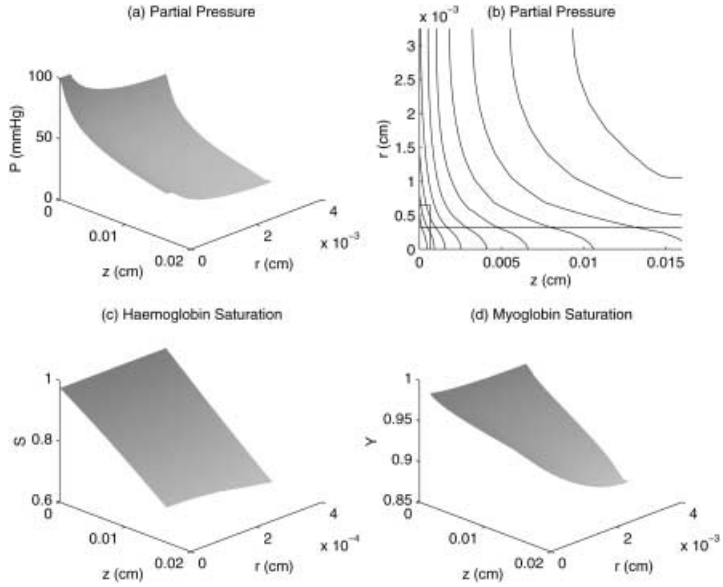

Fig. 8. The solution of the governing equations, Eqs. 1-6 and 9, but neglecting axial diffusion, with $P_a = 100$ mmHg.

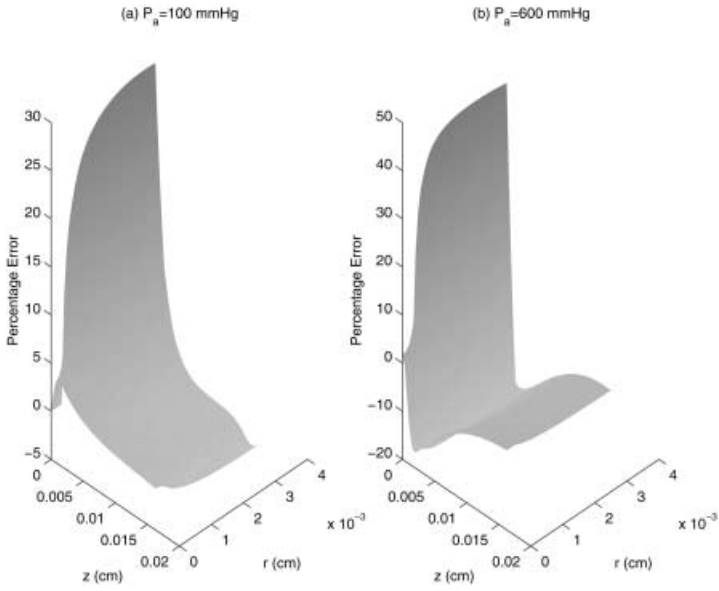

Fig. 9. The percentage error in P induced by neglecting axial diffusion.

We have already noted that $\partial P/\partial r \neq 0$ on $r = R_c$, the boundary between blood and tissue. As a result, by writing $S = f(P)$ and $Y = g(P)$ it is impossible to satisfy the boundary conditions of no flux of haemoglobin or myoglobin across the blood–tissue boundary, Eqs. 16 and 18.

We may investigate the effect of assuming an instantaneous reaction by considering the difference between the solution to both the full equations, Eqs. 1-9, and the equations assuming an instantaneous reaction, Eqs. 39 and 40. We do this for both the parameters used to generate Fig. 6 and a simulation with the same parameters except $q = 7.5 \times 10^{-8}$ mol cm^{-3} s^{-1}, a higher than normal oxygen consumption. The high oxygen consumption case was chosen so that the lowest value of P was reduced to less than 0.5 mmHg in the tissue region. Let P, S and Y be the solution of the full equations. Let $\hat{P}$ be the approximation to P calculated from Eqs. 39 and 40, and define $\hat{S} = f(\hat{P})$ in the capillary region, and $\hat{Y} = g(\hat{Y})$ in the tissue region. In Table 2 we give the maximum differences between P and $\hat{P}$; S and $\hat{S}$; Y and $\hat{Y}$.

