REDUCTION OF ANOXIA THROUGH MYOGLOBIN-FACILITATED DIFFUSION OF OXYGEN

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ABSTRACT At relatively low perfusion rates, anoxic regions may occur in tissue even though oxygen remains in the blood as it leaves the capillary at the venous end. In this paper a mathematical theory of facilitated diffusion is developed and used to determine the extent to which myoglobin increases the removal of oxygen from blood and aids in the reduction or elimination of regions of anoxia.

INTRODUCTION

Myoglobin in skeletal muscle facilitates the diffusion of oxygen from the capillaries into the tissue. It also serves as a source of oxygen to delay or prevent the onset of anoxia when perfusion levels fall to critically low values, since myoglobin-bound oxygen alone can supply the metabolic needs of resting skeletal muscle for brief periods. The effectiveness of myoglobin in facilitating oxygen transport into tissue has been inferred from the analysis of diffusion from the surface into the interior of a semiinfinite region of tissue in which oxygen is being consumed. When the surface is maintained at a fixed concentration, the distance to which oxygen will penetrate and the amount of oxygen delivered to the tissue is increased when myoglobin is present in the medium. It may therefore be concluded that a single capillary maintained at fixed oxygen concentration and imbedded in a tissue of infinite extent would deliver a greater quantity of oxygen to the tissue in the presence of myoglobin. Such a concept, however, is not physiologically reasonable. Instead, a fixed amount of oxygen, determined by the blood flow rate and arterial concentration, is supplied to a finite portion of tissue surrounding the capillary. The physiologically significant problem is to determine the effectiveness of myoglobin in increasing the amount of oxygen removed from the blood as it flows through the capillary. In some cases oxygen remains in the blood as it leaves the capillary at the venous end, although there are anoxic regions in the tissue some distance from the capillary. The significance of myoglobin as a mediator of oxygen transport to tissue should be evaluated by examining the extent to which myoglobin increases the removal of oxygen before the blood exits into the venous system, so that regions of anoxia are reduced or eliminated. It is this question that we shall examine in this paper.

The potential physiological importance of facilitated diffusion was recognized by Wittenberg (1) and Scholander (2) as a result of experiments on solutions of myoglobin and hemoglobin. Wyman (3) derived the differential equations that have become basic to the mathematical study of myoglobin facilitated transport. These equations were analyzed in the equilibrium and near equilibrium limit in various papers by Murray (4–6). A singular perturbation solution was given for diffusion in a slab by Rubinow and Dembo (7), for the near equilibrium limit. Recently, Kolkka and Salathe (8) used a singular perturbation approach to study diffusion-consumption in a slab for both the near-equilibrium and small diffusion limit.

An analysis of the physiologically realistic model of a capillary supplying oxygen to a region of tissue surrounding it was given by Fletcher (9). Following the methods of Murray, Fletcher solved the equilibrium case and constructed a boundary layer solution at the capillary wall, where departures from equilibrium are dominant. He illustrated the extent to which the radial oxygen concentration profiles within the tissue are altered as a result of myoglobin facilitated diffusion.

We use the same model as Fletcher, but consider the case where perfusion levels are sufficiently low that regions of anoxic tissue occur, in order to examine the role of myoglobin in reducing or eliminating anoxia. We use the method of approach of our previous paper (8), extended to the much more complex situation where tissue and capillary concentrations are coupled. We determine the effect of departures from equilibrium by obtaining the higher order terms in the perturbation expansion about the equilibrium limit. The nature of the boundary layer and the underlying mathematical character of the problem formulated are clarified.

MATHEMATICAL MODEL

We will investigate the effectiveness of myoglobin in facilitating transport of oxygen from the blood to sites in

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the tissue where it is consumed. The mathematical model we use is based on the concept introduced by Krogh (10) of a single capillary exchanging oxygen with a concentric circular cylinder of tissue. This is an appropriate model for uniformly perfused skeletal muscle, for which it is reasonable to assume that oxygen supplied by each capillary is consumed only in an immediately surrounding region of tissue, and that there is no other source of oxygen for this tissue. However, it does not provide an adequate description of oxygen distribution throughout all areas of the muscle when perfusion is nonuniform (11).

If $\bar{q}$ denotes volume blood flow rate and $\bar{z}$ denotes distance measured along the capillary, then the oxygen concentration in the blood, $\bar{C}(\bar{z})$, satisfies:

$$\bar{q}\frac{d}{d\bar{z}}\{\bar{C}(\bar{z}) + \bar{N}\bar{S}[\bar{C}(\bar{z})]\} = -2\pi R_c F, \tag{1}$$

where F is the oxygen flux per unit area into the tissue, $\bar{S}(\bar{C})$ is the oxyhemoglobin dissociation relationship, $\bar{N}$ is the oxygen capacity of the blood, and R_c is the capillary radius. Radial variation of concentration in the capillary has been neglected in this equation, since convective mixing within the bolus of fluid between each red blood cell results in a fairly uniform distribution of oxygen (12).

Within the tissue, oxygen combines reversibly with myoglobin according to the reaction

$$O_2 + Mb \underset{k^-}{\overset{k^+}{\rightleftharpoons}} MbO_2, \tag{2}$$

and so is transported by diffusion of free oxygen and by diffusion of the complexed myoglobin molecule. We denote by $\bar{y}$ and $\bar{w}$ the concentration of the complexed and uncomplexed myoglobin molecules, and by $\bar{c}$ the concentration of oxygen in the tissue. The equations governing the simultaneous diffusion and reaction of these molecules are

$$D_c\frac{1}{\bar{r}}\frac{\partial}{\partial\bar{r}}\bar{r}\frac{\partial\bar{c}}{\partial\bar{r}} = Q(\bar{c},\bar{y},\bar{w}) + \bar{M}, \tag{3}$$

$$D_p\frac{1}{\bar{r}}\frac{\partial}{\partial\bar{r}}\bar{r}\frac{\partial\bar{y}}{\partial\bar{r}} = -Q(\bar{c},\bar{y},\bar{w}), \tag{4}$$

$$D_p^*\frac{1}{\bar{r}}\frac{\partial}{\partial\bar{r}}\bar{r}\frac{\partial\bar{w}}{\partial\bar{r}} = Q(\bar{c},\bar{y},\bar{w}), \tag{5}$$

where $\bar{r}$ is distance measured radially from the capillary axis, $\bar{M}$ is the rate of oxygen consumption in the tissue, and D_c, D_p, D_p^* are the respective diffusivities in the tissue. The reaction rate, Q, is given by

$$Q(\bar{c},\bar{y},\bar{w}) = k^+\bar{c}\,\bar{w} - k^-\bar{y}. \tag{6}$$

In these equations the effect of axial diffusion within the tissue has been neglected. We have shown that this is a reasonable assumption under a broad range of conditions (13). However, the importance of axial diffusion when anoxia is present in the tissue has not been examined. In our previous studies of anoxia (14, 15), we neglected axial diffusion to obtain a tractable problem; this will also be done in the present analysis.

