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Substrate Transport in Cylindrical Multi-Capillary Beds with Axial Diffusion

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ABSTRACT

It is known that in oxygen concentration profiles for capillary beds of skeletal muscles, radial diffusion most likely has considerably more effect on oxygen transport in long and parallel capillary beds than axial diffusion. However, axial diffusion may still play a significant role in oxygen transport in tissue, especially in relatively short pathways. Our model adds to known solutions the component of axial diffusion to multi-capillary beds inside a tissue cylinder, where arbitrary characteristics include random locations and uneven oxygen strengths. Discussion of the solutions for oxygen supply in multicapillary beds near the arterial ends, in the central regions, and near the venous ends in capillaries is introduced in the remainder of the article. To account for relatively small longitudinal diffusivities, we use perturbation methods to solve the associated governing equations.

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1 Problem Review and Analysis

1.1 Formulation

Let n be the number of capillaries in a cylinder of tissue with radius R_u. Assume that the capillaries are parallel to each other, that they all have length L, and that the radius of each capillary is given by R_j^c, where $1 \le j \le n$, as shown in Figure 1, similar to a Krogh cylinder (Krogh, 1919). In such cylindrical models, axial diffusion may not be neglected (Whiteley, Gavaghan, and Hahn, 2002).

Oxygen is diffused from the capillaries to the tissue at a constant rate of κ per volume of tissue. Let z denote the centered axis parallel to the capillaries, and let r denote the radial distance from the center axis of the tissue cylinder, with both normalized with respect to L, $0 \le z \le 1$, and R_u, $0 \le r \le 1$.

The governing equation for the oxygen concentration in the tissue, $c_u(r, \theta, z)$, is

$$\frac{1}{r}\frac{\partial}{\partial r} r \frac{\partial c}{\partial r} + \frac{1}{r^2}\frac{\partial^2 c}{\partial \theta^2} + \varepsilon^2 \frac{\partial^2 c}{\partial z^2} = \kappa_0, \qquad r \le 1, \qquad 0 \le z \le 1, \tag{1}$$

where $c = c_u/C_A$ is nondimensionalized with respect to the oxygen concentration in the arterial blood, C_A; $\varepsilon = \sqrt{D_z/D_r}(R_u/L)$; $R_j = R_j^c/R_u$; and $\kappa_0 = R_u^2\kappa/D_rC_A$. Here D_r, D_z are the radial and axial diffusivities of the tissue.

On the boundary of the region we require no flux:

$$\frac{\partial c}{\partial r} = 0, \qquad r = 1, \qquad 0 \le z \le 1, \tag{2}$$

$$\frac{\partial c}{\partial z} = 0, \qquad z = 0, 1, \qquad r \le 1. \tag{3}$$

Within the j^{th} capillary, the oxygen substrate per unit volume of blood, C_j^o, depends on the quantity of dissolved oxygen, C_j, and the oxygen capacity in blood cells. Denote the oxygen capacity at 100% saturation by V_c. The oxyhemoglobin dissociation curve can be approximated by

$$S(C_j)^* = \frac{K(C_AC_j)^\lambda}{1 + K(C_AC_j)^\lambda}. \tag{4}$$

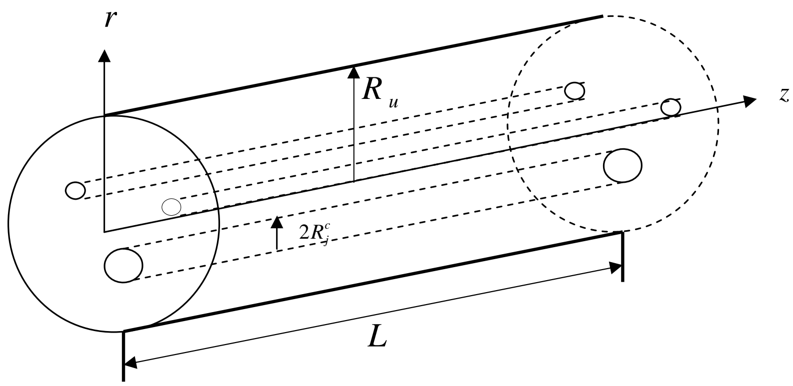

Figure 1: N capillaries, with uneven locations and diffusion strengths, surrounded by a cylinder of tissue

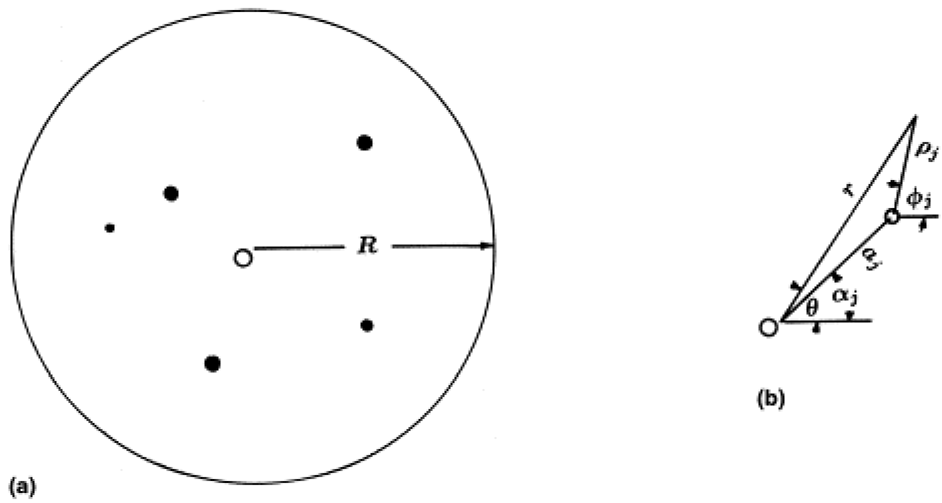

Figure 2: (a) General distribution of capillaries in the circular perpendicular cut (b) The coordinate system: O reprensents the origin of the polar coordinate system.

The relationship above states that the rate approaches 1 for large oxygen concentration and grows without bound for small oxygen concentration. Alternative forms can be found in (Go, 2007). Particular forms of the representation of oxyhemoglobin dissociation do not affect the analysis. A linear form of C_j^o is then given by $C_j + V_c S(C_j)^*$ (Salathe and Wang, 1980).

