A compartmental model is developed for oxygen (O\textsubscript{2}) transport in brain microcirculation in the presence of blood substitutes (hemoglobin-based oxygen carriers). The cerebrovascular bed is represented as a series of vascular compartments, on the basis of diameters, surrounded by a tissue compartment. A mixture of red blood cells (RBC) and plasma/extracellular hemoglobin solution flows through the vascular bed from the arterioles through the capillaries to the venules. Oxygen is transported by convection in the vascular compartments and by diffusion in the surrounding tissue where it is utilized. Intravascular resistance and the diffusive loss of oxygen from the arterioles to the tissue are incorporated in the model.

The model predicts that most of the O\textsubscript{2} transport occurs at the level of capillaries. Results computed from the present model in the presence of hemoglobin-based oxygen carriers are consistent with those obtained from the earlier validated model (Sharan et al., 1989, 1998a) on oxygen transport in brain circulation in the absence of extracellular hemoglobin. We have found that: (a) precapillary PO\textsubscript{2} gradients increase as PO\textsubscript{2} in the arterial blood increases, P\textsubscript{50p} (oxygen tension at 50% saturation of hemoglobin with O\textsubscript{2} in plasma) decreases, i.e. O\textsubscript{2} affinity of the extracellular hemoglobin is increased, the flow rate of the mixture decreases, hematocrit decreases at constant flow, metabolic rate increases, and intravascular transport resistance in the arterioles is neglected; (b) precapillary PO\textsubscript{2} gradients are not sensitive to (i) intracapillary transport resistance, (ii) cooperativity (n\textsubscript{p}) of hemoglobin with oxygen in plasma, (iii) hemoglobin concentration in the plasma and (iv) hematocrit when accounting for viscosity variation in the flow; (c) tissue PO\textsubscript{2} is not sensitive to the variation of intravascular transport resistance in the arterioles. We also found that tissue PO\textsubscript{2} is a non-monotonic function of the Hill coefficient n\textsubscript{p} for the extracellular hemoglobin with a maximum occurring when n\textsubscript{p} equals the blood Hill coefficient. The results of the computations give estimates of the magnitudes of the increases in tissue PO\textsubscript{2} as arterial PO\textsubscript{2} increases, P\textsubscript{50p} increases, flow rate increases, hematocrit increases, hemoglobin concentration in the plasma increases, metabolic rate decreases, the capillary mass transfer coefficient increases or the intracapillary transport resistance decreases.

Introduction

The primary function of the hemoglobin inside the red blood cells (RBC) present in the blood is...
to transport oxygen to the tissue. An extensive research is being carried out to develop blood substitutes for clinical applications (Winslow, 2000). The advantages associated with the use of blood substitutes include easing shortages of blood for transfusions, avoiding viral disease transmission and mismatching the blood types of donors and patients receiving transfusions, and saving the patient’s own blood during the surgical operation. In view of these, the majority of blood substitute products are being developed based on the hemoglobin (Hb) Fa natural oxygen carrier of red cells. Recent advances in biotechnology such as cross-linking, recombinant modification and encapsulation have resulted in the development of hemoglobin-based oxygen carriers (HBOC) that can temporarily replace RBCs. Hemoglobin-based oxygen carriers can be prepared using human and non-human hemoglobins, e.g. human or bovine polymerized and recombinant Hb.

Experimental studies have been carried out with the modified hemoglobin products in different animal species and tissues to measure arterial blood pressure and cardiac output (Sehgal et al., 1984; Rosen et al., 1990; Biro et al., 1991; Palaparthy et al., 2001), regional blood flow (Ulatowski et al., 1996a), pial arteriolar diameters (Asano et al., 1998) cerebral blood flow and oxygen transport (Ulatowski et al., 1996b, 1998), and the effect of O2 affinity on microvascular flow and oxygen tension (Sakai et al., 1999). Experiments with hemoglobin-based oxygen carriers in the plasma have demonstrated an improvement in the delivery of oxygen to the tissues, especially in the cases where the blood hematocrit is small (Habler & Messmer, 2000). Experimental (Duling & Berne, 1970; Pittman & Duling, 1977; Duling et al., 1979; Ivanov et al., 1982; Swain & Pittman, 1989; Kuo & Pittman, 1990) and theoretical studies suggest that significant longitudinal gradients in blood oxygen tension and Hb saturation exist in precapillary vessels. A model for oxygen transport in the microcirculatory network by red blood cells and hemoglobin solutions has not been developed.

Sharan et al. (1989) have developed a compartmental model for oxygen transport in the brain microcirculation. This model has been applied (Sharan et al., 1998a) to analyse the experimental data on cerebral flow and oxygen content collected in sheep in hypoxic (Koehler et al., 1983, 1984), anemic (Jones et al., 1981) and carbon monoxide hypoxia (Koehler et al., 1984). Prediction from the model (Sharan et al., 1998a) supported the proposition that the differences in the cerebral blood flow responses among various types of hypoxia are wholly or in large part correlated with differences in tissue $P_{O_2}$. Ye et al. (1992) have described an averaging procedure to derive equations from the spatially distributed to a compartmental model. Using this procedure, Ye and his co-workers have also proposed a compartmental...
model in the microcirculation, similar to ours, for oxygen transport (Ye et al., 1993) and combined oxygen and carbon dioxide transport (Ye et al., 1994, 1998).

In the present study, we develop a compartmental model for oxygen transport in the presence of blood substitutes, which considers the arterioles, capillaries and venules, and apply it to the brain microcirculation. The intravascular transport resistance and the exchange between the arterioles and capillaries are incorporated.

**Mathematical Description**

A mixture of red blood cells and plasma/extracellular hemoglobin solution flows through the vascular bed from the arterioles through the capillaries to the venules. The vascular bed is represented as a series of vascular compartments surrounded by a tissue compartment (Fig. 1), which is similar to that of Sharan et al. (1998a) and Ye et al. (1994). The vascular bed consists of $m$ arteriolar and $m$ venular compartments, and a capillary compartment. Each vascular compartment contains vessel segments, arranged in parallel, with similar diameter and length. Each compartment exchanges oxygen with the tissue compartment.

The oxygen in the blood/mixture is present in the form: (i) the dissolved component in the plasma/extracellular fluid, (ii) in combination with hemoglobin inside the RBC and (iii) in combination with hemoglobin in the extracellular fluid. As the solution flows through the vascular bed, oxygen is transported by convection in the vascular compartments and by diffusion in the surrounding tissue where it is utilized. In steady state, the transport of oxygen in the vascular compartments is governed by the equations (Appendix A):

$$g(C_{fi,i} - Cat) - E_{ai} \Delta P_{ai} - P_i \phi = 0;$$
$$i = 1, 2, ..., m;$$

$$Q \delta C_{am} - C_{vm} - E_c \delta P_c - P_t \phi = 0;$$

where $C_{fi,i}$ is the total oxygen concentration at the outlet of $i$-th arteriolar compartment, $P_{ai}$ is the oxygen partial pressure in the $i$-th arteriolar compartment, $Q$ is the blood flow rate, $E_{ai}$ is the diffusion conductance across the $i$-th arteriolar compartment, $P_t$ is the oxygen partial pressure in the tissue, and $C_{ao} = C_a$ is the total oxygen concentration in the mixture entering the vascular network with the partial pressure $P_a$. The corresponding quantities in the venular and capillary compartments are referred to by the subscripts 'V' and "c", respectively. $C_{vi}$ represents the total oxygen concentration at the inlet of $i$-th venular compartment and $C_{vo} = C_v$ is the total oxygen concentration in the mixture.

FIG. 1. Schematic diagram of the model.
leaving the vascular network with the partial pressure $P_v$.

