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A SIMPLE MODEL FOR SIMULATION OF OXYGEN TRANSPORT IN THE MICROCIRCULATION*

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A mathematical model of deoxygenation of blood in the microcirculation is used to estimate the mass transfer resistance in the blood and to examine certain assumptions used in prior work on simulation of the microcirculation: the treatment of blood as a continuum and the use of a single-step reaction kinetics model. The erythrocytes are treated as cylindrical slugs which alternate with plasma gaps such that oxygen transport is by radial diffusion in the cell. The system of equations including reaction kinetics and oxyhemoglobin diffusion is solved numerically. The results are of direct applicability in estimation of oxygen concentration profiles in tissue. The results also indicate that the resistance to oxygen transport in the capillary (relative to that in the surrounding tissue) is much higher than predicted by the continuum approach used by most prior workers. The resistance in the capillary is a significant fraction of the overall resistance. Other results give quantitative estimates of the error incurred from use of a single-step kinetic model.

Keywords *— Microcirculation, Oxygenation, Diffusion.*

INTRODUCTION

There has been considerable activity in recent years on the mathematical simulation of oxygen transport in the microcirculation. This paper is the third in a sequence (8,16) in which the bases for treatment of the processes in the capillary

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are examined. In the present work attention is focused on the diffusion and chemical reaction in the blood (specifically in the erythrocyte) under conditions of oxygen fluxes, geometrical configuration, space and time scales pertaining to deoxygenation in the capillaries. The studies are carried out in a simplified model in which the erythrocytes are idealized as cylindrical "slugs" which completely fill the lumen of the capillary. Experimental evidence has been interpreted to indicate that this simplified geometry is useful as a first approximation in the capillaries (8,9) because in the small capillaries the deformed erythrocyte approximates a cylindrical shape (9).

The primary purpose of the present work is to obtain numerical values of the mass transfer Nusselt number for conditions of the microcirculation. These values can be coupled with a model for tissue diffusion to yield a simulation of the oxygen distribution in the tissue. In addition to this primary purpose, the approach has been used to address two specific questions. The first pertains to the kinetic model used in much of the prior work on oxygen transport in hemoglobin solutions. As blood traverses the systemic microcirculation there is a relatively large reduction in oxygen saturation. The single-step, constant coefficient kinetic model which is often used will be evaluated in comparison to a more accurate variable rate coefficient model.

The second question pertains to the resistance to oxygen transport in the blood relative to that in the surrounding tissue. Many previous treatments of the diffusion problem have neglected the resistance in the blood under the tacit assumption that the resistance in the tissue is of dominant importance. Previous workers who have considered the resistance in the blood have often treated it as a continuum (a homogeneous hemoglobin solution). It will be shown that the resistance in the blood is a significant fraction (about 40%) of the total resistance, and that the continuum approach significantly underestimates this resistance. This finding on the resistance in the blood was previously reported (8) based on a highly simplified model which could be solved analytically. The present work confirmed that finding by use of a more elaborate model in which finite chemical reaction rates and oxyhemoglobin diffusion are taken into account.

FORMULATION AND NUMERICAL METHODS

Basis for the Calculations

Consider an idealized solid, cylindrical erythrocyte which fills the capillary radially. The erythrocytes alternate with cylindrical plasma gaps of the same dimensions (Fig. 1, the discrete cell model). Axial transport and transport in the

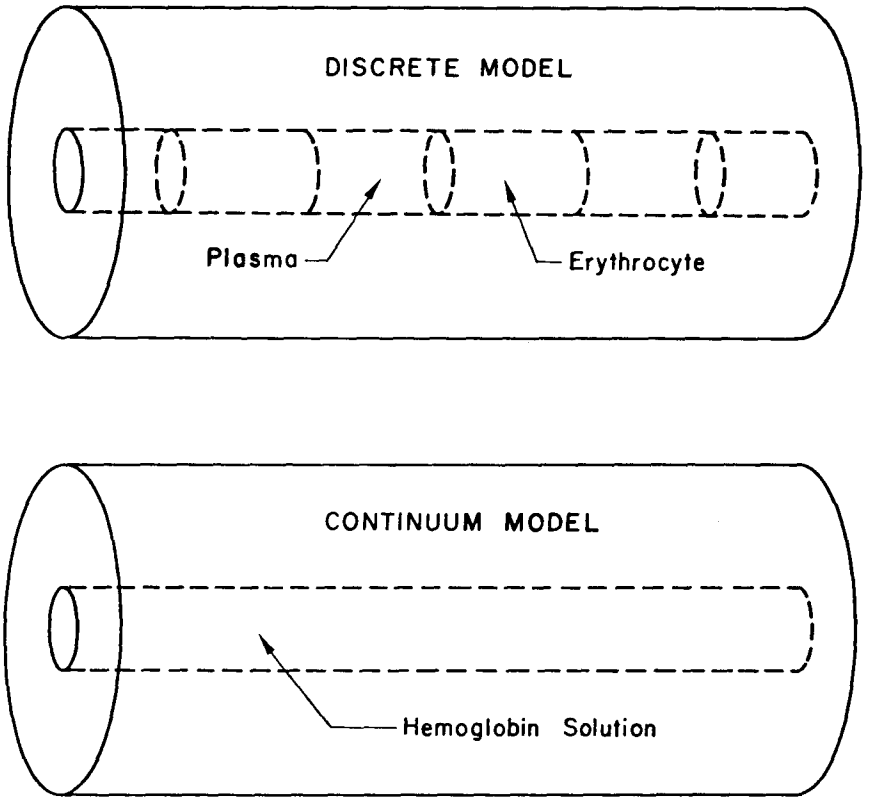

FIGURE 1. Comparison of discrete and continuum models.