Table 2. The maximum differences between the model with a reaction term and the model assuming an instantaneous reaction. P, S, Y correspond to the model with a reaction term; $\hat{P}$, $\hat{S}$, $\hat{Y}$ correspond to the model assuming an instantaneous reaction.

Oxygen consumption	$\max \lvert P - \hat{P} \rvert$	$\max \lvert S - \hat{S} \rvert$	$\max \lvert Y - \hat{Y} \rvert$
5×10^{-8} mol cm^{-3} s^{-1}	0.27 mmHg	0.009	0.001
7.5×10^{-8} mol cm^{-3} s^{-1}	0.72 mmHg	0.016	0.019

Table 3. The maximum differences between the model taking account of facilitated myoglobin transport and neglecting facilitated myoglobin transport. P, S correspond to the model taking account of facilitated myoglobin transport; $\hat{P}$, $\hat{S}$ correspond to the model neglecting facilitated myoglobin transport.

Oxygen consumption	$\max \lvert P - \hat{P} \rvert$	$\max \lvert S - \hat{S} \rvert$
5×10^{-8} mol cm^{-3} s^{-1}	0.96 mmHg	0.006
7.5×10^{-8} mol cm^{-3} s^{-1}	3.79 mmHg	0.011

The relatively large maximum error in Y for $q = 7.5 \times 10^{-8}$ mol cm^{-3} s^{-1} may be explained by Figs. 2 and 3. For a higher oxygen consumption, the calculated value of P will be lower. We see in these figures that, for small P, the dissociation curve for both haemoglobin and myoglobin has a very large derivative. Therefore, a small error in $\hat{P}$ may lead to a relatively large error in $\hat{S}$ and $\hat{Y}$.

4.4. Myoglobin

The analysis leading up to Eqs. 36 and 37 predicted that the effect of myoglobin on the solution of these equations was negligible provided that $P > 13$ mmHg. We investigate this by solving the full governing equations, Eqs. 1-6 and 9, and then repeating this for the full governing equations, but taking $c_M = 0$. We take $P_a = 100$ mmHg and perform this for both $q = 5 \times 10^{-8}$ mol cm^{-3} s^{-1} and $q = 7.5 \times 10^{-8}$ mol cm^{-3} s^{-1}. The maximum differences are shown in Table 3. P and S are the values of partial pressure and saturation that are calculated from the model that allows facilitated myoglobin transport, $\hat{P}$ and $\hat{S}$ are the values calculated when facilitated myoglobin transport is neglected. We see that, as expected, the simulation with the higher oxygen consumption is affected the most by neglecting facilitated myoglobin transport.

5. Discussion

We began by presenting the equations governing oxygen transport to tissue in a model, with cylindrical symmetry, of a single capillary supplying the oxygen consumed by a region of tissue. In the blood flowing through the capillary, we considered the effect of the reaction term between oxygen and the haemoglobin molecule. In the tissue region, we considered the effect of the reaction term between oxygen and the myoglobin molecule. This model took account of convection of blood through the capillary and, in both regions, of diffusion of oxygen, haemoglobin and myoglobin in both the axial and radial directions.

The aim of this paper, as stated in the Introduction, was to investigate the assumptions made by other authors, such as neglecting axial diffusion, assuming an instantaneous reaction between oxygen and both haemoglobin and myoglobin, and neglecting the contribution of facilitated myoglobin transport to oxygen diffusion in tissue. We achieved this by non–dimensionalising the governing equations,

Eqs. 1-9 in Section 3. These predictions were then confirmed by numerical experiments in Section 4.

5.1. Boundary conditions

A more realistic geometry to model this problem would have the capillary region extended both upstream and downstream from the tissue region. We could then apply the boundary conditions given by Eqs. 11 and 15 at $z = -\infty$ and $0 \leq r \leq R_c$, and the boundary conditions given by Eqs. 14 and 17 at $z = \infty$ and $0 \leq r \leq R_c$. However, we have found in this study that transport is convection dominated in the axial direction inside the capillary. As a result, there will be little diffusive flux of oxygen along the inflow tube and so the assumption $P = P_a$ for blood entering the geometry used is valid. Similarly, at the exit the transport is convection dominated and we may assume that diffusion is negligible and write $\partial P/\partial z = 0$. We have performed numerical simulations using this geometry, extending the capillary a distance $2a$ in both directions. The new boundary conditions give only a tiny difference to the solution, with the solution for P differing by less than 5% in all places. The greatest difference between these two solutions was in the region of $z = 0, r = R_T$.