The total concentration of oxygen in the blood/mixture can be expressed as

$$C = a_m p + \beta_r S_r(p) + \beta_p S_p(p), \quad (2)$$

where $a_m$ is the solubility of O2 in the mixture, $p$ is the PO2, $S_r$ and $S_p$ are, respectively, the fractional saturation of hemoglobin with O2 inside RBC and in extracellular fluid. Coefficients $b_r$ and $b_p$ represent the oxygen carrying capacity of RBC and extracellular fluid.

Solubility of free O2 in the mixture is given by

$$\alpha_m = Hoc + (1 - H)oc', \quad (3)$$

where $H$ is the blood hematocrit representing volume fraction of RBC, $a$ and $a^0$ are solubilities of O2 in the RBC and extracellular fluid.

The coefficients $b_r$ and $b_p$ in eqn (2) are defined as

$$\beta_r = 1.34[Hb]_r H$$

$$\beta_p = \sqrt{34[Hb]_p}(-H)$$

where $[Hb]_r$ is the total hemoglobin in the RBC in gmP$^{-1}$ and $[Hb]_p$ is the total hemoglobin content in the extracellular fluid in gmP$^{-1}$.

In the non-capillary vascular compartments, oxygen partial pressure is taken as the arithmetic mean of inlet and outlet PO2 (Ye et al., 1994):

$$P_i = (pi-i \cdot p_i \cdot b)^{0.2}, \quad i = 1, 2, ..., m. \quad \square$$

whereas the average PO2 in the capillary compartment is obtained as described in Appendix B. In steady state, net transport of O2 from the vascular compartments is balanced by the utilization of O2 in the metabolic processes in the tissue and accordingly, we have

$$\sum_{i=1}^{m} E_{ai}(P_{ai} - P_{ai}) + E_{ei}(P_{ei} - P_{ei}) + \sum_{i=1}^{m} E_{ri}(P_{ri} - P_{t}) - MV_t = 0, \quad \square$$

where $M$ is the metabolic rate and $V_t$ is the volume of the tissue compartment.

BLOOD FLOW

Let $q_a$ and $q_v$ be the arterial and venous hydraulic pressures. Since the vascular compartments are arranged in series, the total blood flow, $Q$, is expressed as

$$Q = (q_a - q_v)R^{-1} \quad (7)$$

where the total vascular hydraulic resistance is

$$R = \sum_{i=1}^{m} R_{ai} + R_c + \sum_{i=1}^{m} R_{ei}, \quad (8)$$

in which $R_i$ is the resistance of i-th compartment. Assuming the vessels are arranged parallel to each other in each of the vascular compartments, the total resistance in i-th compartment is given by

$$R_i = \frac{\sqrt{2SLi}}{\pi NiLi^4}[Hb]_p(D_i, H_D) \quad (9)$$

where $N_i$ is the number of vessels in the i-th compartment, $L_i$ is a characteristic length of each of the vessels, $D_i$ is the vessel diameter, $m$ is the viscosity of the suspending medium or plasma in presence of hemoglobin solution, $\eta_{app}$ is the apparent viscosity, and $m_{rel} = m_{app}/m_s$ is the relative viscosity that depends on the vessel diameter and hematocrit.

In the model, we would like to include the dependence of apparent viscosity of blood on tube diameter and hematocrit (Fahraeus-Lindqvist effect). We use an empirical equation developed by Pries et al. (1992) for the variation of relative apparent blood viscosity with $H_D$ and $D$: $m_{rel} = m_{app}/m_s = f(H_D, D)$. This equation was developed on the basis of comprehensive analysis of data based on measurements at high shear rates in tubes with diameters ranging from 3.3 to 1978 mm at hematocrits up to 90%. The data were corrected for differences in suspending medium viscosity and temperature.

We assume that viscosity $m_s$ in eqn (9) varies with extracellular hemoglobin concentration and can be determined using the fit of Mooney's relationship to experimental data (Monkos, 1994):

$$\mu_s = mpl \exp \left(\frac{A[Hb]_p}{1 - B[Hb]_p}\right) \quad \square$$

where $mpl$ is the maximum viscosity of the plasma and $A$ and $B$ are constants determined by the fit.
where \( n_{pl} \) is the viscosity of the plasma without hemoglobin and \([\text{Hb}]_p\) is the concentration of hemoglobin in g ml\(^{-1}\) in the plasma. Constants \( A \) and \( B \) are adjustable parameters of the equation determined from an experimental fit of data, having values of 2.77 and 12 ml g\(^{-1}\), respectively, for human tetrameric hemoglobin solution (Monkos, 1994).

**HEMOGLOBIN SATURATION**

The relationship between the fractional saturation of hemoglobin with oxygen, \( S_{O_2} \), and oxygen tension, \( P_{O_2} \), is known as the oxygen dissociation curve (ODC). A number of formulations (Sharan & Popel, 1989) are available to represent the ODC in the modeling of oxygen transport. However, for hemoglobin-based oxygen carriers, two-parameter Hill's is commonly used:

\[
S(p) = \frac{(p/P_{50}T)}{1 + (p/P_{50}f)}
\]

where \( P_{50} \) is the oxygen tension at 50% saturation and \( n \) is the dimensionless exponent. The saturation in RBC and extracellular hemoglobin can be computed using the corresponding values of \( P_{50} \) and \( n \). The advantage of using Hill's equation is that the values of \( P_{50} \) and \( n \) are available for hemoglobin-based oxygen carriers (Ulatowski et al., 1996a, 1998). Kinetic properties of \( O_2 \) binding to either RBC or extracellular hemoglobin are not taken into account here.

**DIFFUSION CONDUCTANCE FOR THE CAPILLARY COMPARTMENT**

The diffusion conductance for the capillary compartment is computed from the Krogh-like tissue cylinder model by considering the intracapillary resistance (Sharan et al., 1998b) and a diffusive influx term at the wall of the tissue cylinder (Appendix C):

\[
E_c = \frac{2\pi N_c L_c (1 - w^2)(\lambda - y)}{\left[1 - w^2\right] - \rho = r_c k_c - \left(1/2D_{r_c}\right) \left(\left[2(1 - w^2)\right] \ln(w) + (3 - w^2)/2 + (y/D_{r_c})(\ln(w) + (1 - w^2)/2)\right]}
\]

where \( w = r_c/r_t \), the ratio of radius of the capillary, \( r_c \), to radius of tissue cylinder, \( r_t \); \( N_c \) is the number of capillaries in the compartment and \( L_c \) is the characteristic length of the capillaries. \( D_t \) and \( a_t \) are the diffusion and solubility coefficients of \( O_2 \) inside the tissue and \( k_c \) is the mass transfer coefficient in the capillary. The diffusive influx \( g \) in eqn (12) is calculated as the diffusive loss from the arterioles/venules per unit volume occupied by the tissue surrounding the capillaries:

\[
\gamma = \frac{ZtL_e (P_{ai} - P_i) + ZtL_e (P_{vi} - P_i)}{pMN_r r_c^2 \partial l - w^2} \cdot \frac{1}{D_t a_t (\ln(w) + (1 - w^2)/2)}
\]

**DIFFUSION CONDUCTANCES FOR THE ARTERIOULAR/VENULAR COMPARTMENTS**

Transport of oxygen from the arteriolar vessel to the surrounding tissue depends on: (i) transport inside the vessel, (ii) transport through the vessel wall, and (iii) transport in the surrounding tissue. A part of oxygen that diffuses from the arteriolar vessel may be convected away by the blood capillaries, located in close proximity of the arteriole in the surrounding tissue region (Weerapulli & Popel, 1989). In the earlier compartmental models (Sharan et al., 1989, 1998a; Ye et al., 1994), the diffusion conductance through the arteriole was computed by considering a capillary-perfused tissue region with a characteristic penetration depth \( l_i \). Ye et al. (1994) have used the Krogh tissue cylinder model applied to arterioles for computing the diffusion conductance. However, this approach is based on the assumption that arteriolar vessel is the only source of oxygen to the tissue in the vicinity of the arteriole. The intravascular transport resistance was taken into account by assuming parabolic radial profiles of \( P_{O_2} \) in the vessel.