The governing equation for the rate of change in oxygen concentration within the j^{th} capillary at location z $(0 \leq z \leq 1)$ is

$$\frac{d}{dz}[C_j + VS(C_j)] = \gamma \oint \left.\frac{\partial c}{\partial \rho_j}\right|_{\rho_j = R_j} d\phi + \varepsilon^2 \nu \frac{d^2 C_j}{dz^2}, \tag{5}$$

where $\gamma = 2\pi D_r L R_j / Q$ and $\nu = R_j D_p / 2 D_z \gamma$. Q is the blood flow rate and D_p is the diffusivity in blood. The first term on the right gives the rate of oxygen diffusion from the j^{th} capillary to surrounding tissue as radial diffusion and the second term on the right represents the axial diffusion along the z axis.

The oxygen concentration at the arterial end is

$$C_j(0) = 1. \tag{6}$$

1.2 Perturbation of substrate concentration

Equation (5) will be solved for $R_j \ll 1$ and $\varepsilon \ll 1$. The equation shows that axial diffusion becomes negligible as $\varepsilon \to 0$, and for $\varepsilon = 0$, the equation reduces to a 2-dimensional problem. Perturbation technique will be used for higher orders of ε $(\varepsilon \ll 1)$, and corresponding solutions will give the effect of axial diffusion. Let $C(z) = C_j(z)$. The solutions for $C(z)$ and $c(r, \theta, z)$ will be obtained in the form of an asymptotic series, for small ε:

$$\begin{aligned} C(z) &\sim C_0(z) + \varepsilon^2 C_1(z) + \cdots \\ c(r,\theta,z) &\sim c_0(r,\theta,z) + \varepsilon^2 c_1(r,\theta,z) + \cdots \end{aligned} \tag{7}$$

The oxyhemoglobin dissociation relationship can be expanded for small ε by using Taylor series expansion to obtain

$$S(C_0 + \varepsilon^2 C_1) = S(C_0) + \varepsilon^2 C_1 S'(C_0) + \cdots \tag{8}$$

By letting $\varepsilon = 0$, the equations for the leading terms $C_0(z)$ and $c_0(r,\theta,z)$, along with the boundary conditions at the arterial end, capillary wall, and outer boundary of the cylindrical cut, become

$$\frac{1}{r}\frac{\partial}{\partial r} r \frac{\partial c_0}{\partial r} + \frac{1}{r^2}\frac{\partial^2 c_0}{\partial \theta^2} = \kappa, \qquad r \le 1, \qquad z \le 1, \tag{9}$$

$$\left.\frac{\partial c_0}{\partial r}\right|_{r=1} = 0, \qquad z \le 1, \tag{10}$$

$$\left.\frac{\partial c_0}{\partial z}\right|_{z=0} = 0, \qquad \left.\frac{\partial c_0}{\partial z}\right|_{z=1} = 0, \qquad r \le 1, \tag{11}$$

$$\frac{d}{dz}[C_0 + VS(C_0)] = \gamma \int_0^{2\pi} \left.\frac{\partial c_0}{\partial \rho}\right|_{\rho=R_u} d\phi, \tag{12}$$

$$C_0(0) = 1. \tag{13}$$

We then need to give solutions for $C_0(z)$ and $c_0(r,\theta,z)$ in the above equations. For c_0, the oxygen concentration in tissue, we employ a matching technique similar to the results in (Wang and Bassingthwaighte, 2001). It follows from Equations (9)–(11) that

$$c_0(r,\theta,z) = r^2/4 + \sum_{j=1}^{N}\{C_{0,j} - \kappa/4 \cdot \ln[r^2 + a_j^2 - 2ra_j\cos(\theta-\alpha_j)]\} + \kappa \cdot \sum_{n=0}^{\infty} r^n (A_n \cos n\theta + B_n \sin n\theta) \tag{14}$$

where A_n and B_n are constant coefficients:

$$A_n = \frac{1}{2n}\sum_{j=1}^{N} a_j^n \cos(n\alpha_j), \qquad n \ge 1, \tag{15}$$

$$B_n = \frac{1}{2n}\sum_{j=1}^{N} a_j^n \sin(n\alpha_j), \qquad n \ge 1. \tag{16}$$

The solution states that the oxygen concentration in tissue is a combination of oxygen diffusion from each capillary within the circular region parameterized by $0 \le r \le 1$. ρ_j is the distance from the j^{th} capillary. The effect of oxygen diffusion from the j^{th} capillary diminishes as ρ_j increases. A_0 is a constant due to the Nuemann boundary condition and can be set to make $c_0 > 0$. This analytical solution gives a sufficiently good description of oxygen concentration in the cylindrical cross section. Next, substitute Equation (14) into Equation (12); it follows from boundary condition (13) that the solution for C_0, the leading term of $C(z)$, can be obtained by letting $\varepsilon = 0$:

$$C_0 + VS(C_0) = \left[\pi\gamma\,(R - \frac{\kappa}{R} - N) + \widehat{\varphi}_0(R)\right] \cdot z + VS(1) + 1, \tag{17}$$

where N is the number of capillaries, and $\widehat{\varphi}_0(R)$ is

$$\widehat{\varphi}_0(R) = \sum_{j=1}^{N} a_j^2 \kappa \cdot \pi R + o(R) \qquad \text{for } R \ll 1. \tag{18}$$

The oxygen concentration in a capillary, $C_0(z)$, can be obtained from Equation (17) through the monotonicity of the oxyhemoglobin dissociation function $S(C)$.