plasma are neglected. The resulting diffusion problem reduces to two independent variables: radial position and time (considered to be time of flight of the erythrocyte at a constant velocity along the capillary). For purposes of comparison we considered an analogous model without erythrocytes (Fig. 1, the continuum model) in which the hemoglobin is distributed uniformly throughout the capillary. Values of the parameters used in the calculations are given in Table 1. In most cases they are the same as those used by Moll (15) and in a previous paper (16).

Equations and Conditions

The differential equations and conditions are the same for the discrete cell and continuum models:

$$\frac{\partial C_l}{\partial t} = D_l \frac{1}{r} \frac{\partial}{\partial r}\left(r \frac{\partial C_l}{\partial r}\right) + R, \tag{1}$$

$$\frac{\partial C_2}{\partial t} = D_2 \frac{1}{r} \frac{\partial}{\partial r}\left(r \frac{\partial C_2}{\partial r}\right) - R, \tag{2}$$

$$R = k_1 C_2 - k_2 C_1 (C_t - C_2), \tag{3}$$

where C_1 and C_2 denote concentrations of oxygen and oxyhemoglobin, respectively. D_1 and D_2 are the diffusion coefficients and k_1 and k_2 the reaction velocity coefficients. C_t, the total heme concentration, can be shown to be constant in this system under the assumption of equal diffusivity of oxyhemoglobin and deoxyhemoglobin.

It can be seen that these equations treat the system as a one-step reversible reaction:

$$HbO_2 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Hb + O_2.$$

If k_1 and k_2 are constants, the one-step reaction scheme is not compatible with the experimentally observed shape of the equilibrium curve. Thus, the one-step

TABLE 1. Values of Parameters

	discrete cell model	continuum model
heme group concentration, C_t, molarity (four times the hemoglobin concentration)	0.022	0.011
hematocrit, H	0.50	–
diffusivity of oxygen, D_1, cm^2/sec,	8×10^{-6}	16×10^{-6}
diffusivity of oxyhemoglobin, D_2, cm^2/sec	6.5×10^{-8}	6.5×10^{-8}
reaction velocity coefficient, k_1, sec^{-1}	variable	variable
reaction velocity coefficient, k_2, $M^{-1}sec^{-1}$	3.5×10^{6}	3.5×10^{6}
Hill equation constant, K (equation 7)	1.179×10^{12}	1.179×10^{12}
Hill equation constant, N (equation 7)	2.75	2.75
tissue oxygen consumption, G, M/sec	5×10^{-5}	5×10^{-5}
initial oxygen concentration, M	1.45×10^{-4}	1.45×10^{-4}
initial hemoglobin oxygen saturation	0.974	0.974
oxygen flux in erythrocyte at the capillary wall, q, M-cm/sec		
4 μm capillary diameter	1.0×10^{-6}	0.5×10^{-6}
6 μm capillary diameter	1.5×10^{-6}	0.75×10^{-6}

scheme was modified in some cases by varying k_1 as a function of oxygen tension such that the desired compatibility was obtained.

The equations were solved subject to a constant flux boundary condition at $r = r_c$, the radius of the capillary:

$$-D_1 \frac{\partial C_1}{\partial r} = q, \tag{4}$$

$$\frac{\partial C_2}{\partial r} = 0, \tag{5}$$

where q denotes the (specified) constant interfacial oxygen flux. The constant flux condition corresponds to a constant tissue metabolic rate neglecting axial diffusion. In the microcirculation the oxygen flux at the tissue wall is not constant but must fluctuate in response to the delivery of oxygen from passing erythrocytes. An observer riding along on the erythrocyte would see a constant radial oxygen flux at the cell boundary. An observer fixed in space on the capillary wall would see high fluxes during the period when an erythrocyte is passing–alternating with periods of zero flux when the plasma gap between cells is passing. For example, if the hematocrit were 50%, the peak tissue flux (equal to the cell flux) would be approximately twice the average tissue flux. However, it has been shown that the response time of the tissue is an order of magnitude smaller than the cycle time of the erythrocyte-induced transients (8). Thus the assumption of a steady flux through the tissue is suitable in a first-order approximation to the tissue wall average oxygen concentration.