Diffusion resistance to \( O_2 \) transport is the sum of the intravascular and extravascular
resistances:

\[
\frac{1}{F} = \frac{1}{F} + \frac{1}{F}, \quad \text{(14)}
\]

where \(E_{inv}\) and \(E_{exv}\) are the intravascular and extravascular conductances.

To overcome the limitations associated with the Krogh tissue cylinder model for arterioles and venules and the estimation of penetration depth, Weerapulli & Pope (1989) formulated a model to analyse the effect of capillary convection on oxygen transport around arterioles and venules. The model predicts the Sherwood number \((Sh)\) representing the dimensionless flux of oxygen from the vessel. The results were corroborated by a more detailed model of Hsu & Secomb (1992) where discrete capillaries were considered. Here, we adopt this model for computing the extravascular conductance in ith arteriolar compartment:

\[
E_{exv} = NiLiD_{pl}a_pl\pi Sh, \quad \text{(15)}
\]

Hellums et al. (1996) have expressed the mass transfer Nusselt number \((Nu)\), which is equivalent to Sherwood number, as a function of hemoglobin saturation with oxygen, vessel diameter and hematocrit on the basis of a two-phase model (Nair et al., 1989) for the blood flowing in the arteriolar-size vessels. The intravascular conductance is expressed in terms of \(Sh\) as

\[
E_{inv} = NiLiD_{pl}a_pl\pi Sh, \quad \text{(16)}
\]

where \(D_{pl}\) and \(a_{pl}\) are the diffusion and solubility coefficients in the plasma.

In the present study, we use diffusion conductances corresponding to the blood according to eqns (15) and (16). Notice that the diffusive influx \(g\) in eqn (13) dependent on partial pressures in the vascular and tissue compartments which are, in turn, depended on \(g\) through \(E_c\) [eqn (12)]. Further, eqns (1) and (6) with the relations (2), (5), (7) and (11) form a nonlinear system of algebraic equations. The system is solved numerically using the Newton-Raphson method (Press et al., 1986).

**Parameters of the Model**

To compute the distribution of \(PO_2\) in the vascular and tissue compartments in any particular tissue, the values of the parameters such as geometrical parameters pertaining to the vascular bed, blood flow, metabolic rate, arterial \(PO_2\), the solubility and diffusion coefficients, Hill’s parameters \(P_{50}\) and \(n\) for hemoglobin in RBC and extracellular fluid, hematocrit, hemoglobin concentrations in the blood and extracellular fluid, blood viscosity, intracapillary resistance, etc. have to be specified. Here we have taken values of most of the parameters from our earlier study (Sharan et al., 1998a) on the analysis of hypoxia in sheep brain; in that study the model was validated against experimental data.

A set of morphological parameters (Sharan et al., 1998a) for the cerebral vascular bed of the lamb are given in Table 1.

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<th>Capillaries</th>
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**Note:** Weight = 75g, \(Q = 70ml(100g^{-1})mkT^{-1}\).
sheep is given in Table 1. The total number of vascular compartments is 11 with \( m = 5 \) in eqns (1) and (6). For computing the flow, we have used the relations proposed by Pries et al. (1992) in vitro for relative apparent blood viscosity depending on discharge hematocrit and diameter of the tube. We have also chosen: arterial pressure (at the inlet of the arterioles with diameter 120 mm) \( q_a = 60\text{mmHg} \), venous pressure \( q_v = 10\text{mmHg} \) and plasma viscosity, in the absence of free hemoglobin, \( m_{p,f} = 1.28 \text{CP} \).

The solubility coefficient for \( \text{O}_2 \) in the blood is assumed to be the same as in the tissue \( a = a_t = 3 \times 10^{-9} \text{cm}^2 \text{s}^{-1} \text{atm}^{-1} \). The value of \( a_t^0 \) in the hemoglobin solution is taken as \( 2.8 \times 10^{-9} \text{cm}^2 \text{s}^{-1} \text{atm}^{-1} \) (Roy & Popel, 1996). The value of tissue diffusion coefficient is \( D_t = 1.5 \times 10^{-5} \text{cm}^2 \text{s}^{-1} \). For the sheep: hemoglobin in the blood \( [\text{Hb}] = 11 \text{gm}^{-1} \) at normal blood hematocrit of \( 30\% \), metabolic rate \( \dot{M} = 4.8 \text{ml} \text{(100g}^{-1})\text{min}^{-1} \) (Koehler et al., 1984), arterial blood oxygen tension \( P_a = 95 \text{mmHg} \) and Hill's parameters for whole blood \( P_50 = 40 \text{mmHg} \) and \( n = 3.23 \) (Maginniss et al., 1986) are taken under normal conditions.

The experiments with hemoglobin-based-oxygen carriers have not been carried out in sheep brain. However, experiments have been carried out with plasma-based hemoglobin in cat (Ulatowski et al., 1996b, 1998). With the hemoglobin solution exchange transfusion, the hematocrit is reduced from 0.3 to 0.2. The transfusion is carried out with the hemoglobin solution with a concentration \( 7 \text{gdl}^{-1} \), which under the experimental conditions leads to the same total hemoglobin available for transport of \( \text{O}_2 \) before and after the transfusion. To simulate these experimental conditions, we take \( [\text{Hb}] = 4.58 \text{gdl}^{-1} \) so that total hemoglobin concentration remains \( 11 \text{gdl}^{-1} \). For the hemoglobin solution, we take \( P50 = 40 \text{mmHg} \) and \( n_p = 3.23 \) in control case, matching the whole blood characteristics, and then change these parameters within a wide range to simulate hemoglobin-based oxygen carriers with different properties.

The values of diffusion conductances for non-capillary vascular compartments used in the computations are given in Table 1 based on the values reported by Hellums et al. (1996).

Recently, Vadapalli et al. (2002) have analysed the oxygen transport by red blood cells and hemoglobin solution in capillaries and computed the intracapillary mass transfer coefficients for a number of conditions; we take a typical value \( k_s = 2 \times 10^{-6} \text{ml} \text{O}_2 \text{cm}^{-2} \text{s}^{-1} \). We will show that these parameters do not play very important role under the present set of conditions.

### Results and Discussion

Results obtained from the model on oxygen transport in the brain circulation with the whole blood have been discussed in our earlier paper (Sharan et al., 1989) and this model has been used to analyse the experimental data (Jones et al., 1981; Koehler et al., 1984, 1986) on hypoxia in sheep. We will now simulate the effect of extracellular hemoglobin on the \( \text{O}_2 \) transport to tissue.

The total blood flow computed from the model without extracellular hemoglobin is 0.924 \( \text{cm}^3 \text{s}^{-1} \), equivalent to 74ml(100g^{-1})\text{min}^{-1}, which is in good agreement (about 5%) with the measured flow of 70ml(100g^{-1})\text{min}^{-1} in the cerebral part of the brain weighing 75 g (Koehler et al., 1984). The relative viscosity of the blood depends on discharge hematocrit. By reducing the hematocrit from 30 to 20% with the hemoglobin solution, the model predicts rise in blood flow from 74 to 84.5ml(100g^{-1})\text{min}^{-1}. By considering the dependence of plasma viscosity on hemoglobin concentration [eqn (10)], the blood flow predicted from the model in the presence of hemoglobin solution is 74ml(100g^{-1})\text{min}^{-1}, which is the same as obtained with the blood at normal hematocrit of 30% without the hemoglobin solution. Thus, the model that uses the relative apparent blood viscosity depending on tube diameter and discharge hematocrit (Pries et al., 1992) and the plasma viscosity as a function of hemoglobin concentration (Monkos, 1994) predicts the blood flow in the presence of hemoglobin solution, the same as blood flow under the control conditions. Note that this model does not consider changes in vascular tone as a result of hemoglobin solution transfusion.