The equations for the second terms, $c_1(r,\theta,z)$ and $C_0(z)$, can be obtained by substituting Equation (7) into Equations (1), (2), (3), (5) and (6) and retaining terms of order ε^2. Then (8) gives

$$\frac{1}{r}\frac{\partial}{\partial r}r\frac{\partial c_1}{\partial r}+\frac{1}{r^2}\frac{\partial^2 c_1}{\partial \theta^2}=-\frac{\partial^2 c_0}{\partial z^2},\qquad r\le 1,\qquad z\le 1, \tag{19}$$

$$\left.\frac{\partial c_1}{\partial r}\right|_{r=1}=0,\qquad z\le 1, \tag{20}$$

$$\left.\frac{\partial c_1}{\partial z}\right|_{z=0}=0,\qquad \left.\frac{\partial c_1}{\partial z}\right|_{z=1}=0,\qquad r\le 1, \tag{21}$$

$$\frac{d}{dz}C_1[1+VS'(C_0)]=\gamma\int_0^{2\pi}\left.\frac{\partial c_1}{\partial \rho}\right|_{\rho=R}d\phi+\nu\frac{d^2C_0}{dz^2},\qquad 0<z<1, \tag{22}$$

$$C_1(0)=0. \tag{23}$$

Note that the system of equations above includes the effect of axial diffusion. The solution for $c_1(r,\theta,z)$ in Equation (19) satisfying boundary conditions (20) and (21) is found to be

$$c_1(r,\theta,z)=r^2/4+\sum_{j=1}^{N}\{C_{1,j}+C_0''(z)/4\cdot\ln[r^2+a_j^2-2ra_j\cos(\theta-\alpha_j)]\}-C_0''(z)\cdot\sum_{n=0}^{\infty}r^n(A_n\cos n\theta+B_n\sin n\theta), \tag{24}$$

where A_n and B_n are constant coefficients defined as

$$A_n=\frac{1}{2n}\sum_{j=1}^{N}a_j^n\cos(n\alpha_j),\qquad n\ge 1, \tag{25}$$

$$B_n=\frac{1}{2n}\sum_{j=1}^{N}a_j^n\sin(n\alpha_j),\qquad n\ge 1. \tag{26}$$

In the above solution, the zero-th order term, $C_0(z)$, has already been found in (17). At this point, the oxygen concentration $c=c_0+\varepsilon^2c_1$ at any location z in the tissue cylinder around N capillaries is completely known. For the oxygen concentration in a capillary, $C=C_0+\varepsilon^2C_1$, that takes into account axial diffusion, substitute (24) into Equation (22) with boundary condition (23). It follows that

$$C_1[1+VS'(C_0(z))]=\left[\pi\gamma\,(R-N)\right]\cdot z+\left(\nu-\widehat{\varphi}_1(R)+\frac{\pi\gamma}{R}\right)\cdot[\,C_0'(z)-C_0'(0)\,]+C_1(0)[1+VS'(1)], \tag{27}$$

where N is the number of capillaries, and $\widehat{\varphi}_1(R)$ equals

$$\widehat{\varphi}_1(R)=\sum_{j=1}^{N}a_j^2\cdot\pi R+o(R)\qquad \text{for } R\ll 1. \tag{28}$$

C_1 can be obtained from the above because $S(C)$ is monotone and concave down. The solutions are valid throughout the cylindrical region except near $z=0$. At the arterial end of the cylinder, radial diffusion, D_r, and axial diffusion, D_p, are of equal importance. Therefore the small perturbation, ε^2, cannot be employed for z near zero, and the solutions from (27) and boundary condition (23) are no longer valid. The expansions need to be adjusted for a small layer near $z=0$. The adjustment also needs to satisfy the boundary condition with no flux through the end of the cylinder.

1.3 Small z boundary layer

For small z, there exists a boundary layer for which solutions need to be constructed differently. The thickness of the layer diminishes as $\varepsilon\to 0$. Instead of z, we use $Z=z/\varepsilon$ ($z\to 0$ as $\varepsilon\to 0$ for fixed Z) as the variable for this boundary layer. The new functions for oxygen concentration in tissue and capillary now become $\widetilde{c}(r,\theta,Z)=c(r,\theta,\varepsilon Z)$ and $\widetilde{C}(Z)=C(\varepsilon Z)$. The governing equations are

$$\frac{1}{r}\frac{\partial}{\partial r}r\frac{\partial \widetilde{c}}{\partial r}+\frac{1}{r^2}\frac{\partial^2\widetilde{c}}{\partial\theta^2}+\frac{\partial^2\widetilde{c}}{\partial Z^2}=\kappa,\qquad r\le 1,\qquad Z\ge 0, \tag{29}$$

$$\frac{d}{dz}[\widetilde{C}+VS(\widetilde{C})]=\varepsilon\gamma\int_0^{2\pi}\left.\frac{\partial\widetilde{c}}{\partial\rho}\right|_{\rho=R}d\phi+\varepsilon\nu\frac{d^2\widetilde{C}}{dZ^2},\qquad Z\ge 0, \tag{30}$$

$$\left.\frac{\partial\widetilde{c}}{\partial r}\right|_{r=1}=0,\qquad z\le 1, \tag{31}$$

$$\left.\frac{\partial\widetilde{c}}{\partial Z}\right|_{Z=0}=0,\qquad r\le 1, \tag{32}$$

$$\widetilde{C}(0)=1. \tag{33}$$

Equation (30) can be written as

$$\frac{d}{dz}[\widetilde{C}+VS(\widetilde{C})]=\varepsilon\gamma\int_0^{2\pi}\left.\frac{\partial\,\widetilde{c}_p+\widetilde{c}_s+\widetilde{c}_h}{\partial\rho}\right|_{\rho=R}d\phi+\varepsilon\nu\frac{d^2\widetilde{C}}{dZ^2},\qquad Z\ge 0, \tag{34}$$

where $\widetilde{c}_p,\widetilde{c}_p,\widetilde{c}_p$ give respectively the particular solution, source solution, and homogenous solution of oxygen concentration in tissue. Discussion of the explicit expressions is in the next section.

The solutions to $\widetilde{c}(r,\theta,Z)$ and $\widetilde{C}(Z)$ near $z=0$ should be uniformly consistent with solutions throughout the cylinder away from the boundary layer. To satisfy

$$\lim_{Z\to\infty}\widetilde{C}(r,\theta,Z)=\lim_{z\to 0}c(r,\theta,z), \tag{35}$$

$$\lim_{Z\to\infty}\widetilde{C}(Z)=\lim_{z\to 0}c(z), \tag{36}$$

it is necessary to look at the solutions of $c(r,\theta,Z)$ and $C(Z)$ near the boundary layer at $z=0$ and match the inside solutions $\widetilde{C}$, $\widetilde{c}$ to the outside solution C,c at the first few orders of ε. We write $c(r,\theta,Z)+\varepsilon^2c(r,\theta,Z)$ and $C(Z)+\varepsilon^2C(Z)$ in terms of r, θ, and Z and expand in terms of ε:

$$C(\varepsilon Z)=C(0)+\varepsilon\mu_1Z+\varepsilon^2\mu_2Z+o(\varepsilon^3), \tag{37}$$

where $\mu_1=C_0'(0)$ and $\mu_2=C_0''(0)/2$. Expand $C_0(\varepsilon Z)+VS(C_0(\varepsilon Z))$ using Taylor expansion:

$$C_0(\varepsilon Z)+VS(C_0(\varepsilon Z))=1+VS(1)+\varepsilon\mu_1(1+VS'(1))Z+\varepsilon^2\left[(1+VS'(1))\mu_2+\frac{VS''(1)}{2}\mu_1^2\right]Z^2+O(\varepsilon^3). \tag{38}$$