Numerical Methods

The system of equations was solved numerically for ranges of the parameters pertinent to oxygen transport in the microcirculation. Two independent methods were used. The first was an adaptation due to Douglas (5,16) of the Crank–Nicholson finite difference method. The second was a basis spline collocation method of Madsen and Sincovec (13,14). Extensive comparative convergence and efficiency tests were carried out on the two methods, and results were compared to the analytical solution which is valid for small times. The collocation method was found to be the more efficient of the two methods by at least an order of magnitude (computer time for comparable accuracy). All results reported here are by the collocation method, and the error in the numerical procedure is estimated to be less than 0.1% in terms of either the Nusselt number or the oxygen concentration. A detailed report on the numerical work including the convergence tests is given by Baxley (2).

RESULTS

Results were obtained for several capillary diameters and over a range of parameters and are reported in detail by Baxley (2). Here attention will be focused on typical results for 4 and 6 μm capillaries. The interphase oxygen flux (Table 1) was selected for the two capillary diameters as required to give the same overall change in average oxygen saturation with time – from an inlet saturation of 0.97 to an average saturation of about 0.65 at t = 0.70 sec.

Equilibrium and Kinetic Expressions

Most prior work on mathematics of oxygen transport in hemoglobin solutions has been based on mass action kinetics for the single-step reaction scheme of Eq. 3 with k_1 and k_2 treated as constants. This constant coefficient approach has the advantage of simplicity. The reaction scheme is compatible with a hyperbolic equilibrium curve:

$$\frac{C_1}{C_t} = \frac{(k_2/k_1)C_1}{1+(k_2/k_1)C_1}. \tag{6}$$

The Hill equation, Eq. 7, is a more accurate expression of the equilibrium relationship:

$$\frac{C_1}{C_t} = 1 + \frac{KC_1^N}{1 + KC_1^N}. \tag{7}$$

These equilibrium relationships actually shift as the erythrocyte traverses the capillary in response to carbon dioxide and other fluxes. However, for purposes of comparing models for oxygen transport, the Hill equation with constant K and N (Table 1) is adequate. Figure 2 (ignore the points for the moment) gives a comparison of the hyperbolic and Hill equilibrium expressions. They can be forced to agree at only one point, and there are very significant deviations in the range of practical interest.

A variable rate coefficient (VRC) Kinetic model was constructed following Moll (15) to attain compatibility with the Hill equation. In the VRC model k_2 was constant, but k_1 was varied as a function of oxygen concentration to attain compatibility with the Hill equation. This requirement yields $k_1 = k_2/(KC_1^{N-1})$. As shown in Fig. 3, k_1 varied over a five-fold range in the VRC model. The constant value of k_1 used in the constant coefficient model is near the middle of the range of values of k_1 used in the VRC model. There are several other kinetic models which could be employed. However, comparison of the single-step model

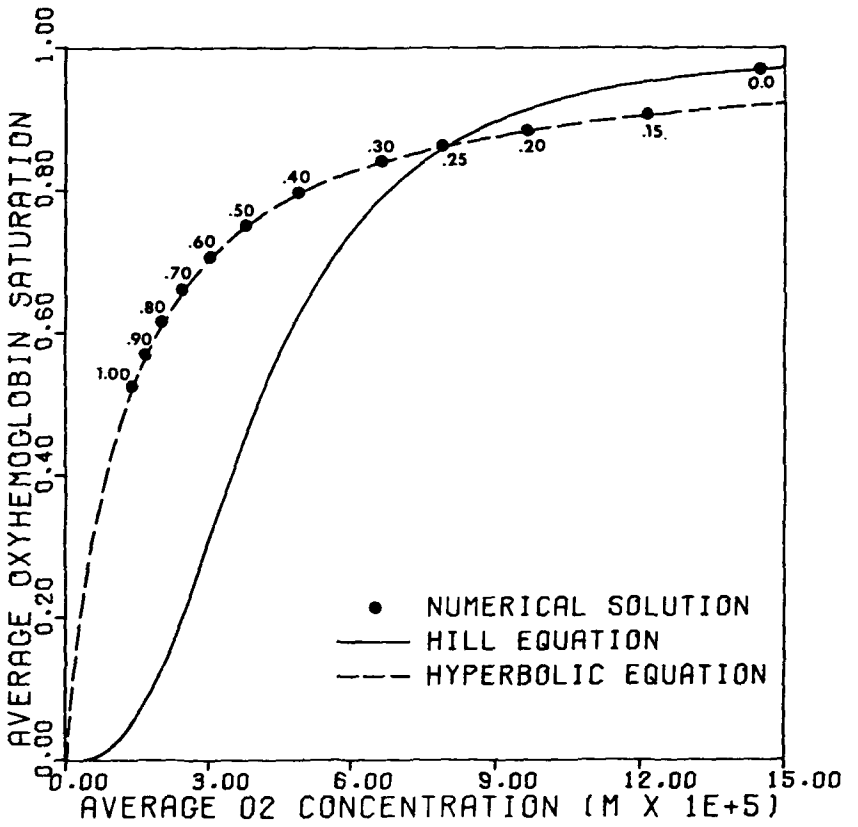

FIGURE 2. Reaction path diagram for mass action kinetics model of a 6 micron capillary.

with the Moll VRC model is sufficient to illustrate the importance of compatibility with the equilibrium relationship under the fluxes, and space and time scales of the microcirculation.