The consumption rate is taken to be constant for nonzero concentration and to fall discontinuously to zero at zero concentration. This results in a sharp boundary between anoxic tissue, in which consumption is zero, and oxygenated tissue, in which consumption occurs at the fixed rate $\bar{M}$. It is known, however, that although the consumption rate is uniform for normal values of concentration, at sufficiently low values the consumption rate falls continuously to zero. For a continuous drop in consumption rate there is no sharp border between normoxic and anoxic tissue. However, in an analysis of oxygen transport without myoglobin facilitated diffusion, Berger et. al. (16) found that when consumption remained constant until very low concentration, the solution differed very little from the solution corresponding to a step discontinuity in consumption obtained by Crank and Gupta (17).

The mathematical formulation is completed by specifying appropriate boundary conditions. At the arterial end, the capillary oxygen concentration is known:

$$\bar{C}(0) = C_A. \tag{7}$$

At the capillary wall, the partial pressure of oxygen in the blood and in the tissue are equal. Therefore, the concentrations satisfy

$$\bar{c}\,(R_c,\bar{z})/\alpha_t = \bar{C}(\bar{z})/\alpha_b, \tag{8}$$

where α_t and α_b are the solubility coefficients of oxygen in tissue and in blood, respectively. In the subsequent analysis they are assumed to be equal.

Since oxygen supplied by the capillary is consumed only within a surrounding concentric cylinder of tissue of radius R_t,

$$\frac{\partial\bar{c}}{\partial\bar{r}} = 0 \text{ at } \bar{r} = R_t, \tag{9}$$

and since myoglobin is confined within this cylinder of tissue,

$$\frac{\partial\bar{y}}{\partial\bar{r}} = \frac{\partial\bar{w}}{\partial\bar{r}} = 0 \text{ at } \bar{r} = R_c, R_t. \tag{10}$$

Finally, the rate of flux per unit area out of the capillary is given by

$$F = -D_c\frac{\partial\bar{c}}{\partial\bar{r}}\bigg|_{\bar{r}=R_c} \tag{11}$$

The formulation given here is identical to that presented by Fletcher (9).

ANALYSIS

Adding Eqs. 4 and 5 and integrating twice, subject to the boundary condition, Eq. 10, and the assumption that $D_p^* =$

D_p, gives $\bar{w} + \bar{y} = \beta$, illustrating that the sum of the complexed and uncomplexed myoglobin concentrations is constant throughout the tissue. This result will be used to eliminate $\bar{w}$ from Eqs. 3 and 4.

Introducing the nondimensional variables $r = \bar{r}/R_t$, $z = \bar{z}/L$, $c = \bar{c}/C_A$, $C = \bar{C}/C_A$, $N = \bar{N}/C_A$, $y = \bar{y}/\beta$, the governing equations can be rewritten in the form

$$\epsilon \frac{1}{r}\frac{\partial}{\partial r} r \frac{\partial c}{\partial r} = -Ky + c(1 - y) + \epsilon M, \tag{12}$$

$$\epsilon \delta \frac{1}{r}\frac{\partial}{\partial r} r \frac{\partial y}{\partial r} = Ky - c(1 - y), \tag{13}$$

$$q \frac{d}{dz}[C + NS(C)] = \frac{2}{R}\frac{\partial c}{\partial r}\bigg|_{r=R}, \tag{14}$$

$$C(0) = 1, \tag{15}$$

$$c(R, z) = C(z), \tag{16}$$

$$\partial y/\partial r = 0 \text{ at } r = R, \tag{17}$$

$$\partial c/\partial r = \partial y/\partial r = 0 \text{ at } r = 1, \tag{18}$$

where $R = R_c/R_t$, $q = \bar{q}/\pi R^2 D_c L$, $M = \bar{M} R_t^2/D_c C_A$, $K = k^-/k^+ C_A$, $\epsilon = D_c/k^+ \beta R_t^2$, $\delta = \beta D_p/C_A D_c$, and $S(C) = \bar{S}(C_A C)$. The parameter ϵ is the ratio of the reaction time to the diffusion time, and so measures departures from chemical equilibrium.

When the tissue is fully oxygenated an no anoxic regions exist, the oxygen supplied by the blood per unit length, $2\pi R_c F$ in Eq. 1, is equal to $\bar{M}\pi(R_t^2 - R_c^2)$, and Eq. 14 becomes

$$\frac{d}{dz}[C + NS(C)] = \frac{M}{q}\left(1 - \frac{1}{R^2}\right). \tag{19}$$

Together with the initial condition $C(0) = 1$, this uniquely determines $C(z)$. Therefore, the problem posed by Eqs. 12, 13, and 16–18 is similar to the problem of diffusion in a one-dimensional slab, which has been studied extensively in the past. The present problem, although developed for an axisymmetric geometry, differs essentially from the slab problem only in that the concentration is specified on one surface ($c = C$ at $r = R_c$), while a zero flux condition is specified on the other surface ($r = R_t$); for the slab the concentration is specified on both surfaces. A singular perturbation analysis of the problem for a one-dimensional slab in which consumption occurs has been given by Kolkka and Salathé (8). The solution to the present problem can easily be obtained for the case of chemical equilibrium ($\epsilon = 0$), and has been given by Fletcher (9). When $\epsilon = 0$, Eq. 13 yields $y = c/(K + c)$. Adding Eqs. 12 and 13 and using this result, we obtain

$$\frac{1}{r}\frac{\partial}{\partial r} r \frac{\partial}{\partial r}\left[c + \delta \frac{c}{K + c}\right] = M. \tag{20}$$

The solution, subject to the boundary conditions, Eqs. 16 and 18, is

$$c = \tfrac{1}{2} f + \tfrac{1}{2}[f^2 + 4K(f + K + \delta)]^{1/2} \tag{21}$$

where

$$f = \frac{1}{4} M(r^2 - R^2) - \frac{1}{2} M \ln \frac{r}{R} + C + \frac{\delta C}{K + C} - K - \delta. \tag{22}$$

The above solution is the first term in an asymptotic expansion for the concentration in the limit $\epsilon \to 0$. The next term in the expansion gives the effect of small departures from chemical equilibrium. However, this expansion is not valid in the neighborhood of the capillary, and cannot satisfy the boundary condition $\partial y/\partial r = 0$ at $r = R$. In this narrow boundary layer an entirely different expansion must be constructed, and joined to the expansion in the region bounded away from the capillary using the techniques of singular perturbation theory. This is described in Appendix I, where we use an approach similar to, but more complex than, our previous analysis of facilitated diffusion in a slab (8).

In the limit $\epsilon \to 0$, Eq. 21 provides a good approximation to the solution, except in a boundary layer of vanishing thickness. When anoxia occurs in the tissue, however, a simple analysis corresponding to that leading to Eq. 21 does not exist. The oxygen concentration in the capillary cannot be determined a priori, since it depends on the amount of tissue oxygenated. The capillary and tissue concentrations and the region of tissue oxygenated must be determined simultaneously. Since the oxygen flux from the capillary is related to the radial derivative of the tissue oxygen concentration at the capillary wall (Eq. 14), the solution in the boundary layer must also be obtained. The analysis in this case is presented in the next section.