From (17), $C_0(\varepsilon Z)+VS(C_0(\varepsilon Z))$ can be explicitly written as

$$C_0(\varepsilon Z)+VS(C_0(\varepsilon Z))=1+VS(1)+\varepsilon\left[\pi\gamma(R-\frac{\kappa}{R}-N)+\widehat{\varphi}_0(R)\right]Z. \tag{39}$$

Compare (38) with (39); μ_1 and μ_2 are found to be respectively

$$\mu_1=\frac{\pi\gamma(R-\frac{\kappa}{R}-N)+\widehat{\varphi}_0(R)}{1+VS'(1)}, \tag{40}$$

$$\mu_2=-\frac{VS''(1)\left[\pi\gamma(R-\frac{\kappa}{R}-N)+\widehat{\varphi}_0(R)\right]^2}{2\left(1+VS'(1)\right)^3}, \tag{41}$$

where $\widehat{\varphi}_0(R)$ is as given in (18). The oxygen concentration in capillaries is approximated to the order of ε^2. Adding the C_1 term to the above gives us

$$\begin{aligned}C(z)&\sim C_0(z)+\varepsilon^2C_1(z)\\&\sim 1+\varepsilon\mu_1Z+\varepsilon^2\left(\mu_2Z^2+C_1(0)\right)+O(\varepsilon^3),\end{aligned} \tag{42}$$

where μ_1 and μ_2 are given in (40) and (41). The oxygen concentration in tissue, $c_0(r,\theta,z)+\varepsilon^2 c_1(r,\theta,z)$, can be expanded to

$$\begin{aligned} c(r,\theta,z) &\sim c_0(r,\theta,z)+\varepsilon^2 c_1(r,\theta,z) \\ &\sim N + r^2/4 - \kappa/4\cdot\sum_{j=1}^{N}\ln[r^2+a_j^2-2ra_j\cos(\theta-\alpha_j)] + \kappa\sum_{n=0}^{\infty} r^n(A_n\cos n\theta + B_n\sin n\theta) + \varepsilon\sum_{j=1}^{N}\mu_{1,j}Z \\ &\quad + \varepsilon^2\left\{\mu_2 Z^2 + r^2/4 + \sum_{j=1}^{N} C_{1,j}(0) + \mu_2/2\cdot\sum_{j=1}^{N}\ln[r^2+a_j^2-2ra_j\cos(\theta-\alpha_j)]\right. \\ &\quad \left. - 2\mu_2\sum_{n=0}^{\infty} r^n(A_n\cos n\theta + B_n\sin n\theta)\right\} + O(\varepsilon^3), \end{aligned} \tag{43}$$

where (for the j^{th} capillary)

$$\mu_{1,j} = \frac{\pi\gamma(R_j - \frac{\kappa}{R_j} - N) + \widehat{\varphi}_0(R_j)}{1 + VS'(1)}. \tag{44}$$

To match the boundary layer solutions to outside solutions C and c, expansions of $\widetilde{C}$ and $\widetilde{c}$ in terms of ε must be in the form

$$\widetilde{C}(z) \sim 1 + \varepsilon\mu_1 Z + \varepsilon^2 H(Z), \tag{45}$$

$$\begin{aligned} \widetilde{c}(z) &\sim N + r^2/4 - \kappa/4\cdot\sum_{j=1}^{N}\ln[r^2+a_j^2-2ra_j\cos(\theta-\alpha_j)] \\ &\quad + \kappa\sum_{n=0}^{\infty} r^n(A_n\cos n\theta + B_n\sin n\theta) + \varepsilon\psi(r,\theta,Z) + \varepsilon^2\varphi(r,\theta,Z). \end{aligned} \tag{46}$$

$H(Z)$, $\psi(r,\theta,Z)$, and $\varphi(r,\theta,Z)$ are to be determined. Use the expansions given in (45) and (46) and substitute into Equations (29) and (30) with boundary conditions (31)–(34). Match first and second order ε terms corresponding to $\widetilde{C}$ and $\widetilde{c}$. The set of differential equations for $H(Z)$, $\psi(r,\theta,Z)$, and $\varphi(r,\theta,Z)$ are the following:

I. For $H(z)$, after matching the ε^2 terms from Equation (30), we have

$$\frac{dH}{dZ} = 2\mu_2 Z + \frac{\gamma}{1+VS'(1)}\oint \left.\frac{\partial\psi}{\partial\rho}\right|_{\rho\to R} d\phi, \tag{47}$$

$$H(0) = 0, \tag{48}$$

and in order to match the outside solution $C(z)$ in (42) for $O(\varepsilon)$ terms we have

$$\lim_{Z\to\infty} H(Z) = \mu_2 Z^2 + C_1(0). \tag{49}$$

II. For $\psi(r,\theta,Z)$, after matching corresponding terms with respect to ε, we have

$$\frac{1}{r}\frac{\partial}{\partial r} r\frac{\partial\psi}{\partial r} + \frac{1}{r^2}\frac{\partial^2\psi}{\partial\theta^2} + \frac{\partial^2\psi}{\partial Z^2} = 0, \qquad r\le 1, \qquad Z\ge 0, \tag{50}$$

$$\left.\frac{\partial\psi}{\partial r}\right|_{r=1} = 0, \qquad Z\ge 0, \tag{51}$$

$$\left.\frac{\partial\psi}{\partial Z}\right|_{Z=0} = 0, \qquad r\le 1, \tag{52}$$

$$\widehat{C}_\psi(r,\theta,Z) = \mu_1 Z, \qquad \text{at } \rho = R, \qquad Z\ge 0, \tag{53}$$

where $\widehat{C}_\psi$ is the capillary source concentration associated with ψ. In order to match the outside solution $c(r,\theta,z)$ in (43) at the ε terms, where $\mu_{1,j}$ is defined in (44), we have