In the figures, "In" corresponds to the network inlet, "a1" to "a5" correspond to the
arteriolar compartments, "c" denotes the capillary compartment, "v5" to "v1" the venular compartments, and "t" designates the tissue compartment.

The $PO_2$ distribution in the vascular and the tissue compartments is found to be the same without/with hemoglobin solution if the total amount of hemoglobin remains constant and the characteristics of the hemoglobin in the plasma are the same as those in RBC. We refer to this case as the control case. The distribution of $PO_2$ and the total oxygen content ($CaO_2$) in the vascular compartments and the $PO_2$ in the tissue compartment are shown in Fig. 2. The $PO_2$ gradient increases in the successive arteriolar branch levels of the network. Total oxygen content falls marginally from 14.2 to 13.5% in the arterioles, it is constant (7.7%) in the venules and a significant fall occurs in the capillaries. The corresponding $PO_2$ decreases from 95 to 78.5 mmHg in the arterioles and it is almost constant in the venules. About 30% of the total drop of $PO_2$ between the inlet and outlet of the vascular network occurs in the precapillary vessels and the remaining 70% in the capillaries. The venous $PO_2$ is found to be 40.6 mmHg, close to the value 39 mmHg reported in the whole blood experiment in sheep (Koehler et al., 1983). Ulatowski et al. (1998) have also reported a value about 39 mmHg in their control and hemoglobin-transfusion experiments in cat. The calculated value of the tissue $PO_2$ is 38.8 mmHg.

In the earlier models (Sharan et al., 1989, 1998a; Ye et al., 1994), the exchange of oxygen from the arterioles was considered, but it was not accounted for in the total $O_2$ mass balance for the organ in the sense that in the calculations of the capillary transport conductance the contribution of the arterioles was not taken into account. This feature is now incorporated into the model through a diffusive influx term in the capillary model, see Appendix C for detail. We found that out of the total oxygen exchange in the tissue, 18% occurs through the arterioles/venules. However, the effect of taking into account the diffusive influx term in the capillary model on the $PO_2$ in the vascular network is small; without the diffusive influx term, tissue $PO_2$ decreases from 38.8 to 38.5 mmHg.

Recently, Vadapalli et al. (2002) have shown that the intracapillary resistance to oxygen transport is reduced by as much as 60% in the presence of hemoglobin solution with a concentration of 7 g dP$^{-1}$ at 20% hematocrit. They have found that the intracapillary mass transfer coefficient $k_c$ varies approximately in the range $1 \times 10^{-5}$ to $4 \times 10^{-5}$ ml O$_2$ cm$^{-2}$ Torr$^{-1}$ s$^{-1}$. For the sensitivity analysis in the present model, we
have taken \( k_c = 1 \times 10^6 \), \( 2 \times 10^6 \), \( 4 \times 10^6 \) and \( 2 \times 10^6 \). The last value corresponds to the case when there is no intracapillary resistance to oxygen transport. Our calculations show that the effect of intracapillary resistance on vascular \( PO_2 \) in the network is negligibly small under the current conditions. However, the tissue \( PO_2 \) increases from 35.8 to 40.4 mmHg as \( k_c \) increases from \( 1 \times 10^6 \) to \( 4 \times 1 \text{Torr}^{-1} \text{s}^{-1} \). Without intracapillary resistance, tissue \( PO_2 \) is found to be 42.1 mmHg. The model predicts an additional precapillary loss of about 6.5 mmHg when the intravascular resistance in the arterioles is neglected. The change in venous and tissue \( PO_2 \) is small.

During hypoxic hypoxia, arterial \( PO_2 \) is reduced. Figure 3 presents the distribution of \( PO_2 \) in the network with the variation of \( PO_2 \) in the arterial blood entering the network. Loss of oxygen from the precapillary vessels decreases as the \( PO_2 \) in the arterial blood is reduced. The venous and tissue \( PO_2 \) decrease as the arterial \( PO_2 \) decreases. The tissue \( PO_2 \) falls by 2 mmHg when arterial \( PO_2 \) is reduced from 110 to 95 mmHg whereas it drops by 15 mmHg with the reduction in arterial \( PO_2 \) from 60 to 40 mmHg. Hence, for lower \( PO_2 \) a small change in arterial \( PO_2 \) causes a significant variation in the tissue \( PO_2 \). The results found here are similar to those reported in our earlier study (Sharan et al., 1989). The sensitivity analysis with respect to the parameters such as \( Q, M, P50 \) and hemoglobin concentration in the blood is carried out in the same way as was done in Sharan et al. (1989) and similar conclusions are drawn.

The oxygen-binding properties of plasma-based hemoglobin depend on the affinity to \( O_2 \) and cooperativity. Hence, the parametric study involved changing the values of \( P50_p, n_p \), concentration of hemoglobin in the plasma and hematocrit that are likely to influence the \( PO_2 \) distribution in the network. The \( PO_2 \) losses through the precapillary vessels and \( PO_2 \) in the arteriolar and capillary compartments are not affected with the variation of cooperativity \( n_p \) [Fig. 4(a)]. However, the \( PO_2 \) in the venules rises from 35.9 to 40.6 mmHg when \( n_p \) is increased from 1 to 3.23. The changes in venular \( PO_2 \) could be attributed to the high degree of nonlinearity in the oxygen dissociation curve caused by the high value of \( P50_p \). The value \( n_p = 1 \) corresponds to non-cooperative binding that is encountered in some polymerized hemoglobins. The rate of increase of tissue \( PO_2 \) decreases with increase in \( n_p \) [Fig. 4(b)]. Tissue \( PO_2 \) increases rapidly with \( n_p \) initially and then levels off for \( n_p > 2.5 \). The tissue \( PO_2 \) reaches maximum at \( n_p = 3.2 \) and it decreases with a further increase in \( n_p \). The difference between the venous and tissue \( PO_2 \) is increased from 0.5 to 2.4 mmHg as \( n_p \) changes from 1 to 4.

\( P50_p \) describes the position of oxygen dissociation curve in the plasma. In the absence of 2,3-diphosphoglycerate (2,3-DPG) that cross-links the two b-chains of the hemoglobin molecule in the RBC, the value of \( P50_p \) is known to be around 8 mmHg, an unfavorably high oxygen affinity that leads to an insufficient release of oxygen in the body (Alayash, 1999). In modified hemoglobin-based oxygen radicals scavengers and hemoglobin-based oxygen carriers, the value of \( P50_p \) can be as low as 4 mmHg (Doherty et al., 1998). Hence, to improve the oxygen releasing capacity of extracellular hemoglobin it is desirable to modify it (Alayash, 1999). In the modified hemoglobin, the value of \( P50_p \) varies in a wide range (Bucci et al., 1996; Ulatowski et al., 1998; Sakai et al., 1999). Here, we study the \( PO_2 \) distribution in the network by varying \( P50_p \) in the range 4-50 mmHg while \( P50 \) in the red blood cells is held constant.
The distribution of $PO_2$ in the network for various values of $P50_p$ is presented in Fig. 5(a). It shows that precapillary $PO_2$ gradients increase as $P50_p$ is reduced. The total $PO_2$ drop in the arteriolar compartments rises from 14 to 22.3 mmHg when $P50_p$ is reduced from 50 to 10 mmHg. The precapillary $PO_2$ gradients remain almost constant when $P50_p$ is reduced lower than 10 mmHg. A similar trend is observed for capillary and venular $PO_2$. The reason for the increase in precapillary losses with decrease in $P50_p$ is that the oxygen dissociation curve in the plasma becomes steeper with reduced $P50_p$ and the reduction in fractional saturation of hemoglobin with $O_2$ in plasma causes smaller change in plasma $PO_2$ with reduced $P50_p$. As a result the gradient between the intravascular $PO_2$ and the tissue $PO_2$ increases with decrease in $P50_p$. The precapillary $PO_2$ gradients increase further with the decrease in blood flow [Fig. 5(b)]. For $P50_p=10$ mmHg, the drop in $PO_2$ in the precapillary vessels rises from 22.3 to 32.4 mmHg.
When the blood flow is reduced by 40%. However, the drop reduces to 17 mmHg when the blood flow is increased by 40% from the control level.