A comparison in results from the two models is given in Fig. 4 in terms of the Nusselt number and the oxygen concentration at the capillary wall. The results for the oxygen concentration are markedly different. Figure 2 shows a path of space-averaged concentrations from the numerical solutions displayed in comparison to the equilibrium curve for the constant coefficient model. The calculated points (solid black circles) fall almost on the hyperbolic equilibrium curve. Similar calculations (not shown) with the VRC model showed results falling almost on the Hill equilibrium curve. More detail on the VRC results are given in Fig. 5 where the deviation from equilibrium in oxygen concentration is presented as a function of radial position at three axial positions (three different times spent by the erythrocyte in the capillary). The equilibrium concentrations are determined by allowing the calculated concentrations at each point to "equilibrate" (solving the differential equations locally with no diffusion term). The deviation from equilibrium is small, and is confined in large part to a thin "boundary layer" near the capillary wall. The two dotted lines on each part of

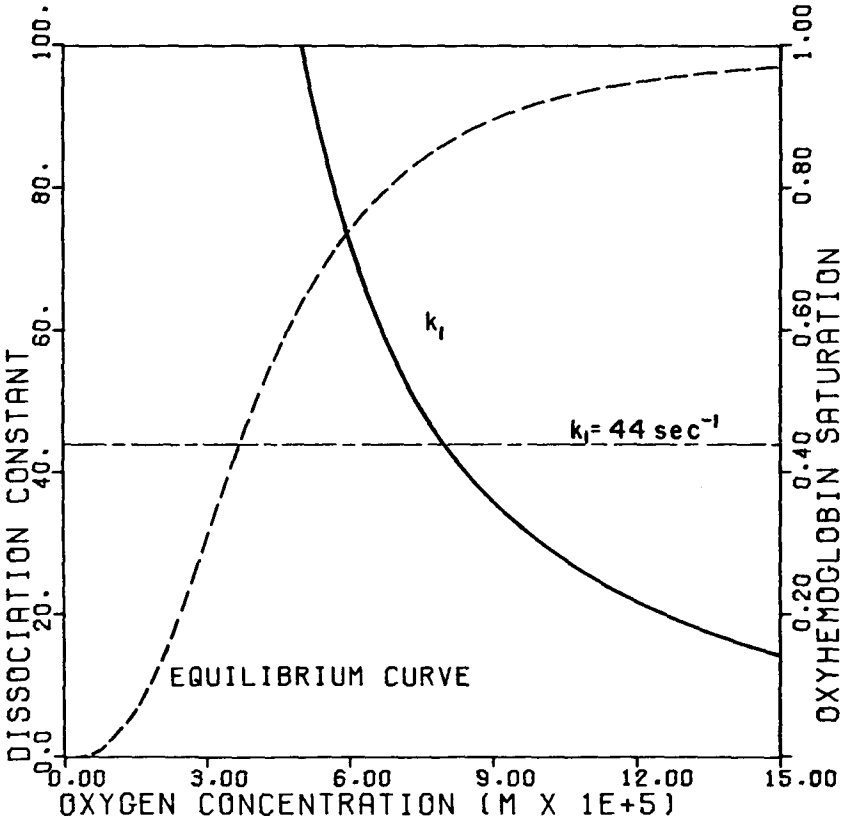

FIGURE 3. Numerical value of dissociation constant k_1 in the VRC kinetic model as a function of oxygen concentration.

Fig. 5 are from calculations in which the rate constants were increased (or decreased) by an order of magnitude. The relatively small change in results from increasing the rate constants is due to the fact that the system is very close to equilibrium except in the thin boundary layer.

The Continuum Model versus the Discrete Cell Model

The continuum model used in much prior work treats blood as a homogeneous hemoglobin solution (no red cells) as illustrated in Fig. 1 in contrast to the discrete cell model. In the discrete cell model the erythrocytes are approximated by cylindrical slugs of hemoglobin solution which alternate with plasma slugs of equal size containing no hemoglobin. Axial diffusion is neglected in both models. Thus in both cases we are dealing with radial diffusion in a cylindrical hemoglobin solution as described by Eqs. 1–5. The parameters for the two cases are significantly different as shown in Table 1. The same amount of hemoglobin is transported in the two cases. As a result the concentration in the discrete cells is twice that of the continuum case. The diffusion coefficient of oxygen is much