ANALYSIS WITH ANOXIA

For sufficiently low perfusion rates, regions of zero oxygen concentration appear in the tissue. Within a cross-section containing the axis $r = 0$, the border separating oxygenated and anoxic tissue is a line, which we have previously referred to as the anoxic curve (14). This curve may originate at $z = 0$ with $R < r \leq 1$, or it may originate at $z > 0$. If all the oxygen in the capillary is depleted before the venous end, the anoxic curve will intersect $r = R$ for $z < 1$. However, when the blood leaving the capillary has non-zero oxygen content, the anoxic curve will intersect $z = 1$ at $r > R$. The equation for the anoxic curve, denoted $R^*(z)$, must be determined simultaneously with the concentration profiles $C(z)$, $c(r, z)$, and $y(r, z)$. If $R^*(z^*) = 1$ for some z^* such that $0 < z^* < 1$, the solution obtained previously is valid for $z \leq z^*$. For $z^* \leq z \leq 1$, the mathematical problem is given by Eqs. 12–17 and the "Stefan" boundary conditions

$$c(R^*, z) = y(R^*, z) = \frac{\partial c}{\partial r}\bigg|_{r=R^*} = \frac{\partial y}{\partial r}\bigg|_{r=R^*} = 0. \tag{23}$$

As discussed above, we must solve this problem using the method of matched asymptotic expansions. In this case the capillary concentration cannot be determined a priori, and so is also expanded in an asymptotic series. The expansions in the region bounded away from the capillary are

$$c \sim c_o(r, z) + \epsilon^{1/2} c_1(r, z) + 0(\epsilon), \tag{24}$$

$$y \sim y_o(r, z) + \epsilon^{1/2} y_1(r, z) + 0(\epsilon), \tag{25}$$

$$C(z) \sim C_o(z) + \epsilon^{1/2} C_1(z) + 0(\epsilon), \tag{26}$$

and the leading terms satisfy

$$\frac{1}{r}\frac{\partial}{\partial r} r \frac{\partial}{\partial r}(c_o + \delta y_o) = M, \tag{27}$$

$$c_o(R^*, z) = (\partial c_o/\partial r)_{r=R^*} = 0, \tag{28}$$

$$c_o(R, z) = C_o(z), \tag{29}$$

$$q\frac{d}{dz}[C_o + NS(C_o)] = \frac{2}{R}\left[\frac{\partial}{\partial r} c_{BL}\right]_{r=R}, \tag{30}$$

with y_o given in terms of c_o as

$$y_o = \frac{c_o}{K + c_o}. \tag{31}$$

The flux into the tissue is found using the radial derivative of the free oxygen concentration at the capillary wall, where the solution is given by the boundary layer expansion. This is emphasized by using the notation c_{BL} in Eq. 30. It is therefore necessary to analyze the boundary layer in order to obtain the leading terms in the asymptotic expansions, Eqs. 24–26.

The solution in the neighborhood of $r = R$ is determined by introducing the boundary layer variables $\eta = (r - R)/\epsilon^{1/2}$, $\tilde{c}(\eta, z) = c(R + \epsilon^{1/2}\eta, z)$ $\tilde{y}(\eta, z) = y(R + \epsilon^{1/2}\eta, z)$, rewriting the governing equations (12–17 and 23), in terms of these variables, and constructing an expansion that can be matched to the expansion, Eqs. 24–26, as $\eta \to \infty$. Following Kolkka and Salathe (8), the boundary layer expansion must be of the form

$$\tilde{c}(\eta, z) \sim C_o(z) + \epsilon^{1/2}\tilde{c}_1(\eta, z) + 0(\epsilon),$$

$$\tilde{y}(\eta, z) \sim \frac{C_o(z)}{K + C_o(z)} + \epsilon^{1/2}\tilde{y}_1(\eta, z) + 0(\epsilon), \tag{32}$$

so that to leading order

$$\left[\frac{\partial}{\partial r} c_{BL}\right]_{r=R} = \frac{\partial \tilde{c}}{\partial \eta}\bigg|_{\eta=0}\frac{\partial \eta}{\partial r} = \frac{\partial \tilde{c}_1}{\partial \eta}\bigg|_{\eta=0}. \tag{33}$$

The first order terms $\tilde{c}_1(\eta, z)$, $\tilde{y}_1(\eta, z)$ are obtained in the appendix, and $\partial\tilde{c}_1/\partial\eta$ at $\eta = 0$ is determined. With those results, Eq. 30 reduces to

$$q\frac{d}{dz}[C_o + NS(C_o)] = \frac{2c_o(R, z)}{R}\left\{1 + \frac{\delta K}{[K + C_o(z)]^2}\right\}, \tag{34}$$

so that Eq. 34 and Eqs. 27–29 and 31 form a complete system for the determination of $c_o(r, z)$, $C_o(z)$, and $R^*(z)$.

From Eqs. 27, 29, and 31 it follows that

$$c_o(r, z) + \frac{\delta c_o(r, z)}{K + c_o(r, z)} = \frac{M}{4}(r^2 - R^2) + A_o(z)\ln\frac{r}{R} + C_o(z) + \frac{\delta C_o(z)}{K + C_o(z)}, \tag{35}$$

while the boundary conditions, Eq. 28, require that

$$A_o(z) = -\frac{1}{2}M[R^*(z)]^2 \tag{36}$$

and

$$\frac{M}{4}(R^{*2} - R^2) - \frac{1}{2}MR^{*2}\ln\frac{R^*}{R} + C_o(z) + \frac{\delta C_o(z)}{K + C_o(z)} = 0. \tag{37}$$

Substituting these results into Eq. 34 yields

$$\frac{d}{dz}\{C_o(z) + NS[C_o(z)]\} = \frac{M}{q}\left\{1 - \left[\frac{R^*(z)}{R}\right]^2\right\}, \tag{38}$$

which is analagous to Eq. 19, and shows that the capillary concentration decreases because oxygen is being provided to a region of tissue of radius R^* instead of radius 1.

The capillary concentration $C_0(z)$ and the anoxic curve $R^*(z)$ are determined from Eqs. 37 and 38. From Eq. 37,

$$C_o(z) = -\frac{\delta + K + G(z)}{2} + \frac{1}{2}[(\delta + K + G(z))^2 - 4KG(z)]^{1/2} \tag{39}$$

where

$$G(z) = (M/4)[(R^*(z))^2 - R^2] - (M/2)(R^*(z))^2\ln[R^*(z)/R]. \tag{40}$$

Differentiating Eq. 37 gives

$$\frac{d}{dz}R^*(z) = \frac{dC_o}{dz}\cdot\left(1 + \frac{\delta K}{[K + C_o(z)]^2}\right)/[MR^*\ln(R^*/R)]. \tag{41}$$

Substituting dC_o/dz from Eq. 38 into this equation yields

$$\frac{dR^*}{dz} = \frac{(1 - R^{*2}/R^2)[1 + \delta K/(K + C_o)^2]}{q[1 + NS'(C_o)]R^*\ln(R^*/R)}. \tag{42}$$

This is a first order differential equation for $R^*(z)$, since C_o is given explicitly in terms of R^* by Eq. 39. It can readily by integrated numerically, subject to the initial

condition R^* (z^*) = 1, where z^* is the axial location at which anoxia first appears at the outer edge of the tissue cylinder.