Figure 5(c) represents the distribution of fractional saturation of hemoglobin with O2 in RBC (Sr) and plasma (Sp) for two values of P50p (50 and 10 mmHg). For P50p = 10 mmHg, the hemoglobin in plasma is almost fully saturated with O2 in the network and a little amount of oxygen is released due to high affinity. On the other hand with P50p = 50 mmHg, Sr falls from 89 to 38% along the network and a significant drop in Sr occurs at the level of capillaries. The drop in Sr in the network increases from 39 to 63% when the P50p is reduced from 50 to 10 mmHg. The saturation Sr in arterioles is practically the same with the change in P50p from 50 to 10 mmHg. The fully saturated hemoglobin in the plasma at low P50p helps in release of oxygen first from red blood cells [Fig. 5(c)].

The venous and tissue PO2 increase as P50p increases [Fig. 5(d)]. The increase in venous PO2 with increased P50p in the cerebral blood has been observed experimentally (Koehler et al., 1983, 1986). However, such measurements are not available with the hemoglobin-based oxygen...
carriers. For the control flow, the difference between the tissue and venous $PO_2$ decreases as $P50_p$ is reduced and the tissue $PO_2$ is lower than the venous $PO_2$. When the blood flow is reduced by 40%, the tissue $PO_2$ becomes higher than the venous $PO_2$ [Fig. 5(d)]. The difference between the tissue and venous $PO_2$ decreases as $P50_p$ is increased from 2 to 30mmHg and it increases when $P50_p$ rises from 30 to 50mmHg. The relationship between the tissue $PO_2$ and the venous $PO_2$ is consistent with our earlier study (Sharan et al., 1998b) on the relationship between end-capillary and mean tissue $PO_2$.

The amount of oxygen being carried by the plasma will depend on the amount of hemoglobin concentration $[Hb]_p$ present in it and the capillary hematocrit. An increase in hemoglobin concentration in the plasma at a constant hematocrit causes an increase in the total hemoglobin concentration in the mixture. Figure 6 shows the $PO_2$ distribution in the vascular and tissue compartments for $[Hb]_p = 0, 2.29, 4.58, 6.87, 9.16 \text{gdP}^1$ by keeping the hematocrit constant at 20%. Figure 6 shows that the precapillary $PO_2$ gradients remain nearly the same when $[Hb]_p$ is decreased by 50% or increased by 50 and 100%. The change in precapillary $PO_2$ gradients is small even in the absence of hemoglobin in the plasma. Thus, the effect of hemoglobin concentration in the plasma on the transport of $O_2$ from the precapillary vessels is marginal under the present conditions. However, the $PO_2$ in the venules and tissue change significantly. The venous $PO_2$ is decreased/increased by 2.4/1.67 from 38.2mmHg when the $[Hb]_p$ is decreased/increased by 50%. The corresponding tissue $PO_2$ is decreased/increased by 2.1/1.5 from 38.8 mmHg. In the absence of hemoglobin in the plasma, the calculated values of venous and tissue $PO_2$ are 34.5 and 33.6mmHg, respectively.

Figure 7(a) and (b) represent the distribution of $PO_2$ in the network by decreasing/increasing the blood hematocrit by 10% from the control value of 20% for a constant and variable flow; the concentration of extracellular hemoglobin remains constant. The hematocrit can change significantly in anemia and polycythemia (Jones...
et al., 1981; Massik et al., 1987) and also as a result of hemodilution. The change in hematocrit is associated with a proportional change of hemoglobin concentration in the RBC. The change in hematocrit modifies the total oxygen content and the blood flow. For a constant flow, the precapillary $PO_2$ gradients increase as the hematocrit is reduced. The tissue $PO_2$ is decreased by 7mmHg as the hematocrit falls from 20 to 10%. The corresponding increase is 4.7mmHg with the rise in hematocrit from 20 to 30%.

Decrease in the blood hematocrit causes the viscosity of mixture to decrease and the flow rate
of the mixture to increase. When the flow rate is allowed to change with the hematocrit [eqn (10)], the difference between $PO_2$ at constant flow for increased or decreased hematocrit and control level at 20% hematocrit in a given compartment is decreased [Fig. 7(b)]. The tissue $PO_2$ is dropped by 4.3 mmHg when the hematocrit falls from 20 to 10%. When the hematocrit rises from 20 to 30%, tissue $PO_2$ increases by 2.2 mmHg.

For a constant flow, the increase in hematocrit increases the $O_2$ content in the mixture and causes an increase of tissue $PO_2$. On the other hand, for constant $O_2$ content, the increase in hematocrit leads to a decrease of blood flow rate resulting in a decrease of tissue $PO_2$ [Fig. 5(b)]. In spite of these opposing tendencies, the model predicts that the tissue $PO_2$ increases as the hematocrit increases [Fig. 7(b)].

Figure 8 presents the distribution of $PO_2$ in the network with 50% elevation and 50% reduction of $O_2$ consumption rate from control level for two values of $P50_p$, as 50 and 10 mmHg. The results show that the precapillary $PO_2$ losses increase as the consumption rate is increased for a given $P50_p$. Additional longitudinal $PO_2$ gradients occur as $P50_p$ is reduced. The venous and tissue $PO_2$ are reduced with an increase in consumption rate. The tissue $PO_2$ is lower than the venous $PO_2$ when the consumption rate is elevated by 50% from the control whereas it becomes higher than the venous $PO_2$ when the metabolic rate is reduced by 50% for both values of $P50_p$. The prediction of tissue $PO_2$ lower/higher than the venous $PO_2$ is consistent with the earlier studies (Ye et al., 1993, 1994; Sharan et al., 1998b).

In the discussion of the sensitivity of the results with respect to an individual parameter in Figs. 4-8, a fixed arterial $PO_2$ is assumed. However, an alteration in the individual parameter might also affect oxygen transport processes in the lungs causing changes in the arterial $PO_2$.

Results computed from the present model in the presence of hemoglobin-based oxygen carriers are consistent with those obtained from the earlier validated model (Sharan et al., 1989, 1998a) on oxygen transport in brain circulation in the absence of blood substitutes. The
variation of mean tissue $PO_2$ predicted from the model with various parameters pertaining to plasma hemoglobin is in qualitative agreement with the study on the transport of oxygen by RBC and hemoglobin solutions in the capillaries (Vadapalli et al., 2002). However, the experimental measurements with hemoglobin-based oxygen carriers have not been carried out in sheep brain and, therefore, quantitative comparisons with experiments are not possible. Some experiments (Ulatowski et al., 1996b, 1998) have been performed to analyse cerebral oxygen transport with plasma-based hemoglobin in cat during hypoxic hypoxia; the results of this study are in qualitative agreement with the experimental data. In the future, we will extend the model by constructing a suitable set of morphological parameters for the cerebral vascular bed of the cat and performing computer simulations for cat brain.