5.2. Axial diffusion

The first prediction of the non–dimensionalisation in Section 3 was of a boundary layer for P, but not for S or Y in the region of the inflow boundary, $z = 0$. This boundary layer was of $\mathcal{O}(R_c)$ inside the capillary, and gave rise to a boundary layer in the tissue, of the same size, near to $z = 0, r = R_c$. This was demonstrated numerically in Figs. 6 and 7. This boundary layer corresponds to diffusion of oxygen dissolved in plasma.

As a result of this, we see that $\partial^2 P/\partial z^2$ is of a significant size in this region and so it is not valid to neglect axial diffusion inside this boundary layer. In the capillary region, outside the boundary layer it is valid to neglect axial diffusion, as shown in Eqs. 29 and 30. These equations correspond to oxygen being convected by the blood bound to haemoglobin and then released and diffusing radially into tissue. However, in tissue, axial diffusion is roughly only ten times smaller than radial diffusion, and so should not be neglected. In Fig. 8 we showed the values of P, S and Y calculated neglecting axial diffusion. We saw that they differ significantly from the values calculated including axial diffusion in Fig. 6. P differed by almost 30 mmHg. In Figure 9 we saw that this corresponded to an error of almost 30%. It may also be seen from this figure that the error induced by ignoring axial diffusion in the boundary layer propagates out radially from the boundary layer.

We can see from Eqs. 33 and 34 that the geometry of the capillary will have an effect on the relative importance of axial diffusion in the tissue. As the ratio L_r/L_z increases, the terms in the equations that govern axial diffusion will become larger, and so wide, short cylinders will have more axial diffusion.

Other authors, [10], have also investigated boundary layers in oxygen partial pressure in the region of the inflow boundary using matched asymptotic expansions.

However, the way in which the axial variable was scaled masked the full extent of the boundary layer. This study found, in agreement with our study, that increasing the arterial oxygen partial pressure increased the influence of the boundary layer.

5.3. Assuming an instantaneous reaction

We have shown, Eqs. 28 and 31, that both inside and outside the boundary layer for P in the capillary region, we may assume an instantaneous reaction between oxygen and haemoglobin and write $S = f(P)$. Similarly, we deduced that we could write $Y = g(P)$ in the tissue region. This was validated numerically in Section 4.3. The errors in S and Y were relatively large for very low P where, due to the very high gradient of the haemoglobin and myoglobin dissociation curve, the small difference in P induced by making this assumption led to comparatively large errors in S and Y.

5.4. Myoglobin

Our analysis of Section 3 predicted that the contribution of myoglobin facilitated oxygen diffusion could be neglected for $P > 13$ mmHg. This was validated by numerical experiments in Section 4.4. When oxygen consumption was increased, thus lowering P, there was a bigger difference seen by neglecting myoglobin. This is because oxygen bound to myoglobin is used as an "emergency store" of oxygen, and is only released when P is low.

Another study (Salathe and Kolkka, [12]) has found that for low perfusion rates there may be regions in tissue where no oxygen reaches even though there is oxygen in the blood that leaves the capillary. These authors used a very different mathematical model to that described in this paper. Oxygen was modelled as being transported in only a very restrictive way: only convection was permitted in the capillary and only radial diffusion was permitted in tissue. It is likely that using the model described in this paper, which allows diffusion in both axial and radial directions, will only allow tissue oxygen partial pressure to reach zero under much more extreme conditions.

6. Conclusions

We have shown that it is valid to assume an instantaneous reaction between oxygen and both haemoglobin and myoglobin. Axial diffusion may only be neglected in the capillary away from the boundary layer for P and may not be neglected in tissue. Myoglobin need only be considered when P is exceptionally low.

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