$$\lim_{Z\to\infty}\psi = \sum_{j=1}^{N}\mu_{1,j} Z. \tag{54}$$

III. For $\varphi\,(r,\theta,Z)$, after matching corresponding terms with respect to ε, we have

$$\frac{1}{r}\frac{\partial}{\partial r}r\frac{\partial\varphi}{\partial r}+\frac{1}{r^2}\frac{\partial^2\varphi}{\partial\theta^2}+\frac{\partial^2\varphi}{\partial Z^2}=0,\qquad r\le 1,\qquad Z\ge 0, \tag{55}$$

$$\left.\frac{\partial\varphi}{\partial r}\right|_{r=1}=0,\qquad Z\ge 0, \tag{56}$$

$$\left.\frac{\partial\varphi}{\partial Z}\right|_{Z=0}=0,\qquad r\le 1, \tag{57}$$

$$\widehat{C}_{\varphi}(r,\theta,Z)=H(Z),\qquad \text{at } \rho=R,\qquad Z\ge 0, \tag{58}$$

where $\widehat{C}_{\varphi}$ is the capillary source concentration associated with ψ. In order to match the outside solution $C(z)$ in (43) for the $O(\varepsilon^2)$ terms, we have

$$\lim_{Z\to\infty}\varphi=\mu_2 Z^2+r^2/4+\sum_{j=1}^{N}C_{1,j}(0)+\mu_2/2\cdot\sum_{j=1}^{N}\ln[r^2+a_j^2-2ra_j\cos(\theta-\alpha_j)]$$
$$-2\mu_2\sum_{n=0}^{\infty}r^n(A_n\cos n\theta+B_n\sin n\theta). \tag{59}$$

From Equation (47) and boundary condition (48), we obtain

$$H(Z)=\mu_2^2 Z+\frac{\gamma}{1+VS'(1)}\int_0^Z\oint\left.\frac{\partial\psi}{\partial\rho}\right|_{\rho\to R}d\phi\,dZ. \tag{60}$$

Substituting (60) into matching condition (49), we have

$$C_1(0)=\frac{\gamma}{1+VS'(1)}\int_0^\infty\oint\left.\frac{\partial\psi}{\partial\rho}\right|_{\rho\to R}d\phi\,dZ. \tag{61}$$

2 Further Discussion on Matching Solutions

In order to successfully match the inner solution with the outer solution inside the cylindrical tissue region, we need to obtain the solutions for perturbation functions ψ and φ. To obtain the solutions for ψ, let

$$\psi=\sum_{j=1}^{N}\widehat{C}_j(z)-1/2\big(\ln\rho_j-\ln R_j\big)+T(r,\theta,Z), \tag{62}$$

where $\widehat{C}_j(z)=\mu_{1,j}Z$. The first two terms in (62) give the combination of oxygen diffusion from each capillary source. The function T, defined in the semi-infinite cylinder $r\le 1, Z\ge 0$, satisfies Laplace's equation:

$$\frac{\partial^2 T}{\partial r^2}+\frac{1}{r}\frac{\partial T}{\partial r}+\frac{1}{r^2}\frac{\partial^2 T}{\partial\theta^2}+\frac{\partial^2 T}{\partial Z^2}=0,\qquad r\le 1,\qquad Z\ge 0, \tag{63}$$

$$\frac{\partial T}{\partial r}=\frac{\partial}{\partial r}(1/2\sum_{j=1}^{N}\ln\rho_j),\qquad \text{at } r=1, \tag{64}$$

$$\left.\frac{\partial T}{\partial Z}\right|_{Z=0}=-\sum_{j=1}^{N}\mu_{1,j},\qquad r\le 1. \tag{65}$$

Notice that on the outer boundary where $r=1$, T has no flux in or out of the cylindrical region. T satisfies a well-posed problem that can be solved first by separation of variables:

$$T(r,\theta,Z)=R(r)\,\Theta(\theta)\,\Gamma(Z) \tag{66}$$

Then for some unknown constant λ, we have

$$\frac{1}{\Gamma}\Gamma'' = \lambda^2, \qquad \frac{1}{\Theta}\frac{\partial^2\Theta}{\partial\theta^2} = -n^2, \tag{67}$$

$$r^2\frac{\partial^2 R}{\partial r^2} + r\frac{\partial R}{\partial r} + (r^2\lambda - n^2)R = 0. \tag{68}$$

Equation (63) is reduced to a Helmholtz equation in two variables, with circular supports. T is then solved to be in a general form:

$$T(r,\theta,Z) = \int_0^\infty e^{-\lambda Z}\sum_{n=0}^{\infty}\Big\{\big[A_n(\lambda)\sin(n\theta) + B_n(\lambda)\cos(n\theta)\big]\cdot\big[D_nJ_n(\lambda r) + E_nY_n(\lambda r)\big]\Big\}\,d\lambda, \tag{69}$$

where J_* and Y_* are Bessel functions of the first and second kind, and $A_n(\lambda)$, $B_n(\lambda)$, $D_n(\lambda)$, and $E_n(\lambda)$ are constants that are limited to the boundary conditions.

The radial derivative of Equation (69) is

$$\frac{\partial T}{\partial r} = \int_0^\infty e^{-\lambda Z}\sum_{n=0}^{\infty}\Big\{\big[\widehat{A}_n(\lambda)\sin(n\theta) + \widehat{B}_n(\lambda)\cos(n\theta)\big]\cdot\lambda\Big[\widehat{D}_n(\lambda)\Big(J_{n-1}(\lambda r) - J_{n+1}(\lambda r)\Big) + \widehat{E}_n(\lambda)\Big(Y_{n-1}(\lambda r) - Y_{n+1}(\lambda r)\Big)\Big]\Big\}\,d\lambda. \tag{70}$$

The boundary condition (64) gives at $r = 1$

$$\frac{\partial T}{\partial r} = \sum_{j=1}^{N}\frac{r - a_j\cos(\theta-\alpha_j)}{r^2 + a_j^2 - 2ra_j\cos(\theta-\alpha_j)} \tag{71}$$

$$\Rightarrow \sum_{j=1}^{N}\frac{1 - a_j\cos(\theta-\alpha_j)}{1 + a_j^2 - 2a_j\cos(\theta-\alpha_j)} = \int_0^\infty e^{-\lambda Z}\sum_{n=0}^{\infty}\Big\{\big[\widehat{A}_n(\lambda)\sin(n\theta) + \widehat{B}_n(\lambda)\cos(n\theta)\big]\cdot\lambda\Big[\widehat{D}_n(\lambda)\big(J_{n-1}(\lambda) - J_{n+1}(\lambda)\big) + \widehat{E}_n(\lambda)\big(Y_{n-1}(\lambda) - Y_{n+1}(\lambda)\big)\Big]\Big\}\,d\lambda \tag{72}$$