In the present model, the relationship between the relative viscosity of the blood and the tube diameter and hematocrit is used proposed by Pries et al. (1992) based on in vitro data. The flow computed from the model using in vivo viscosity relationship from Pries et al. (1994) is found to be $0.535 \text{cm}^3\text{s}^{-1}$ equivalent to $42.8\text{ml}(100\text{g}^{-1})\text{min}^{-1}$ and this is lower than the measured flow $70\text{ml}(100\text{g}^{-1})\text{min}^{-1}$. In order to predict the flow consistent with that measured, it is necessary to modify the length of the vessels at all the levels (Table 1). Further, relationship for relative viscosity in vivo has not been developed for sheep. Since the results computed using the set of morphological data constructed in our earlier study (Sharan et al., 1989) are close to the measurements (Sharan et al., 1998a) and the computed flow from the in vitro relationship is consistent with that measured, we have retained the same morphological data and accordingly we have used the in vitro relation for relative viscosity for comparing the results from the present model with those obtained for whole blood from the earlier model.

Conclusions

A compartmental model is formulated for oxygen transport in brain microcirculation in the presence of blood substitutes. The cerebrovascular bed is represented as a series of vascular compartments, on the basis of diameters, surrounded by a tissue compartment. A mixture of RBC and plasma/extracellular hemoglobin solution flows through the vascular bed from the arterioles through the capillaries to the venules. In the flow model, the relative viscosity of the blood dependency on the tube diameter and hematocrit proposed by Pries et al. (1992) in vitro is included. The dependence of the viscosity of the plasma on the hemoglobin concentration is also taken into account. The computed flow is found to be consistent with the measurements of whole blood. In the model, intravascular resistance and the diffusive loses of oxygen from the arterioles to the tissue are incorporated.

The model predicts that taking into account the amount of oxygen leaking from the arterioles in calculating the capillary transport conductance does not significantly affect the $PO_2$ in the vascular and tissue compartments. The significant diffusion takes place at the level of capillaries. The computed venous blood $PO_2$ is close to that measured in the experiments in the absence of extracellular hemoglobin. We have also found that:

(a) Precapillary $PO_2$ gradients increase as: $PO_2$ in the arterial blood increases; $P_{50}$ is reduced; the flow rate of the mixture decreases; hematocrit decreases at constant flow; metabolic rate increases; intravascular transport resistance in the arterioles is neglected;

(b) Precapillary $PO_2$ gradients are not sensitive to: (i) intracapillary transport resistance, (ii) cooperativity of oxygen with hemoglobin in plasma, (iii) hemoglobin concentration in the plasma and (iv) hematocrit when accounting for viscosity variation in the flow;

(c) For a given set of parameters, the $PO_2$ is almost the same in all the venular compartments;

(d) Tissue $PO_2$ increases as: arterial $PO_2$ increases; $P_{50}$ rises; flow rate increases; hematocrit increases; hemoglobin concentration in the plasma rises; metabolic rate decreases; the capillary mass transfer coefficient increases or the intracapillary transport resistance decreases;
(e) Tissue $PO_2$ can be higher/lower than venous $PO_2$, depending on the choice of the parameters in the model.

(f) Tissue $PO_2$ increases as $n_p$ increases from 1 to 3.23 and then it decreases with a further increase in $n_p$.

(g) Tissue $PO_2$ is not sensitive to the variation of intravascular transport resistance in the arterioles.

The predictions from the model are found to be consistent with those based on the whole blood. This model in brain will be validated either with the availability of experimental data with the hemoglobin-based oxygen carrier as blood substitute in sheep or in cat (Ulatowski et al., 1996b, 1998) after constructing a set of morphological data for its cerebrovascular bed and performing computer simulations similar to those presented here.

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REFERENCES


**Appendix A**

**Derivation of Equations for O2 Transport in a Mixture of RBC, Plasma and Hemoglobin Solution in a Compartment**

We consider a mixture of red blood cells, plasma and extracellular hemoglobin flowing through a tube of radius r, c and c0 are, respectively, the concentration of O2 dissolved in RBC and in the plasma/hemoglobin solution. y is the fractional saturation of hemoglobin with O2 inside RBC and / is the fractional saturation of extracellular hemoglobin with O2. The RBCs are moving with velocity \( v_r \) and the solution of extracellular hemoglobin is moving with a velocity \( v_p \). \( h(r) \) is the volume fraction of plasma/
extracellular hemoglobin. According to the model proposed by Page et al. (1998), we briefly describe below the partial differential equations governing the oxygen transport by erythrocyte/hemoglobin solution mixtures.

Equations

THE RED BLOOD CELLS

Nair et al. (1989) have modeled the RBC phase as hemoglobin layer with the ratio of surface \( S \) to volume \( V \) of a RBC for estimating the intracellular resistance to oxygen transport. The interior of RBC is considered as a compartment with all intracellular and extracellular resistances lumped into mass transfer coefficients. Inside an RBC, the species are the oxygen, oxyhemoglobin and free hemoglobin. Since the hemoglobin molecule cannot penetrate through the cell membrane, the total hemoglobin concentration remains constant. The concentration of free hemoglobin can be expressed as a function of oxyhemoglobin concentration. Concentrations of oxygen and oxyhemoglobin inside an RBC are given by

\[
V = -F \frac{\partial}{\partial z} + C_{hf}(c, y), \quad (A.1)
\]

where \( CH \) is the total hemoglobin concentration in RBC, \( F \) is the oxygen flux through the red cell membrane into the extracellular fluid and \( f \) represents the relationship between the fractional saturation of hemoglobin with oxygen and the concentration of oxygen. This relationship is described by the oxygen dissociation curve.

EXTRACELLULAR HEMOGLOBIN SOLUTION

In the extracellular fluid, oxygen is transported by molecular diffusion and convection in the free form and in combination with the hemoglobin. Also, an amount of oxygen is transported from the RBCs to the extracellular fluid. Concentrations of oxygen and oxyhemoglobin in the extracellular fluid are governed by

\[
\hat{\mathbf{v}}_x \cdot \nabla \left( c + C_{Hb} y \right) + \frac{\partial}{\partial z} \left( C_{Hb} y \right) = \frac{D_{O_2}}{r} \frac{\partial}{\partial r} \left( \frac{\partial}{\partial r} C_{Hb} y \right) + \frac{F(h(r))}{V_{RBC}} \left( \hat{\mathbf{r}} \cdot \nabla \right) C_{Hb} y. \quad (A.3)
\]

where \( D_{O_2} \) and \( D_{HbO_2} \) are diffusion coefficients for \( O_2 \) and \( HbO_2 \) and \( C_{Hb} \) is the total hemoglobin concentration in the extracellular fluid. In equations (A.3) and (A.4), the diffusion of \( O_2 \) and \( HbO_2 \) in the axial direction is ignored.