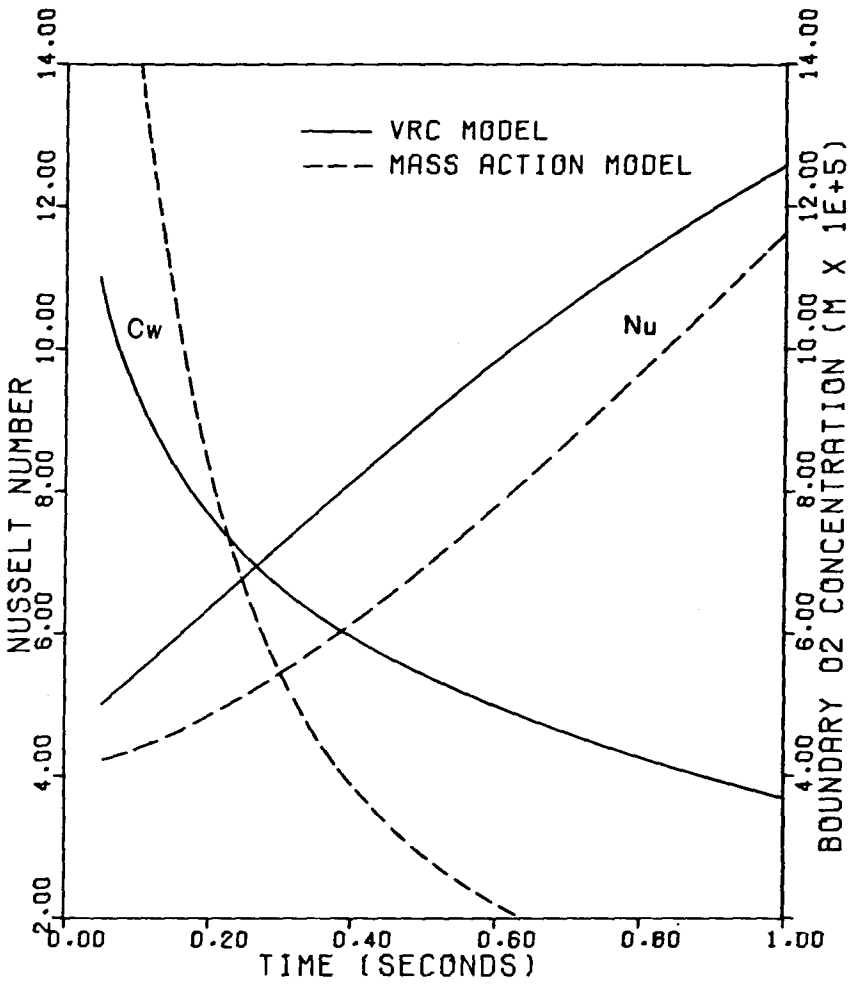

FIGURE 4. Comparison of mass action and VRC kinetic model solutions for a 6 micron capillary.

lower at the higher concentration. The oxygen flux averaged over the capillary wall is the same in the two cases. Therefore, in the discrete cell case the flux in the hemoglobin is twice that of the continuum case.

The results are presented in terms of the Nusselt number, Nu, (Figs. 6 and 7), a dimensionless flux parameter defined below:

$$\mathrm{Nu} = \frac{q(r_c)}{D_f(\bar{C} - C_w)}, \tag{8}$$

where $\bar{C}$ is the mixed-mean oxygen concentration and C_w is the oxygen concentration at the capillary wall. The Nusselt Numbers are unbounded at the entrance (zero time), but diminish and approach a value of approximately 4 so rapidly that the high values near the entrance cannot be displayed on the scale of Figs. 6 and 7. A Nusselt number of 4 is the long tube asymptote of the well-