The problem formulated in this section assumes that a solution to Eqs. 12–17 and 23 exists for $r \leq R^*$, and that $y = c = 0$ for $r \geq R^*$. This, however, is only true to order $\epsilon^{1/2}$, and order ϵ terms in the expansion, Eqs. 24 and 25, cannot be obtained that satisfy these equations. An alternate formulation was given by Van Ouwerkerk (18), for the problem of diffusion from the boundary into the interior of a cylinder of tissue. In terms of the present problem, Van Ouwerkerk's approach is to assume that $c \equiv 0$ beyond $r = R^*$, and to determine y in that region from Eqs. 12–17. This is possible only if M is no longer a constant, but is given by $M = y/\epsilon$ for $r > R^*$. Then the solution

$$y = \epsilon B \exp\left[\sqrt{\frac{K}{\epsilon\delta}}(r - R^*)\right] \tag{43}$$

can be found for $\epsilon << 1$, where B is an undetermined constant. Clearly, for small ϵ, y vanishes extremely rapidly with distance into the anoxic region. For $r \leq R^*$, the problem is to solve Eqs. 12–17 with $c = \partial c/\partial r = 0$ at $r = R^*$, and to match y and $\partial y/\partial r$ at $r = R^*$ to y given by Eq. (43). This matching condition also determines the constant B. Van Ouwerkerk used an asymptotic expansion analagous to Eqs. 24 and 25 in the region bounded away from the anoxic border, and constructed a boundary layer solution near the anoxic border in order to match the solution for y to that given by Eq. 43. Clearly, this is a mathematically sound approach. However, it may be of limited significance as a description of the physical phenomena. As noted earlier, in the neighborhood of the anoxic region M varies rapidly but continuously from a constant value to zero as oxygen concentration drops to zero. In the exponentially thin layer beyond $r = R^*$, the assumption that $c = 0$ is not valid, M is determined by reaction-consumption kinetics and is not equal to y/ϵ, and y is not given by Eq. 43. Since we do not obtain our solutions to order ϵ, and since we do not analyze the structure to the sharp anoxic border that occurs when M drops continuously, these questions do not arise in the present study. Our analysis provides a first approximation to the size of the anoxic region in the limit $\epsilon \rightarrow 0$, and approximates the anoxic border as a sharp discontinuity.

NUMERICAL RESULTS AND DISCUSSION

Typical data corresponding to resting skeletal muscle are shown in Table I; for this data, sufficient oxygen is supplied to meet the metabolic needs of the tissue. Anoxia occurs only when the blood flow rate or arterial oxygen concentration is too low, or the volume of tissue to be oxygenated is too large, for the corresponding consumption rate. Numerical results will be presented for a wide range of physiological situations in which anoxia occurs, by altering one or more of the values shown in Table I, and the effectiveness of myoglobin in reducing the size of the anoxic region will be examined. The oxyhemoglobin dissociation relationship will be taken to be of the form $\bar{S}(\bar{C}) = K^*\bar{C}^n/(1 + K^*\bar{C}^n)$, where the constants K^* and n are also given in Table I. Other approximations to the oxyhemoglobin dissociation curve have been given, some of which are more accurate at low oxygen concentrations, and these can easily be substituted in place of the above assumption.

TABLE I
DATA USED IN THE NUMERICAL EXAMPLES

Parameter	Value	Reference
Arterial concentration, c_A ($cm^3 o_2/cm^3$ *blood*)	0.003	9
Oxygen capacity of blood, $\bar{N}$ ($cm^3/o_2/cm^3$ *blood*)	0.204	13
Myoglobin concentration, β (*mol*/cm^3)	2.8×10^{-7}	5
Flow rate, q (cm^3/s)	1.13×10^{-8}	19
Capillary length, L (*cm*)	0.06	19
Capillary radius, R_c (*cm*)	3×10^{-4}	19
Tissue radius, R_t (*cm*)	0.003	19
Oxygen diffusivity, D_c (cm^2/s)	1.5×10^{-5}	9
Myoglobin diffusivity, D_p (cm^2/s)	5×10^{-7}	20
Forward reaction rate, k^+ (cm^3/*mol* s)	2.4×10^{10}	5
Backward reaction rate, k^- (s^{-1})	65	5
Dissociation constant, K^*	8.55×10^5	13
Dissociation exponent, n	2.0	13
Oxygen consumption rate, M (*mol*/cm^3 *s*)	3.0×10^{-9}	29

The value of C_A shown in Table I corresponds to an inlet PO_2 of 85–100 mmHg, depending on the value chosen for the solubility of oxygen in blood (9, 19, and 21). This is within the normal physiological range for arterial PO_2, although Duling and Berne (22) have suggested that precapillary oxygen losses may result in somewhat lower PO_2 levels for the blood reaching the capillaries. Greater PO_2 values can be achieved if the inspired air has a higher oxygen concentration. We have, therefore, examined the effect of lowering C_A to 0.002 cm^3 O_2/cm^3 blood and of raising it to 0.004 cm^3 O_2/cm^3 blood.

Wittenberg (1) gives myoglobin concentration values for skeletal muscle ranging from 3.8×10^{-7} mol/cm^3 for bovine gastrocnemius muscle to 4.9×10^{-7} mol/cm^3 for dog gastrocnemius muscle. Taylor and Murray (23) and Fletcher (9) use a concentration of 2.8×10^{-7} mol/cm^3 as characteristic of skeletal muscle. We have chosen this value for the basic data shown in Table I and have examined the effect of increasing myoglobin concentration beyond this level.

The flow rate of 1.13×10^{-8} cm^3/s given in Table I is characteristic of light exercise. Lower values are generally found for resting muscle (0.78×10^{-8}, Fletcher [9]; 0.91 ×

10^{-8}, Klitzman et. al. [19]), and the resting value increases by a factor of two to three during exercise (19). Therefore, we have examined the effect of varying $\bar{q}$ over a range of values from 10^{-8} cm^3 s to 2×10^{-8} cm^3/s.

The capillary radius and length shown in Table I are found in a broad variety of skeletal muscles (cat tenuissimus, Erikson and Myrage [24]; rat cremaster, Smaje et al. [25]; hamster cremaster, Klitzman et al. [19]; rat spinotrapezius, Boseck [26]). However, smaller values for the capillary length have been observed (24), and so we have also examined several cases using $L = 400$ μm. The tissue radius of 30 μm shown in Table I, appropriate for resting skeletal muscle (19 and 26), yields a tissue volume that is too large to be totally oxygenated at elevated consumption rates during exercise, and anoxia occurs unless the number of flowing capillaries increases and the corresponding tissue volume decreases. We have examined a number of cases using a smaller tissue radius of 15 μm, a value characteristic of the intercapillary spacing during exercise (19 and 27), for which anoxia occurs only at greatly elevated consumption rates.