We assume chemical equilibrium of hemoglobin with oxygen inside the RBC as well as in extracellular fluid and neglect the transport resistance inside the RBC. From eqns (A.1-A.4), we have

\[
\hat{\mathbf{v}}_r \frac{\partial}{\partial r} \left( c + C_{Hb} y \right) = -F \left( \frac{\partial}{\partial r} \right) V_{RBC}, \quad (AS)
\]

\[
(h(r)) \frac{\partial}{\partial r} \left( c + C_{Hb} y \right) = \frac{D_{O_2}}{r} \frac{\partial}{\partial r} \left( \frac{\partial}{\partial r} C_{Hb} y \right) + \frac{F(h(r))}{V_{RBC}} \left( \hat{\mathbf{r}} \cdot \nabla \right) C_{Hb} y. \quad (A.6)
\]

Adding eqns (A.5) and (A.6):

\[
\hat{\mathbf{v}}_r \frac{\partial}{\partial r} \left( c + C_{Hb} y \right) = -F \left( \frac{\partial}{\partial r} \right) V_{RBC}. \quad (A.7)
\]

The resistance across the RBC membrane is small, implying the partial pressures of \( O_2 \) at the interface of RBC and extracellular fluid are continuous, i.e.

\[
p = \rho c = c/a = p', \quad (A.8)
\]

where \( a \) and \( a' \) are solubilities of \( O_2 \) in RBC and extracellular fluid.
Taking the cross-sectional average in eqn (A.7), we get
\[
2p \frac{d}{dz} \left[ \int_{r_{c}}^{r_{e}} (-h(r)) v_p(r) (c' + C_{bb} y') r dr \right]
+ \int_{0}^{r_{c}} h d r \delta c \frac{\partial \{ C_{bb} y \} r dr}{\partial r}
= D'_{O2} 2 \pi \left[ r \frac{\partial c'}{\partial r} \right]_{r_{c}}.
\] (A.9)

Now we introduce the flow averages:
\[
c_{pm} = \frac{2 n v_p(r) (-h(r)) c' r dr}{Q(1 - H_D)}, \quad \text{\( \delta A, 11\Phi \)}
\]
\[
s_{pm} = \frac{2 n v_p(r) (-h(r)) y' r dr}{Q(1 - H_D)}, \quad \text{\( \delta A, 11\Phi \)}
\]
\[
C_{rm} = \frac{2 \pi \int_{0}^{r_{c}} r v_p(r) h dr \delta r pr dr}{QH_D}, \quad \text{\( \delta A, 12\Phi \)}
\]
\[
s_{rm} = \frac{2 n v_p(r) h(r) y r dr}{QH_D}, \quad \text{\( \delta A, 13\Phi \)}
\]

where,
\[
Q = \int_{0}^{r_{c}} \int_{0}^{r_{c}} v_p(r) h dr \delta r pr dr, \quad \text{\( \delta A, 16\Phi \)}
\]

in which \( H_D \) is the discharge hematocrit and
\[
v_p \delta r = v_p(r) \mid _{- h d r} \delta \{ v_p \}, \quad \text{\( \delta A, 17\Phi \)}
\]

Using the definitions from eqns (A.10)-(A.16) in eqn (A.9), we get
\[
\frac{\partial}{\partial z} \left[ Q(1 - H_D) C_{pm} \right] \frac{1}{\partial H_D} C_{rm} \delta c
+ \frac{d}{dz} \left[ Q(1 - H_D) C_{pm} \right] \frac{1}{\partial H_D} C_{rm} = 2 p r_{w}.
\] where \( j_w \) is the flux at the wall per unit area from the vessel wall.

Equation (A.18) can be rewritten as
\[
\frac{d}{d\delta c} Q_{C_{pm}} \frac{1}{\partial S_{m}} = 2 p r_{w} j_{w}, \quad \text{\( \delta A, 19\Phi \)}
\]

where
\[
S_{m} = \delta 1 - H_D C_{pm} + H_D C_{rm} \quad \text{\( \delta A, 20\Phi \)}
\]
in which \( S_{m} \) is the amount of oxygen carried by the hemoglobin in the mixture.

Integrating eqn (A.19) with respect to \( z \) from 0 to \( z \),
\[
\int_{0}^{r} Q(1 - H_D) C_{pm} \frac{1}{\partial S_{m}} = 2 p r_{w} \int_{0}^{r} j_{w} dz \frac{1}{\partial \delta c} \quad \text{\( \delta A, 21\Phi \)}
\]

where the first term on the right-hand side represents the total flux \( J \) which can be expressed as
\[
J = E \delta P_{m} - P_{t} \quad \text{\( \delta A, 22\Phi \)}
\]

where \( E \) is the conductance, \( P_{m} \) is the mean partial pressure of \( O_2 \) in the vascular compartment and \( P_{t} \) is the corresponding partial pressure in the surrounding tissue compartment.

Equation for oxygen transport in a compartment becomes
\[
Q \left( \alpha_{m} - C_{m} \right) + Q \left( S_{m} - S_{m} \right) = - E \delta P_{m} - P_{t}, \quad \text{\( \delta A, 24\Phi \)}
\]

where the superscripts "\( e \)" and "\( o \)" denote the entry and outlet of the compartment. Notice that eqn (A.24) involves the unknowns \( C_{pm} \), \( C_{rm} \), \( S_{pm} \) and \( S_{rm} \). It is necessary to close eqn (A.24) by defining additional relationships. At the moment, it is not clear how to derive these in terms of flow-averaged variables. Ye et al. (1992, 1993) have derived the compartmental equation for the homogeneous blood by considering the cross-sectional averages which are in general valid for a uniform flow. Also, they have pointed out the discrepancy in evaluation of cross-sectional average of fractional saturation in terms of cross-sectional average of partial pressure.

In the present study, we assume that \( p_{pm} = pr_{w} = pm \) i.e., the averaged partial pressures in
the extracellular fluid, RBC and in the mixture are the same. This satisfies the relation (A.20) provided:

\[ a_m = \delta_1 - H_D p_d - H_D a \delta A \Phi \]

where \( a_m \) is the solubility of oxygen in the mixture.

Also, we assume that \( S \) can be expressed as a function of partial pressure of oxygen through oxygen dissociation curve in the RBC as well as extracellular fluid. Further, we take the flow average of \( S \) as the fractional saturation of hemoglobin with \( O_2 \) evaluated using averaged partial pressure \( p_m \). Accordingly, \( S_{pm} = S_p \delta p_m \Phi \) and \( S_{rm} = S_r \delta p_m \Phi \) where \( S_p \) and \( S_r \) will be described by a functional relationships for oxygen dissociation curves for extracellular fluid and RBC respectively. With these assumptions, eqn (A.24) will be well defined and involve only one unknown.

In terms of partial pressure, the transport of oxygen in a compartment is governed by

\[ S°J E(P_m - P_t) = 0 \]

\( \delta A \Phi \)

where \( p \) is the partial pressure at the inlet/outlet of the compartment, \( P \) is the partial pressure inside the compartment and \( S_m \) is defined in terms of \( S_{pm} \) and \( S_{rm} \) through eqn (A.21). As a particular case when \( a = a^0 \) (solubilities in RBC and extracellular fluid are same) in eqn (A.25), the averaged dissolved concentrations of \( O_2 \) in the extracellular fluid, RBC and mixture are the same.

**Appendix B**

**Average PO2 in the Capillary Compartment**

For computing the average \( PO_2 \) in the capillary compartment, we assume a linear drop of total concentration of \( O_2 \) along the capillary in the form

\[ C \delta z \Phi = C_{am} - (C_{am} - C_{im} \Phi) \delta L \]

\( \delta A \Phi \)

where \( C_{am} \) and \( C_{im} \) are the total oxygen concentrations corresponding to inlet and outlet capillary \( PO_2 \). \( L \) is the capillary length and \( z \) is the coordinate along the capillary.

Equation (B.1) is a nonlinear algebraic equation in \( p_c \) (i.e. capillary \( PO_2 \)), which is solved numerically using the method of bisection (Press et al., 1986).

Average partial pressure of \( O_2 \) in the capillary is defined by

\[ P_c = \frac{1}{L} \int_0^L p_c \delta z \Phi dz \]

The integral in eqn (B.2) is evaluated numerically using Simpon's's rule (Press et al., 1986).