Multiplying the above equation by $\cos(m\theta)$ and integrating from 0 to 2π with respect to θ yield

$$\frac{\partial T}{\partial r} = \sum_{j=1}^{N}\frac{r - a_j\cos(\theta-\alpha_j)}{r^2 + a_j^2 - 2ra_j\cos(\theta-\alpha_j)} \tag{73}$$

$$\Rightarrow \widehat{B}_m\pi\int_0^\infty e^{-\lambda Z}\cdot\lambda\Big[\widehat{D}_m(\lambda)\big(J_{m-1}(\lambda) - J_{m+1}(\lambda)\big) + \widehat{E}_n(\lambda)\big(Y_{m-1}(\lambda) - Y_{m+1}(\lambda)\big)\Big]\,d\lambda = \sum_{j=1}^{N}\int_0^{2\pi}\frac{1 - a_j\cos(\theta-\alpha_j)}{1 + a_j^2 - 2a_j\cos(\theta-\alpha_j)}\cos(m\theta)\,d\theta \tag{74}$$

Letting $\vartheta = \theta - \alpha_j$ and using integration formulas in (Gradshteyn and Ryzhik, 1994), we have

$$\begin{aligned}\widehat{B}_m\pi\int_0^\infty e^{-\lambda Z}\cdot\lambda\Big[\widehat{D}_m(\lambda)\big(J_{m-1}(\lambda) - J_{m+1}(\lambda)\big) + \widehat{E}_n(\lambda)\big(Y_{m-1}(\lambda) - Y_{m+1}(\lambda)\big)\Big]\,d\lambda \\ = \sum_{j=1}^{N}\int_0^{2\pi}\frac{1 - a_j\cos(\theta-\alpha_j)}{1 + a_j^2 - 2a_j\cos(\theta-\alpha_j)}\big[\cos(m\vartheta)\cos(m\alpha_j) - \sin(m\vartheta)\sin(m\alpha_j)\big]\,d\vartheta \\ = \sum_{j=1}^{N}\pi a_j^m\cos(m\alpha_j), \qquad m \ge 1,\end{aligned} \tag{75}$$

and thus, we can achieve

$$\widehat{B}_m = \frac{\sum_{j=1}^{N}a_j^m\cos(m\alpha_j)}{G_m(Z)}, \tag{76}$$

where

$$G_m(Z) = \int_0^\infty e^{-\lambda Z} \cdot \lambda \left[\widehat{D}_m(\lambda)\big(J_{m-1}(\lambda) - J_{m+1}(\lambda)\big) + \widehat{E}_n(\lambda)\big(Y_{m-1}(\lambda) - Y_{m+1}(\lambda)\big)\right] d\lambda. \tag{77}$$

In the same manner, multiplying Equation (74) by $\sin(m\theta)$ and integrating from 0 to 2π with respect to θ yield

$$\begin{aligned}
\widehat{A}_m\pi \int_0^\infty e^{-\lambda Z} \cdot \lambda \left[\widehat{D}_m(\lambda)\big(J_{m-1}(\lambda) - J_{m+1}(\lambda)\big) + \widehat{E}_n(\lambda)\big(Y_{m-1}(\lambda) - Y_{m+1}(\lambda)\big)\right] d\lambda& \\
= \sum_{j=1}^N \int_0^{2\pi} \frac{1 - a_j\cos(\theta-\alpha_j)}{1 + a_j^2 - 2a_j\cos(\theta-\alpha_j)} \sin(m\theta)\, d\theta& \\
= \sum_{j=1}^N \int_0^{2\pi} \frac{1 - a_j\cos(\theta-\alpha_j)}{1 + a_j^2 - 2a_j\cos(\theta-\alpha_j)} \left[\sin(m\vartheta)\cos(m\alpha_j) + \cos(m\vartheta)\sin(m\alpha_j)\right] d\vartheta& \\
= \sum_{j=1}^N \pi a_j^m \sin(m\alpha_j), \qquad m \ge 1,&
\end{aligned} \tag{78}$$

and thus, we can achieve

$$\widehat{A}_m = \frac{\sum_{j=1}^N a_j^m \sin(m\alpha_j)}{G_m(Z)}. \tag{79}$$

The axial derivative of Equation (69) is

$$\left.\frac{\partial T}{\partial Z}\right|_{Z=0} = \sum_{j=1}^N \mu_{1,j} = \int_0^\infty (-\lambda) \sum_{n=0}^\infty \frac{\widehat{D}_n(\lambda)J_n(\lambda r) + \widehat{E}_n(\lambda)Y_n(\lambda r)}{G_n(Z)} \sum_{j=1}^N a_j^n \left[\big(\sin(n\alpha_j)\sin(n\theta) + \cos(n\alpha_j) cos(n\theta)\big)\right] d\lambda. \tag{80}$$

$\widehat{D}_n$ and $\widehat{E}_n$ can be solved in terms of an eigenfunction expansion involving Bessel functions, where the set of eigenfunctions is

$$\big\{J_n(\lambda r)\sin(n\theta), \quad Y_n(\lambda r)\sin(n\theta), \quad J_n(\lambda r)\cos(n\theta), \quad Y_n(\lambda r)\cos(n\theta)\big\}.$$

Then ψ, which describes the oxygen concentration near the arterial boundary layer to the first order of ε, can be expressed as

$$\psi = \sum_{j=1}^N \widehat{C}_j(z) - 1/2\big(\ln\rho_j - \ln R_j\big) + \int_0^\infty \sum_i \sum_{n=0}^\infty A_{i,n}(\lambda) f_{i,n}(r,\theta) e^{-\lambda Z} d\lambda, \tag{81}$$

where

$$A_{i,n} \in \begin{Bmatrix} \widehat{A}_n\widehat{D}_n \\ \widehat{A}_n\widehat{E}_n \\ \widehat{B}_n\widehat{D}_n \\ \widehat{B}_n\widehat{E}_n \end{Bmatrix} \qquad \text{and} \qquad f_{i,n}(r,\theta) \in \begin{Bmatrix} J_n(\lambda r)\sin(n\theta) \\ Y_n(\lambda r)\sin(n\theta) \\ J_n(\lambda r)\cos(n\theta) \\ Y_n(\lambda r)\cos(n\theta) \end{Bmatrix}.$$