There is general agreement on the value of oxygen diffusivity in skeletal muscle, with a range from 1.2×10^{-5} cm^2/s (1) to 1.6×10^{-5} cm^2/s (19), and the value of 1.5×10^{-5} cm^2/s in Table I has been quoted by several authors (9 and 27).

There is somewhat less agreement on the value of myoglobin diffusivity in skeletal muscle. Murray (4) uses a value of 4.35×10^{-7} cm^2/s, which is close to the value given by RiverosMareno and Wittenberg (20) shown in Table I; however, Wittenberg has also estimated the value to be as high as 7×10^{-7} cm^2/s (1).

The oxygen consumption rate for skeletal muscle varies over a large range of values as the muscle changes from a state of rest to a state of heavy exercise. Landis and Pappenheimer (27) quote values as low as 2.2×10^{-9} mol/cm^3 s for resting muscle to 1.4×10^{-7} mol/cm^3 s for exercising muscle. The slightly higher values given in Table I are found by Roughton (29) and by Klitzman et al. (19). At moderate exercise, values of 1×10^{-8} to 2.5×10^{-8} mol/cm^2 s have been measured by Stainsby and Otis (30), Folkow and Halicka (31), and Whalen and Collins (32). Values from 5×10^{-8} mol/cm^3 s to as high as 8×10^{-7} mol/cm^3 s are quoted by Taylor and Murray (23). Therefore, we have used a wide range of values for consumption rate in our numerical examples, corresponding to various states from mild to very heavy exercise.

Fig. 1 shows the anoxic curve for various values of the consumption rate $\bar{M}$. Corresponding results without myoglobin facilitation are shown as broken lines. The values of $\bar{M}$ chosen, and the flow rate $\bar{q}$ given in Table I, are characteristic of moderate to heavy exercise. Under normal physiological conditions anoxia is prevented by an increase in the number of flowing capillaries. However, the tissue radius of 30 μm shown in Table I is characteristic of

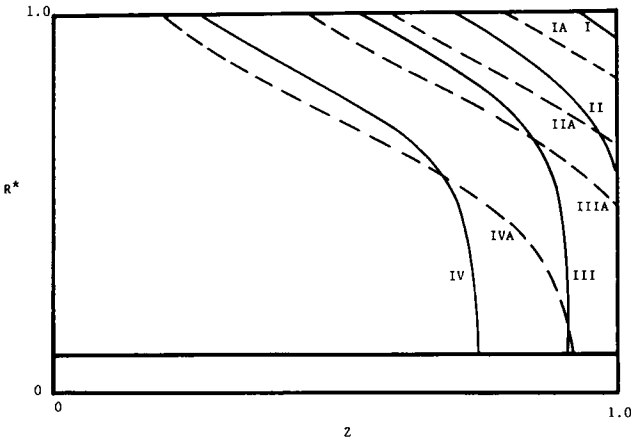

FIGURE 1 The anoxic curve for the data shown in Table I and various values of the consumption rate *M. I, IA,* $\bar{M} = 5 \times 10^{-8}$ mol/cm^3 s; *II, IIA,* $\bar{M} = 6 \times 10^{-8}$ mol/cm^3 s; *III, IIIA,* $\bar{M} = 7 \times 10^{-8}$ mol/cm^3 s; *IV, IVA,* $\bar{M} = 10^{-7}$ mol/cm^3 s. The broken lines are the corresponding results without myoglobin facilitation.

the resting state, and so there is not sufficient oxygen delivered to prevent the occurrence of anoxia.

For $\bar{M} = 5 \times 10^{-8}$ mol/cm^3 s, sufficient oxygen is delivered by the arterial blood to meet the metabolic needs of the tissue, but much of this oxygen is carried away in the venous blood, and anoxic regions occur in the tissue. However, comparing curves I and IA shows that when myoglobin is present more oxygen is removed from the blood and the anoxic region is decreased. Curves II and IIA, corresponding to $\bar{M} = 6 \times 10^{-8}$ mol/cm^3 s, again show the effect of myoglobin in reducing the amount of anoxic tissue. However, because of the increased rate of loss of oxygen from the blood with myoglobin facilitated diffusion, the oxygen concentration drops at the venous end to such a low level that curve II crosses over and falls below curve IIA. For large values of $\bar{M}$, insufficient oxygen is delivered by the blood to meet the metabolic needs of the tissue. Curves III and IIIA, corresponding to $\bar{M} = 7 \times 10^{-8}$ mol/cm^3 s, show that with myoglobin all the available oxygen is delivered to the tissue and the anoxic region is diminished to the smallest size possible, whereas without myoglobin oxygen still remains in the venous blood, resulting in a larger volume of anoxic tissue. For $\bar{M} = 10^{-7}$ mol/cm^3 s, all the oxygen is removed from the blood even without myoglobin, and it can be seen from curves IV and IVA that the effect of myoglobin is to change the shape of the anoxic curve without diminishing the amount of anoxic tissue.

Fig. 2 shows the shape of the anoxic curve, with and without myoglobin, for various values of the flow rate $\bar{q}$, and corresponds to $\bar{M} = 8.0 \times 10^{-8}$ mol/cm^3 s. Again, curves I, IA and II, and IIA show the role of myoglobin in removing additional oxygen from the blood and reducing the amount of anoxic tissue. Curves III and IIIA correspond to a flow-rate that is so low that insufficient oxygen

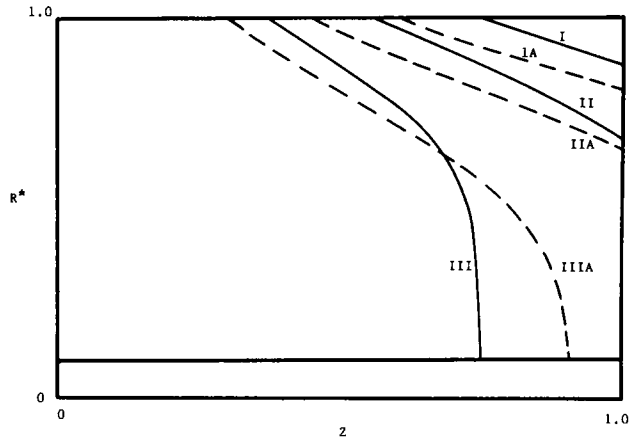

FIGURE 2 The anoxic curve for various values of the flow rate $\bar{q}$, with $\bar{M} = 8.0 \times 10^{-8}$ mol/cm^3 s and the data shown in Table I. *I, IA:* $\bar{q} = 2.0 \times 10^{-8}$ cm^3/s; *II, IIA,* $\bar{q} = 1.5 \times 10^{-8}$ cm^3/s; *III, IIIA,* $\bar{q} = 10^{-8}$ cm^3/s. The broken lines are the corresponding results without myoglobin facilitation.

is delivered to the tissue, and myoglobin only changes the shape of the anoxic curve without diminishing the volume of anoxic tissue.