**Appendix C**

**Diffusion Conductance in the Capillary Compartment**

The capillaries are modeled as a compartment with exchange properties equivalent to spatially averaged Krogh tissue cylinders with a modified boundary condition as described below. The steady-state transport of \( O_2 \) in a tissue cylinder of radius \( r_t \) surrounding a capillary of radius \( r_c \) is governed by

\[ \frac{1}{\delta t} \frac{1}{\delta r} \left( \frac{1}{\delta r} \frac{\partial p_i}{\partial r} \right) - M = 0 \]

\( \delta r \) or \( I \)

where \( p_i \) is the partial pressure of \( O_2 \) in the tissue, \( D_i \) is the diffusion coefficient of \( O_2 \), \( a_i \) is the solubility coefficient of \( O_2 \) and \( M \) is the metabolic rate assumed to be constant. It is assumed that the axial diffusion of \( O_2 \) in the tissue is negligible as compared with the radial diffusion.

Equation (C.1) is subject to the following boundary conditions:

\[ \frac{\partial p_c}{\partial r} \delta z \Phi = p_c \delta r_c \delta z \Phi \]

\( \delta A \Phi \)

\[ \frac{\partial p_i}{\partial r} \delta r_t \delta z \Phi \]

\( \delta A \Phi \)

where \( p_w \) is the \( PO_2 \) at the capillary-tissue interface, \( j_c \) is the diffusive influx of \( O_2 \) through the wall of the cylinder and \( z \) is the coordinate along the length of the capillary; \( j_c \) will be determined from the mass balance in the compartmental model. The existing models
based on Krogh tissue cylinder assume that capillaries are the only source of O\textsubscript{2} to the tissue. However, there are experimental (Duling & Berne, 1970; Pittman & Duling, 1977; Duling \textit{et al.}, 1979; Ivanov \textit{et al.}, 1982; Swain & Pittman, 1989) and theoretical (Popel & Gross, 1979; Sharan & Popel, 1988; Sharan \textit{et al.}, 1989, 1998a; Weerapulli & Popel, 1989) studies demonstrating the losses of oxygen from the pre-capillary vessels. Thus, a part of oxygen diffuses in the tissue from the pre-capillary vessels and is exchanged with capillaries; this is taken into account by the diffusive influx term at the wall of the Krogh tissue cylinder.

Integrating eqn (C.1) and using the boundary conditions (C.2) and (C.3) to obtain

\[ p_t(r, z) = p_w(r_c, z) + \frac{M}{2D_t} \left( \frac{r^2 - r_c^2}{2} + 2 \ln \frac{r}{r_c} \right) \]

The average partial pressure of O\textsubscript{2}, \( P_t \), in the tissue cylinder of length L is defined as

\[ P_t = \frac{1}{\frac{1}{2} L} \int_0^L P_t(r, z) \, dr \, dz \]

Taking the average of eqn (C.4), we get

\[ P_t = P_w + \frac{M}{8D_t} \left( \frac{9}{4} - \frac{r_c^2}{r_t^2} \right) \left( r_t^2 \ln \frac{r_t}{r_c} - \frac{r_c^2}{2} + \frac{r_t^2}{2} \right) \]

in which

\[ P_t^{TM} = \int_0^L P_w(r_c, z) \, dz \]

Assuming the radial mixing of O\textsubscript{2} and neglecting the axial diffusion in comparison to convection, the transport of O\textsubscript{2} in the blood/mixture flowing through a capillary is governed by

\[ J = -2nr_c J \]

where J is the flux of O\textsubscript{2} from the capillary to the tissue from per unit area per unit length, \( Q \) is the blood flow rate and \( C \) is the total oxygen content defined as

\[ C = a_m + PMPc + \beta_p S_p(p_c) \]

in which \( a_m \) is the solubility coefficient in the mixture, \( S_r \) and \( S_p \) are the fractional saturations of hemoglobin with O\textsubscript{2} in the RBC and extracellular fluid, and \( b_r \) and \( b_p \) are carrying capacities of hemoglobin inside the RBC and extracellular fluid respectively.

From the continuity of fluxes across the capillary-tissue interface:

\[ J = -D_t a_t \left( \frac{\partial p_t}{\partial r} \right)_{r=r_c} \]

Using eqn (C.4), we get

\[ J = -M \left( \frac{1}{D_t} \ln \frac{r_t}{r_c} \right) \]

If the O\textsubscript{2} content in the blood entering the capillary at \( z = 0 \) with the partial pressure \( p_a \) is \( C_a \), the O\textsubscript{2} content along the capillary is obtained by integrating eqn (C.8) and using eqn (C.11):

\[ C(z) = C_a + \frac{2\pi}{Q} \left( \frac{M(r_t^2 - r_c^2)}{2} + r_t D_t a_t J \right) \]

This equation can be solved for the partial pressure \( p_c \) in the capillary. The average partial pressure of O\textsubscript{2} in the capillary is defined as

\[ P_c = \frac{1}{L} \int_0^L P_c(r_c, z) \, dz \]

The flux of O\textsubscript{2} from the capillary can be expressed as

\[ J = h(P_c - P_w) \]

where \( k_c \) is the mass transfer coefficient, the inverse of which, \( k_c^{-1} \), characterizes the intracapillary resistance to oxygen transport (Roy & Popel, 1996; Vadapalli \textit{et al.}, 2002).

Eliminating J from eqn (C.1) and (C.14) and taking the average in the capillary region, we get

\[ P_w = P_c - \frac{M}{2k_c} \left( \frac{r_t^2}{r_c^2} - r_c^2 \right) - D_t a_t J \]

\[ J = J(J) \]

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The diffusive flux for the compartment can be represented by the macroscopic transport equation:

\[ J_c = N_c e (P_c - P_t), \]  

(C.16)

where \( N_c \) is the number of capillaries and \( e \) is the diffusion conductance. Total macroscopic flux of \( O_2 \) from capillary to tissue is

\[ J_c = N_c m \rho d r_c^2 - r_c^2 p L - N_c a_j c 2p r_c L. \]  

(C.17)

The conductances:

\[ \frac{1}{E_c} = \frac{1}{E_{im}} + \frac{1}{E_{exv}}, \]  

(C.20)

and

\[ E_{exv} = \frac{2pN_c L d \alpha d l}{(-((1/(1 - w^2)) \ln(w) + (3 - w^2)/4) + y(\ln(w) + (1 - w^2)/2))}. \]  

(C.21)

Using the relations (C.6) and (C.15) - (C.17) we can express the diffusion conductance for the capillary compartment as

\[ E_c = N_c e \]

\[ = \frac{2pN_c L d \alpha d l}{[(1 - w^2)(1 - y)r_c k_c - (l/2D_c r_c^2) \ln(w) + (3 - w^2)/4)]\ln(w) + (1 - w^2)/2)]}, \]  

(C.18)

in which \( w = r_c/r_t \) and \( g \) is the net dimensionless diffusive influx defined by

\[ y = \frac{2r_c D_a j c}{M\rho (r_c - r_c^3)}. \]  

(C.19)

Equation (C.18) can be rewritten in terms of intravascular (\( E_{im} \)) and extravascular (\( E_{exv} \)) conductances:

\[ \frac{1}{E_c} = \frac{1}{E_{im}} + \frac{1}{E_{exv}}. \]  

(C.20)

If there is no diffusive influx from the wall of Krogh tissue cylinder (\( g = 0 \)), this reduces to the expression obtained in Sharan et al. (1998b). In the earlier model (Sharan et al., 1998a), the effect of intracapillary resistance on the diffusion conductance was not taken into account. If the intracapillary resistance is neglected, then \( E_c = E_{exv} \).