The function $H(Z)$ for the oxygen concentration in capillaries can then be determined by substituting the solution for $\psi(r,\theta,Z)$ into Equation (60):

$$H(Z) = \mu_2^2 Z + C_1(0) + \frac{\gamma}{1 + VS'(1)} \int_0^Z \oint \left.\frac{\partial\psi}{\partial\rho}\right|_{\rho\to R} d\phi\, dZ. \tag{82}$$

The third term in ψ is well-posed and has a radial derivative in terms of Bessel functions. Denote $\oint \frac{\partial}{\partial\rho}(\sum_i f_{i,j})|_{\rho\to R}\, d\phi$ by ξ; then

$$H(Z) = \mu_2^2 Z + C_1(0) - \frac{\xi\cdot\gamma}{1 + VS'(1)} \int_0^\infty \left(\sum_{n=0}^\infty \sum_i \frac{A_{i,n}}{\lambda}\right) e^{-\lambda Z} d\lambda. \tag{83}$$

To complete the boundary layer solution (46), compare the oxygen concentration φ in the boundary tissue layer to the second order of ε. This solution can be written in terms of a new variable W as

$$\begin{aligned}
\varphi(r,\theta,Z) = W(r,Z) + \mu_2 Z^2 + r^2/4 + \sum_{j=1}^N C_{1,j}(0) - \widehat{\xi} \int_0^\infty A(\lambda)\, e^{-\lambda Z} d\lambda& \\
+ \mu_2/2 \cdot \sum_{j=1}^N \ln[r^2 + a_j^2 - 2ra_j\cos(\theta-\alpha_j)] - 2\mu_2 \sum_{n=0}^\infty r^n(A_n\cos n\theta + B_n\sin n\theta),&
\end{aligned} \tag{84}$$

where A_n, B_n are defined in (15) and (16), and

$$\widehat{\xi} = \frac{\xi \cdot \gamma}{1 + VS'(1)} \qquad \text{and} \qquad A(\lambda) = \sum_{n=0}^{\infty} \sum_{i} \frac{A_{i,n}}{\lambda}.$$

In Equations (55)–(58), $W(r, Z)$ satisfies

$$\frac{1}{r}\frac{\partial}{\partial r} r \frac{\partial W}{\partial r} + \frac{\partial^2 W}{\partial Z^2} = \widehat{\xi} \int_0^{\infty} \lambda^2 A(\lambda)\, e^{-\lambda Z}\, d\lambda, \tag{85}$$

$$\left.\frac{\partial W}{\partial r}\right|_{r=1} = 0, \qquad Z \geq 0, \tag{86}$$

$$\left.\frac{\partial W}{\partial Z}\right|_{Z=0} = -\widehat{\xi} \int_0^{\infty} \lambda A(\lambda)\, d\lambda, \qquad r \leq 1. \tag{87}$$

Notice that W does not depend on θ. As Salathe and Wang (Salathe and Wang, 1980) show in their paper, the capillary source concentration is already included in the rest of the expression for φ in (84) to the second order of ε as shown in (43). The solution to the Poisson equation (85) with boundary conditions (86) and (87) can be constructed by using eigenfunction expansions $g_n(r)$, in the form of

$$g_n(r) = Y_0(\lambda_n R) J_0(\lambda_n r) - J_0(\lambda_n R) Y_0(\lambda_n r), \tag{88}$$

where J_0 and Y_0 are the zero-order Bessel functions of the first and second kind. Using boundary condition (86), the eigenvalues λ_n are obtained as the roots of

$$Y_0(\lambda R) J_1(\lambda) - J_0(\lambda R)\, Y_1(\lambda) = 0, \tag{89}$$

where J_1 and Y_1 are first-order Bessel functions of the first and second kind. A solution to Equation (85) with boundary conditions (86) and (87) can be found (Salathe and Wang, 1980) by constructing $W(r, Z)$ in the form

$$W(r, Z) = \sum_{n}^{\infty} E_n(Z) g_n(r), \tag{90}$$

where $E_n(Z)$ is a more general function of Z than $e^{-\lambda Z}$, and $g_n(r)$ are eigenfunctions associated with the equation for r after separation of variables, defined in (89). The orthogonality property of the eigenfunctions gives

$$\oint r g_m(r) g_n(r)\, dr = 0, \qquad \text{for } m \neq n, \tag{91}$$

$$\oint r g_n^2(r)\, dr = \frac{\big(g_n(1)\big)^2}{2} - \frac{2}{\lambda_n^2 \pi^2}, \qquad n = 1, 2, 3, 4, \ldots \tag{92}$$

After applying Equations (91) and (92) to relation (90) and using the orthogonality property and multiplying $g_m(r)$ on both sides of (90), one can conclude that

$$E_n(Z) = P_n \cdot \oint r W(r, Z) g_n(r)\, dr \tag{93}$$

with

$$P_n = \left[\frac{\big(g_n(1)\big)^2}{2} - \frac{2}{\lambda_n^2 \pi^2}\right]^{-1}. \tag{94}$$

Differentiating E_n twice with respect to Z gives

$$E_n''(Z) = P_n \cdot \oint r\, g_n(r) \frac{\partial^2 W(r, Z)}{\partial Z^2}\, dr. \tag{95}$$

Together with the governing equation in (85), this yields

$$E_n''(Z) = -P_n \cdot \oint g_n(r) \frac{\partial}{\partial r} r \frac{\partial}{\partial r} W(r, Z)\, dr + P_n \Big(\widehat{\xi} \int_0^{\infty} \lambda^2 A(\lambda)\, e^{-\lambda Z}\, d\lambda\Big) \cdot \oint r g_n(r)\, dr. \tag{96}$$

By using the boundary conditions for W, applying integration by parts twice, and using Equation (93), the first integral on the right side of Equation (96) is reduced to

$$\oint g_n(r)\frac{\partial}{\partial r}r\frac{\partial}{\partial r}W(r,Z)\,dr = -\lambda_n^2\oint rW(r,Z)g_n(r)dr$$
$$= -\lambda_n^2 P_n^{-1}E_n. \tag{97}$$