Fig. 3 shows the anoxic curve for various values of C_A with $\bar{M} = 6.0 \times 10^{-8}$ mol/cm^3 s. Curves I, IA and II, and IIA illustrate the reduction of the anoxic region by myoglobin facilitation. Curve III shows complete removal of oxygen from the blood when myoglobin is present, while curve IIIA illustrates that without myoglobin, oxygen would be carried away in the venous blood. The anoxic region corresponding to curve IIIA is therefore larger than that corresponding to curve III.

Even with the increased capillary density and blood flow rate characteristic of exercise, anoxic tissue occurs if the consumption rate is sufficiently high. Curves I and II in

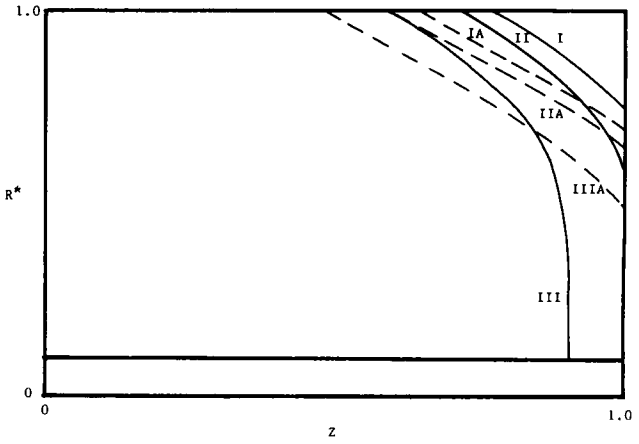

FIGURE 3 The anoxic curve for various values of $\bar{C}_A$, with $\bar{M} = 6.0 \times 10^{-8}$ mol/cm^3 s and the data shown in Table I. *I, IA,* $\bar{C}_A = 0.004$ cm^3 O_2/cm^3 blood; *II, IIA,* $\bar{C}_A = 0.003$ cm^3 O_2/cm^3 blood; *III, IIIA,* $\bar{C}_A = 0.002$ cm^3 O_2/cm^3 blood. The broken lines are the corresponding results without myoglobin facilitation.

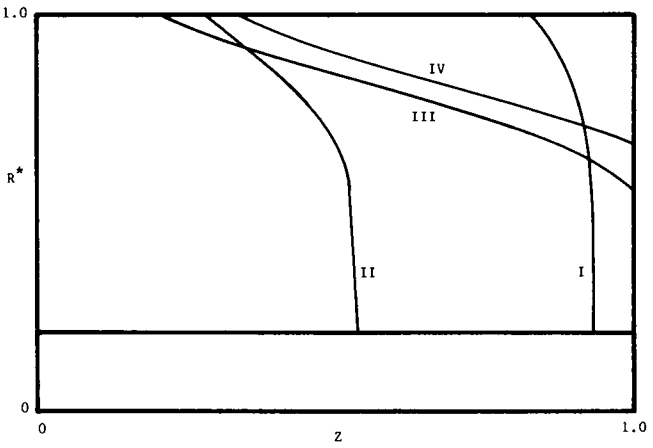

FIGURE 4 The anoxic curve for a reduced tissue radius of 15 μm. *I,* $M = 2.5 \times 10^{-7}$ mol/cm^3 s; *II,* $M = 5 \times 10^{-7}$ mol/cm^3 s. The remaining data is given in Table I. Curves *III* and *IV* correspond to a tissue cylinder of length 400 μm and radius 15 μm and show the effect of changing C_A. *III,* $C_A = 0.002$ cm^3 O_2/cm^3 blood; *IV,* $C_A = 0.004$ cm^3 O_2/cm^3 blood. For these curves $M = 7.5 \times 10^{-7}$ mol/cm^3 s and $\bar{q} = 2.03 \times 10^{-8}$ cm^3/s, and the remaining data is as shown in Table I.

Fig. 4 correspond to a tissue radius of 15 μm and consumption rates of 2.5×10^{-7} and 5.0×10^{-7} mol/cm^3 s, respectively, characteristic of heavy exercise. The remaining data used to obtain these curves are as shown in Table I. Curves III and IV in Fig. 4 show the effect of reducing C_A to 0.002 cm^3O_2/cm^3 blood and increasing it to 0.004 cm^3O_2/cm^3 blood, respectively. These curves correspond to a tissue cylinder of radius 15 μm and length 400 μm, and to consumption rate and flow velocity of 7.5×10^{-7} mol/cm^3 s and 2.03×10^{-8} cm^3/s, respectively.

We have shown that even though sufficient oxygen may be provided to the tissue by arterial blood, anoxic tissue can occur distal to the capillary due to limited oxygen transport through the tissue, while needed oxygen is carried away in

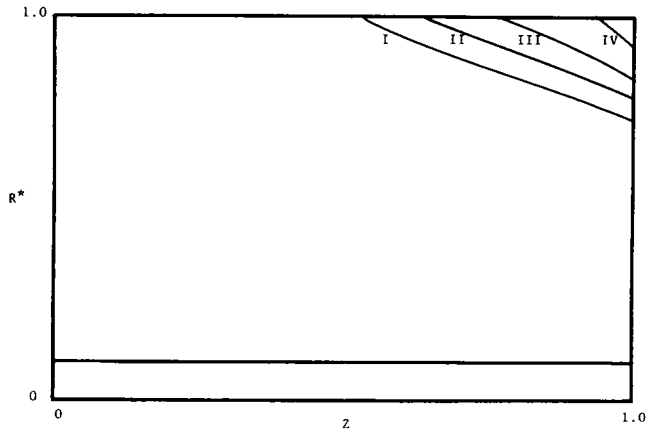

FIGURE 5 The anoxic curve for various values of myoglobin concentration β, with $\bar{M} = 8 \times 10^{-8}$ mol/cm^3 s, $\bar{q} = 1.7 \times 10^{-8}$ cm^3/s, and the data shown in Table I. *I,* $\beta = 0$; *II,* $\beta = 2.8 \times 10^{-7}$ mol/cm^3; *III,* $\beta = 5.6 \times 10^{-7}$ mol/cm^3; *IV,* $\beta = 10^{-6}$ mol/cm^3.