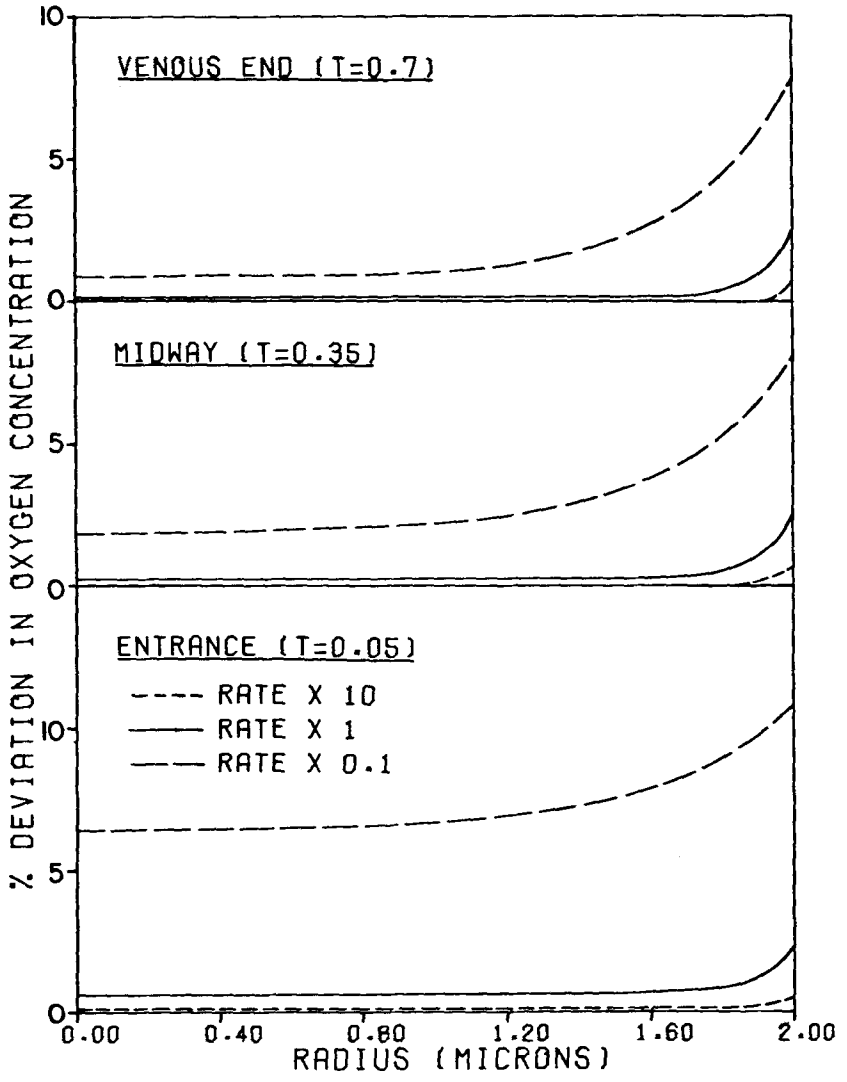

FIGURE 5. Percent deviation from local chemical equilibrium across a 4 micron capillary at several locations along the capillary.

known Graetz solution [see (3) for example]. It is also the long time (or long tube) asymptote for the analytical solution of Eqs. 1–5 for the case of zero k_2 (the case of irreversible deoxygenation) (2). The Nusselt number for the two models are both approximately 4 near the entrance, but near the venous end of the capillary (times of the order of 1 sec.) they differ by a factor of almost two. Expression of results as a Nusselt number is advantageous because the Nusselt number varies much less with the parameters than other dependent variables (such as capillary wall concentration).

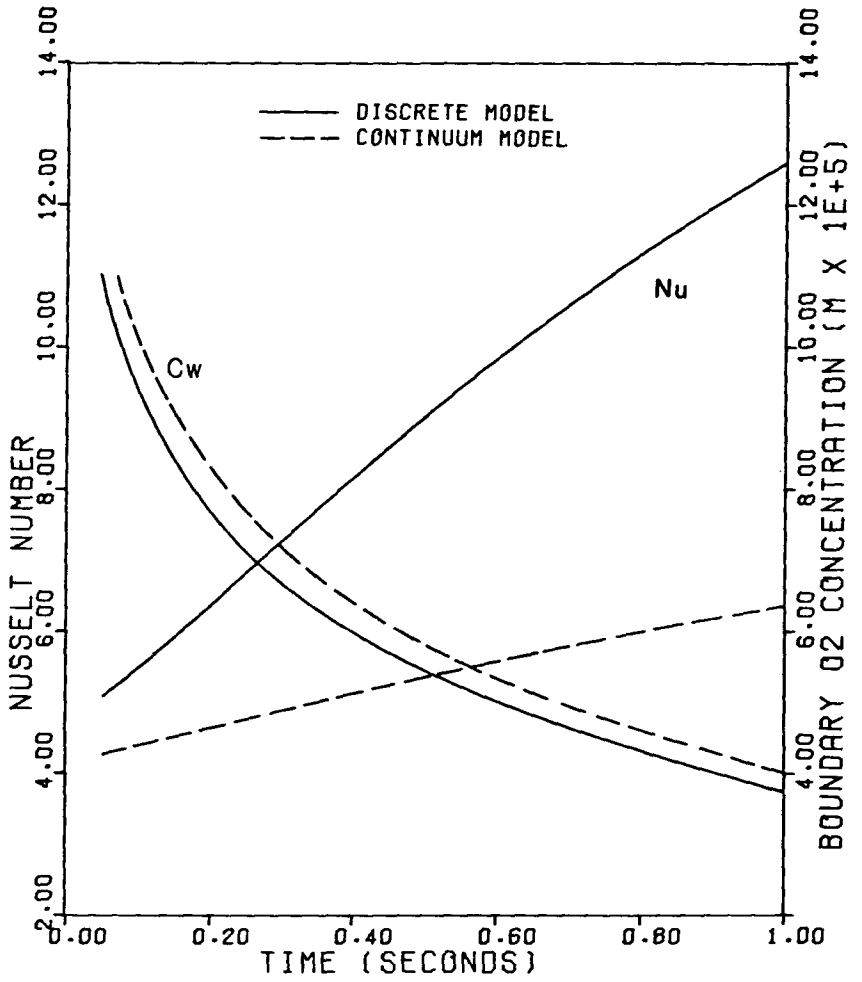

FIGURE 6. Comparison of continuum and discrete capillary models for a 6 micron capillary.