Using properties of Bessel functions (Watson, 1952), the second integral on the right side of Equation (96) can be reduced to

$$\oint rg_n(r)\,dr = -\frac{2}{\lambda_n^2\pi}. \tag{98}$$

Therefore, combining (96), (97), and (98) we have

$$E_n''(Z) = \lambda^2 E_n(Z) - \frac{2\widehat{\xi}P_n}{\lambda_n^2\pi}\int_0^\infty \lambda^2 A(\lambda)\,e^{-\lambda Z}\,d\lambda. \tag{99}$$

From property (93) and boundary condition (87), another boundary condition for $E_n(Z)$ is obtained:

$$E_n'(0) = \frac{2\widehat{\xi}P_n}{\lambda_n^2\pi}\int_0^\infty \lambda A(\lambda)\,d\lambda. \tag{100}$$

General solutions to Equation (99) can be achieved given boundary condition (100).

Calculation of oxygen pressures in tissue with anisotropic capillary orientation are presented in (Hoofd, 1995a) and (Hoofd, 1995b). The solution in cylindrical tissue c and the solution in capillaries C are computed outside the boundary layer where z is relatively small, as well as the boundary layer at the other end (these are the two end regions of our cylindrical model). The solutions obtained in the middle region are valid throughout the cylindrical tube except for the two end regions. For the arterial boundary layer, one can use perturbation by letting $Z = z/\varepsilon$ to find the approximate solutions $\widetilde{C}$ and $\widetilde{c}$ as shown above for the first and second orders of ε. Similarly, for the venous end, by letting $Y = (1-z)/\varepsilon$, one can approach the solutions with respect to the first and second orders of ε. A single solution shall be constructed through the whole cylindrical region from $z = 0$ to $z = 1$, uniformly composed of the outer solutions C, c from section 1 and the inner solutions $\widehat{C}, \widehat{c}$ from section 2. This can be done by adding the outer solutions and inner solutions for both the arterial and venous boundary layers and subtracting the common terms from the expansions:

$$C_{\text{uniform}} = C + \widetilde{C} - C_{\text{common}}, \qquad c_{\text{uniform}} = c + \widetilde{c} - c_{\text{common}}.$$

The common solutions are needed in order to find the uniform solutions for capillary and tissue oxygen concentration. Note the oxygen concentration in central regions of capillaries as approximated by (42) and that in small-z boundary-layer regions as given by (45). These give us

$$C_{\text{comm}} = 1 + \varepsilon\,\mu_1 Z + \varepsilon^2\big(\mu_2 Z^2 + C_1(0)\big). \tag{101}$$

Note the oxygen concentration in the central region of tissue as approximated by (43) and that in the arterial boundary-layer region as given by (46). These give us

$$\begin{aligned} c_{\text{comm}} = {} & N + r^2/4 - \kappa/4\cdot\sum_{j=1}^{N}\ln[r^2 + a_j^2 - 2ra_j\cos(\theta-\alpha_j)] + \kappa\sum_{n=0}^{\infty} r^n(A_n\cos n\theta + B_n\sin n\theta) + \varepsilon\sum_{j=1}^{N}\mu_{1,j}Z \\ & + \varepsilon^2\Bigg\{\mu_2 Z^2 + r^2/4 + \sum_{j=1}^{N}C_{1,j}(0) + \mu_2/2\cdot\sum_{j=1}^{N}\ln[r^2 + a_j^2 - 2ra_j\cos(\theta-\alpha_j)] \\ & \qquad - 2\mu_2\sum_{n=0}^{\infty} r^n(A_n\cos n\theta + B_n\sin n\theta)\Bigg\}. \end{aligned} \tag{102}$$

Therefore the uniform composite solution for the oxygen concentration in a capillary through its central region and the small-z boundary layer, derived from (7) and the above, is

$$C_{\text{ucs}} = C_0(z) + \varepsilon^2 C_1(z) + (\widetilde{C} - C_{\text{comm}}), \tag{103}$$

where

$$\widetilde{C} - C_{\text{comm}} = \varepsilon^2\cdot\left\{-\frac{\xi\cdot\gamma}{1 + VS'(1)}\int_0^\infty\left(\sum_{n=0}^{\infty}\sum_{i}\frac{A_{i,n}}{\lambda}\right)e^{-\lambda Z}\,d\lambda\right\}. \tag{104}$$

From Equations (103) and (104), we have

$$C_{\text{ucs}} = C_0(z) + \varepsilon^2 \left\{ C_1(z) - \frac{\xi \cdot \gamma}{1 + VS'(1)} \int_0^\infty \left(\sum_{n=0}^{\infty} \sum_i \frac{A_{i,n}}{\lambda} \right) e^{-\lambda Z} \, d\lambda \right\}. \tag{105}$$

This solution is valid throughout both the central region and the arterial boundary-layer region, for the last term of Equation (105) vanishes as Z becomes arbitrarily large, implying that the dominant effect is given by $C_0 + \varepsilon^2 C_1$, which gives exactly the solutions for oxygen in capillary through the central region.

Similarly, for the uniform composite solution that gives the oxygen concentration in the tissue through the central region and the arterial boundary layer, we have from (7) and (102)

$$c_{\text{ucs}}(r, \theta, z) = c_0(r, \theta, z) + \varepsilon^2 c_1 + (\widetilde{c} - c_{\text{comm}}). \tag{106}$$

The dominant effect is given by $c_0 + \varepsilon^2 c_1$, and solutions for oxygen concentration can be unified through the mixed layer near the end of the tissue cylinder.

In conclusion, Since capillary length is about 10^2 times its diameter, in most cases the longitudinal diffusion of solute may be negligible compared to radial diffusion and therefore can be treated as a small perturbation to the solution. Equations (17) and (27) are solved implicitly for substrate solution inside the capillaries. The order of small perturbation is determined by the longitudinal location. At both ends of the capillary cylinder, the axial diffusion constant and the radial diffusion constant are of the same order. Axial effect should to be treated differently, and a full three-dimensional analysis is required. Then the two sets of solutions, describing oxygen diffusion in the cylinder and near the two ends of the cylinder, need to be matched completely to obtain the effect of axial diffusion.

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