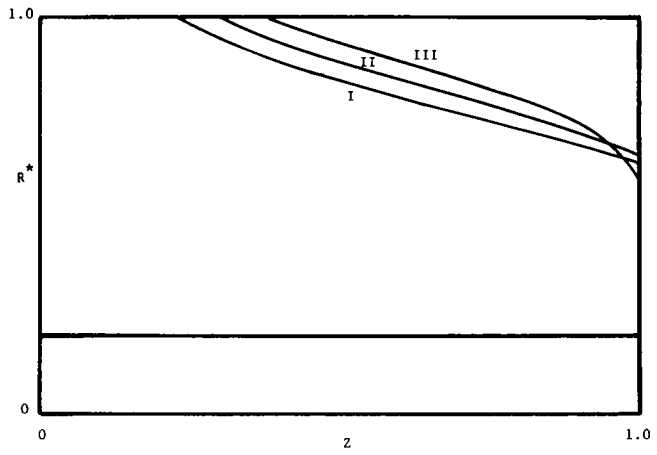

FIGURE 6 The anoxic curve for various values of myoglobin concentration β, with $\overline{M} = 7.5 \times 10^{-7}$ mol/cm^3 s, $\overline{q} = 2.03 \times 10^{-8}$ cm^3/s, $R_t = 15$ μm, and $L = 400$ μm, and the data shown in Table I. *I*, $\beta = 0$; *II*, $\beta = 2.8 \times 10^{-7}$ mol/cm^3; *III*, $\beta = 5.6 \times 10^{-7}$ mol/cm^3.

the venous blood. Myoglobin, however, diminishes the volume of anoxic tissue by facilitating the transport of oxygen through the tissue, and therefore makes available for consumption oxygen that would otherwise be lost into the venous system.

Whenever arterial influx of oxygen is sufficient to meet the metabolic needs of the tissue, it should be possible to completely eliminate anoxia by raising myoglobin concentrations to sufficiently high levels. This is illustrated in Fig. 5, which corresponds to the data in Table I, except $\overline{q} = 1.70 \times 10^{-8}$ cm^3/s and $\overline{M} = 8 \times 10^{-8}$ mol/cm^3 s. The anoxic region that occurs when $\beta = 0$ is continually reduced as β increases, and almost vanishes when $\beta = 10^{-6}$ mol/cm^3.

Similar results are shown in Fig. 6, which corresponds to a tissue cylinder of radius 15 μm and length 400 μm, and to a consumption rate and flow velocity of 7.5×10^{-7} mol/cm^3 s and 2.03×10^{-8} cm^3/s, respectively. In this case, the size of the anoxic region decreases to zero when the myoglobin concentration increases to 7.5×10^{-7} mol/cm^3. For the data used in Figs. 5 and 6, it would be necessary to have un-physiologically high concentrations of myoglobin to completely eliminate the anoxic region. However, the curves for $\beta = 2.8 \times 10^{-7}$ mol/cm^3, corresponding to physiological levels of myoglobin, as well as the results already discussed, show that myoglobin can result in a significant, if not complete, reduction of anoxic regions within tissue.

APPENDIX

For small departures from chemical equilibrium, the concentrations c and y can be expanded in the asymptotic series

$$c(r, z) \sim c_o(r, z) + \epsilon^{1/2} c_1(r, z) + 0(\epsilon)$$
$$y(r, z) \sim y_o(r, z) + \epsilon^{1/2} y_1(r, z) + 0(\epsilon). \quad \text{(A1)}$$

Unless anoxia exists, C can be determined a priori, as described above, and so will not be expanded in a series but applied as a known boundary condition for c at $r = R$. The zero order terms, c_o and y_0, are the equilibrium solutions obtained above. The first order terms satisfy

$$y_1 = \frac{c_1(1 - y_o)}{K + c_o}, \quad \text{(A2)}$$

which follows from Eq. 13. Adding Eqs. 12 and 13 gives

$$\frac{1}{r}\frac{\partial}{\partial r} r \frac{\partial}{\partial r}(c_1 + \delta y_1) = 0, \quad \text{(A3)}$$

which, in view of Eq. A2, may be regarded as an equation for c_1 alone.

The solution must satisfy the boundary conditions $\partial c/\partial r = 0$, $\partial y/\partial r = 0$ at $r = 1$. This already holds for c_o and y_o, and if it is imposed as a boundary condition for Eq. A3, i.e., $\partial c_1/\partial r = 0$ at $r = 1$, it follows from Eq. A2 that $\partial y_1/\partial r = 0$ at $r = 1$. Therefore, the expansion, Eqs. A1, will be applicable at $r = 1$. This is not the case, however, at $r = R$. It is not possible to construct the expansion, Eqs. A1, in such a way that it satisfies both boundary conditions $c = C$ and $\partial y/\partial r = 0$ at $y = R$. This is already evident from the zero-order solutions c_o, y_o. The expansion, Eqs. A1, is not applicable in the neighborhood of $r = R$, and it is not proper to apply boundary conditions at $r = R$ to the terms of this expansion.[1] A different solution must be constructed for the region near $r = R$, and joined to the solution represented by Eqs. A1 using the method of matched asymptotic expansions.

The solution to Eq. A3 subject only to the boundary condition $\partial c_1/\partial r = 0$ at $r = 1$ is

$$c_1(r, z) = B_1(z)/\{1 + \delta K/(K + c_o)^2\}, \quad \text{(A4)}$$

where the function $B_1(z)$ will be determined by matching this solution to the solution for the boundary layer near $r = R$. The solution in the neighborhood of $r = R$ is determined by introducing the boundary layer variables $\eta = (r - R)/\epsilon^{1/2}$, $\tilde{c}(\eta, z) = c(R + \epsilon^{1/2}\eta, z)$, $\tilde{y}(\eta, z) = y(R + \epsilon^{1/2}\eta, z)$, rewriting the governing Eqs. 12 and 13 in terms of these variables, and constructing an expansion that can be matched with the above expansion as $\eta \to \infty$. Following the method of Kolkka and Salathe (8), the boundary layer expansion must be of the form

$$\tilde{c}(\eta, z) \sim C(z) + \epsilon^{1/2}\tilde{c}_1(\eta, z) + 0(\epsilon)$$
$$\tilde{y}(\eta, z) \sim \frac{C(z)}{K + C(z)} + \epsilon^{1/2}\tilde{y}_1(\eta, z) + 0(\epsilon), \quad \text{(A5)}$$

where $\tilde{c}_1(\eta, z)$, $\tilde{y}_1(\eta, z)$ satisfy the equations

$$\frac{\partial^2 \tilde{c}_1}{\partial \eta^2} + [K + C(z)]\tilde{y}_1 - \frac{K\tilde{c}_1}{K + C(z)} = 0 \quad \text{(A6)}$$

$$\delta \frac{\partial^2 \tilde{y}_1}{\partial \eta^2} - [K + C(z)]\tilde{y}_1 + \frac{K\tilde{c}_1}{K + C(z)} = 0 \quad \text{(A7)}$$

and the boundary conditions

$$\tilde{c}_1(0, z) = 0 \quad \text{(A8)}$$

$$(\partial \tilde{y}_1/\partial \eta)_{\eta = 0} = 0 \quad \text{(A9)}$$

[1] Use of the boundary condition, Eq. 16, to obtain the equilibrium solution, Eqs. 21 and 22, for c_o is justified a postiori by obtaining suitable inner and outer expansions. Alternatively, this boundary condition can be left unspecified, and determined by the matching of the inner and outer expansions.