The results in terms of C_w, the oxygen concentration at the capillary wall, displayed in Figs. 6 and 7, differ for the two models. However, the difference is much less marked than in the case of the Nusselt number. It is pertinent to consider differences in oxygen concentration as a fraction of the overall radial drop in oxygen concentration through the blood and the tissue. The oxygen concentration profile in the tissue can be estimated under the assumption of a uniform, constant oxygen consumption rate and neglect of axial diffusion by the Krogh-Erlang equation (10) given below in terms of the oxygen concentration at the outer boundary of the Krogh tissue cylinder, C_T:

$$C_T = C_w - \frac{r_c G}{4D_t}(\delta^2 \ln\gamma^2 - \gamma^2 + 1) \quad , \tag{9}$$

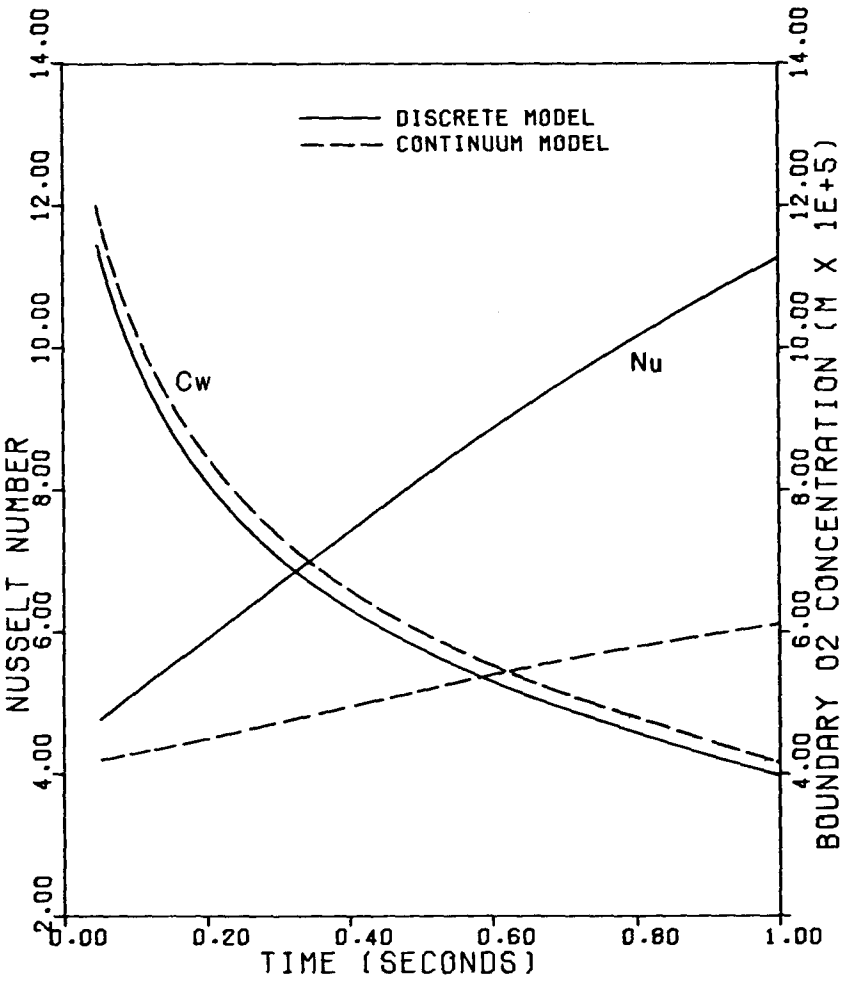

FIGURE 7. Comparison of continuum and discrete capillary models for a 4 micron capillary.

where G is the rate of oxygen consumption per unit volume of tissue,
γ is the ratio of the Krogh tissue cylinder radius to the capillary radius, and
D_t is the diffusivity of oxygen in the tissue.

The fraction concentration drop or fractional resistance, λ, is defined by

$$\lambda = \frac{C_w - C_o}{C_T - C_o}, \tag{10}$$

where C_o is the oxygen concentration at the capillary centerline. The values of λ vary only slightly with axial position. Values at $t = 0.30$ are given in Table 2 in

TABLE 2. Distribution of Resistances

Capillary Diameter	Fraction of Resistance to Oxygen Transport in the Capillaries	
	discrete model	continuum model
4 μm	0.40	0.20
6 μm	0.43	0.21
Previous estimate (8)	0.53	0.22

comparison to a previous estimate made using a highly simplified model (8). It can be seen that the fraction of the resistance to oxygen transport in the blood is indicated to be much higher (about 40% of the total) by the discrete cell model than by the continuum model. This finding is consistant with the earlier estimate (of about 50% versus 25%) using a highly simplified model.

DISCUSSION

Much of the prior work on mathematical analysis of oxygen transport in hemoglobin solutions has used the single-step kinetic model of Eq. 3 with k_1 and k_2 treated as constants (the constant coefficient model). The principal weakness of the constant coefficient model has been recognized for a long time, and Moll (15) devised the variable-rate-coefficient (VRC) model. The results of Figs. 1 through 4 give a direct comparison of results by the two models. This comparison shows that for the conditions of the microcirculation the constant coefficient model is seriously deficient. The problem is related to the fact that there is a relatively wide range of oxygen saturation. The hemoglobin and oxygen are at near equilibrium concentrations except in a relatively thin boundary layer, and the constant coefficient model is compatible with an inaccurate equilibrium curve. Presumably significant error exists in much of the prior work by the constant coefficient model involving a wide range of concentrations. On the other hand the error could be insignificant in problems involving only a small range of oxygen concentrations if the rate coefficients were selected to be compatible to the equilibrium relationship at the mean conditions. Some workers have avoided the problem by use of the more accurate four-step Adair Kinetic model (see (7) for example). The equations of the four-step model are more difficult to integrate. Hence, the single-step model apparently has been used in all prior transient solutions.

The results of Figs. 6 and 7 are of inherent interest for estimation of the mass transfer Nusselt number under the conditions of the microcirculation. The Nusselt number is of practical interest in that it relates oxygen concentrations to the oxygen flux through the capillary wall. Values of the Nusselt number can be "matched" through the capillary wall flux with a model for oxygen transport and consumption in the tissue to yield the oxygen concentration distribution. As

shown by comparison of the figures, the Nusselt number depends only slightly on capillary radius under the conditions of the microcirculation. The results also show that the continuum model used in almost all prior work seriously underestimates both the Nussselt number and the fraction of resistance to oxygen transport in the blood. On the other hand the continuum and discrete models are in much less disagreement on predictions of capillary wall oxygen concentration. This result is due to the fact that the radial gradient in the oxygen concentration is not great. Hence, small differences may correspond to a significant fraction of the overall radial concentration drop as shown by the results of Table 2. A significant fraction (about 40%) of the overall resistance to oxygen transport is in the capillary.

It is important to note that the Nusselt numbers reported here are defined (Eq. 8) in terms of the erythrocyte oxygen flux at the capillary wall. The time-averaged tissue oxygen flux at the capillary wall is different. The erythrocyte wall flux is twice the tissue wall flux for a 50% hematocrit. In application of the results for other hematocrits, the erythrocyte flux should be taken to differ from the tissue flux by a factor of (1/H), where H is the hematocrit expressed as a fraction. There is experimental evidence (11,12) that at least in some circumstances the hematocrit in the capillaries is as low as 10-20%.

The cylindrical slug configuration used in this work is obviously not a precise representation of the shape of the erythrocyte in the capillaries. The deformed shape of the cells is known to be not axisymmetrical. The cells deform from an edge-on-oriented biconcave disc shape into a "slipper"-like shape. However, analysis of measurements on cell dimensions indicates that in the small capillaries (4 μm diameter) the slipper is compressed into an almost cylindrical shape (9). Wiedeman (17,18) has pointed out that only a few careful measurements of capillary dimensions have been made, and they indicate a range of 3 to 5 μm. It is her feeling that the larger diameters (6 to 8 μm) often used in calculations are based on observations of vessels that are not true capillaries. Therefore, the cylindrical "slug" shape would appear to be a suitable first approximation to the actual shape in the capillaries.

Other assumptions of the work presented here are that the erythrocyte completely fills the lumen of the capillary and that the diffusion is entirely radial. This neglects the plasma layer which is known to be present between the erythrocyte and the capillary wall. Baxley (2) has taken this layer into account in some of his calculations and has estimated that is contributes less than 10% of the overall resistance to oxygen transport. Mass transfer through the ends of the capillaries is also neglected. In the space between the cells it is known from prior work that diffusion is of dominate importance (convection can be neglected) (1,4,6). Furthermore for 4 μm capillaries, from the measurements of Hochmuth et al. and others (9), it can be estimated that the surface area ratio (cylinder "ends" to cylinder "sides") is about 0.2, and that the diffusion path length ratio (cylinder "ends" to cylinder "sides") is of the order of 2 to 3. Thus the flux from the "ends" is estimated to be of the order of 10% of that through the plasma layer between

the cell and the capillary wall. Therefore, the two errors from neglect of the diffusion through the plasma are both of the order of 10% and have opposite effects on the distribution of resistances.

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NOMENCLATURE

C_1	Oxygen concentration
C_2	Oxyhemoglobin concentration (heme units which is four times the hemoglobin)
C_o	Oxygen concentration at the capillary centerline in the erythrocyte
C_t	Total heme concentration

C_T	Oxygen concentration at the outer boundary of the Krogh tissue cylinder
C_w	The oxygen concentration at the capillary wall
$\bar{C}$	The mixed-mean oxygen concentration in an erythrocyte
D_1	Diffusion coefficient for oxygen in the erythrocyte
D_2	Diffusion coefficient for hemoglobin in the erythroctye
D_t	Diffusion coefficient for oxygen in tissue
G	Oxygen consumption rate per unit volume of tissue
H	Fractional hematocrit (volume fraction erythrocytes in blood)
k_1	Reaction velocity coefficient for deoxygenation of hemoglobin
k_2	Reaction velocity coefficient for oxygenation of hemoglobin
K	Constant from Hill equation, Eq. 7
N	Constant from Hill equation, Eq. 7
Nu	Nusselt number, defined by Eq. 8
q	Flux of oxygen through the erythrocyte boundary
r	Radial coordinate
r_c	Radius of the capillary
R	Rate of net appearance of oxygen per unit volume
t	Time
VRC	The variable-rate-coefficient kinetic model introduced after Eq. 7
γ	Ratio of the Krogh tissue cylinder radius to the capillary radius
λ	Fraction of resistance to oxygen transport in the tissue, Eq. 10