The matching of the inner or boundary layer expansion, Eqs. A5, to the outer expansion, Eqs. A1, for the region bounded away from $r = R$ requires

$$\tilde{c}_1(\eta, z) \to c_1(R, z) + \eta\, c_{or}(R, z) \tag{A10}$$

$$\tilde{y}_1(\eta, z) \to y_1(R, z) + \eta\, y_{or}(R, z)\,, \tag{A11}$$

as $\eta \to \infty$.

The solutions for $\tilde{c}_1$ and $\tilde{y}_1$ satisfying Eqs. A6–A11 are

$$\tilde{c}_1 \sim \frac{MK}{2\tau^3}\frac{R - 1/R}{K + C(z)} + \frac{M}{2\delta}\left(R - \frac{1}{R}\right)\frac{K + C(z)}{\tau^2}\eta - \frac{MK}{2\tau^3}\frac{R - 1/R}{K + C(z)}\,e^{-\tau\eta} \tag{A12}$$

$$\tilde{y}_1 \sim \frac{MK^2}{2\tau^3}\frac{R - 1/R}{[K + C(z)]^3} + \frac{MK}{2\delta\tau^2}\frac{R - 1/R}{K + C(z)}\eta + \frac{MK}{2\delta\tau^3}\frac{R - 1/R}{K + C(z)}\,e^{-\tau\eta} \tag{A13}$$

where

$$\tau(z) = \left[\frac{K}{K + C(z)} + \frac{K + C(z)}{\delta}\right]^{1/2} \tag{A14}$$

The matching of the inner and outer solutions also provides the unknown function in Eq. A4:

$$B_1(z) = \frac{Mk\delta\,(R - 1/R)}{2\tau(z)\,[K + C(z)]^2} \tag{A15}$$

If the flux from the capillary into the tissue, given by Eq. 11, is calculated using the outer expansion, an incorrect result is obtained, since this expansion is not applicable at $r = R$. However, if the boundary layer expansion is used, we obtain

$$\left.\frac{\partial c}{\partial r}\right|_{r-R} = \epsilon^{1/2}\left.\frac{\partial \tilde{c}_1}{\partial \eta}\right|_{\eta-0}\left.\frac{\partial \eta}{\partial r}\right|_{r-R} = \frac{M}{2}\left(R - \frac{1}{R}\right), \tag{A16}$$

which is the correct result. This is particularly important in the case when anoxic tissue occurs, since the capillary concentration cannot be determined a-priori, but must also be expanded in a series and determined such that it satisfies eqn. (14).

When anoxia is present, the first order terms $\tilde{c}_1$ and $\tilde{y}_1$ in the expansion, Eqns. (32), satisfy eqns. (A6), (A7) with C(z) replaced by $C_o(z)$, the zero order term in the expansion, eqn. (26). The boundary conditions are

$$\tilde{c}_1(o, z) = C_1(z)$$

$$(\partial \tilde{y}_1/\partial \eta)_{\eta-0} = 0 \tag{A17}$$

where $C_1(z)$ is the first order term in the expansion, Eq. 26. The matching conditions are

$$\tilde{c}_1(\eta, z) \to c_1(R, z) + \eta\, c_{or}(R, z)$$

$$\tilde{y}_1(\eta, z) \to y_1(R, z) + \eta\, y_{or}(R, z), \tag{A18}$$

as $n \to \infty$, where c_o, c_1, y_o, y_1 are the terms in the expansion, Eqs. 24, 25, and the subscript r denotes differentiation with respect to r. Solving this system yields

$$\tilde{c}_1(\eta, z) = C_1(z) + \frac{\delta K\, c_{or}(R, z)}{\tau_o(z)\,[K + C_o(z)]^2} + c_{or}(R, z)\eta - \frac{\delta K\, c_{or}(R, z)}{\tau_o(z)\,[K + C_o(z)]^2}\,e^{-\tau_o(z)\eta}, \tag{A19}$$

$$\tilde{y}_1(\eta, z) = \frac{K}{(K + C_o)^2}\left\{C_1(z) + \frac{\delta K\, c_{or}(R, z)}{\tau_o(z)\,[K + C_o(z)]^2} + c_{or}(R, z)\eta\right\} + \frac{K\, c_{or}(R, z)}{\tau_o(z)\,[K + C_o(z)]^2}\,e^{-\tau_o(z)}, \tag{A20}$$

and the additional information

$$c_1(R, z) = C_1(z) + \frac{\delta K\, c_{or}(R, z)}{\tau_o(z)\,[K + C_o(z)]^2} \tag{A21}$$

$$y_1(R, z) = \frac{K}{K + C_o}\,c_1(R, z), \tag{A22}$$

which is needed in obtaining the first order terms in the outer expansions. The function $\tau_o(z)$ is defined analogous to $\tau(z)$ as

$$\tau_o(z) = \left[\frac{K}{K + C_o(z)} + \frac{K + C_o(z)}{\delta}\right]^{1/2}. \tag{A23}$$

With this solution, it follows that

$$\left.\frac{\partial \tilde{c}_1}{\partial \eta}\right|_{\eta-0} = c_{or}\left\{1 + \frac{\delta K}{[K + C_o(z)]^2}\right\}, \tag{A24}$$

which was used to obtain Eq. 34.

The solutions obtained here are applicable in the limit of small departures from chemical equilibrium, $\epsilon \ll 1$. Although Eqs. 12–18 suggest that corrections to the equilibrium solution are order ϵ, the analysis shows that these corrections are actually of order $\sqrt{\epsilon}$ and the asymptotic expansion is of the form shown in Eq. A1. This is because of the boundary layer that exists in the tissue adjacent to the capillary, where the solution must change rapidly in order to satisfy the boundary conditions. The $0(\sqrt{\epsilon})$ terms in Eqs. A1 cannot be found without determining the boundary layer solution. In the case of a slab of tissue there is a boundary layer at each side, required to satisfy the boundary conditions imposed there, and both these boundary layers must be analyzed in order to find the $0(\sqrt{\epsilon})$ term in the outer expansion (Kolkka and Salathe [8]). However, because of the boundary conditions specified at $r = 1$ in the present problem, there is no boundary layer at the outer edge of the tissue cylinder. This is true also at the free boundary $r = R^*$ for the case with anoxia, although the solution breaks down to order ϵ in the neighborhood of $r = R^*$, as discussed above.

For the data used in this analysis, when C becomes small, of the order of K, $\tilde{y}_1$ given by Eq. A13 becomes large, of order $1/\sqrt{\epsilon}$, and the boundary layer expansion, Eq. A5, breaks down. Since the boundary layer solution is needed to find c_1 and y_1 in the outer expansion, Eq. A1, the breakdown of the boundary layer solution suggests that the $0(\sqrt{\epsilon})$ corrections to the equilibrium solution may not be valid for those locations along the capillary at which C is <1 mmHg. This, of course, has no effect on the results shown in the figures, since they correspond to the equilibrium solution given by Eq. 39 and 42.

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