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Simulation of oxygen transport in capillaries

Nair, Pratap Krishnan, Ph.D.
Rice University, 1988
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SIMULATION OF OXYGEN TRANSPORT IN CAPILLARIES

by

PRATAP NAIR

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE

DOCTOR OF PHILOSOPHY

APPROVED, THESIS COMMITTEE:

J. David Hellums, Ph.D.
Foyt Family Professor
Dean of Engineering

Larry V. McIntire, Ph.D.
E. D. Butcher Professor
and Chairman, Department
of Chemical Engineering
Director

John S. Olson, Ph.D.
Professor, Biochemistry

Houston, Texas
April, 1988
ABSTRACT

Simulation of oxygen transport in capillaries

Pratap Nair

A mathematical model is developed to predict oxygen transport from large capillaries. The model includes diffusion and convection in the plasma and rbc and the reaction in the rbc's. It also includes the radial distribution of red cells and flow velocities of red cells and plasma. The calculated oxygen saturations are in good agreement with the results from experiments in which artificial rubber capillaries are perfused with red blood cell suspensions. It is found that in the large capillaries most of the resistance to oxygen transport lies in the plasma. The Nusselt number for mass transfer is determined as a function of various parameters. The fluxes from large capillaries under various conditions can be easily predicted from these Nusselt numbers. The resistance to oxygen transport is found to be greater with rbc suspensions than with equivalent Hb solutions.

A mathematical model is developed for small capillaries. The effects of various parameters on oxygen transport are studied using this model. The physiological significance of these effects is discussed. The Nusselt number is calculated as a function of various parameters. It is found that a significant fraction of the transport resistance lies outside
the tissue. The model is applied to certain physiological situations and is found to predict the observed behaviour.

The experimental methodology developed by Boland et al (13) is validated with the help of a well established mathematical model for hemoglobin solutions. The experimental system is characterized with the help of the model. The effects of physiological factors on oxygen transport from hemoglobin solutions is studied.
ACKNOWLEDGEMENTS

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CHAPTER 1

INTRODUCTION

There is a great interest in understanding the mechanism by which oxygen is transported from the blood to tissue and from the alveolar gas to blood, and how this transfer can be controlled. The work of August Krogh (78) from about 1918 to 1929 is credited with motivating and laying the basis for the first conceptual models of the microcirculation.

According to Krogh, the rate of oxygen transport was related to the number and distribution of capillaries in tissue and the permeability of the capillary walls and tissue to oxygen. From his experimental observations of the distribution of capillaries in a cross-section of striated muscle, he concluded that each capillary could be regarded as running parallel to the muscle tissues and supplying a concentric region of tissue surrounding that capillary, and this tissue region was independent of the other parallel capillaries and tissues they supplied. He determined the average tissue radius by dividing the area of the muscle cross section by the number of capillaries. These ideas were described mathematically by the Krogh-Erlang equation given by
\[ U(r,z) = U_0(z) - \frac{R_0}{2D_t} \left[ r_t^2 \log \left( \frac{r_t}{r_c} \right) - \frac{1}{2} (r_t^2 - r_c^2) \right] \quad \text{(1.1)} \]

where \( U(r,z) \) is the oxygen concentration in the tissue

\( r_t \) is the radius of the annular tissue space surrounding the capillary

\( r_c \) is the capillary radius

\( R_0 \) is the constant rate of oxygen consumption

\( D_t \) is the radial oxygen diffusion coefficient in tissue

\( U_0(z) \) is the oxygen concentration in the capillary

This model neglects all intracapillary resistance under the tacit assumption that the tissue offers the major resistance to oxygen transport. The oxygen is assumed to be consumed uniformly by the tissue.

Krogh's work initiated and set the course for the analytical study from 1919 to the present. Following Krogh's initial studies, most of the work till 1957 focussed on tissue oxygen transport. The intra-capillary conditions were first included in 1957 by Kety (73), who assumed a linear drop in oxygen content of capillary blood from arterial to venous end. He pointed out the error in the results by omission of axial gradients in the capillary. Thews (115) was the first
to consider the effect of radial partial pressure gradients in the capillary. In a lot of the work that followed, radial concentration gradients within the capillary were neglected and only axial convection was included under the tacit assumption that the resistance to mass transfer within the tissue is dominant. Until recent years the workers who considered the blood diffusional resistance, treated blood as a continuum. That is, the diffusion problem was treated as if the hemoglobin were dispersed uniformly in the plasma rather than contained in the erythrocytes. Extensive reviews on the work till about 1977 may be found in references 41, 80, 81, 83, 88, 100. Work with red cells in the past, had indicated that the presence of red cells increased the oxygenation resistance, even though the cell membrane offered negligible resistance (88). Some workers felt that the increased resistance was due to the plasma boundary layers around the red cells. However the experimental apparatus, in which these observations were made, were very large as compared to the size of the conduits in the capillaries. Hellums (55) showed by a simple analysis that—a significant amount of the resistance lies in the blood even in the more physiological capillary geometry. Honig et al (62) measured the transcapillary and intracellular oxygen gradients from measurements of myoglobin saturation in dog gracilis muscles frozen in situ. They found that
transcapillary gradients are larger and tissue gradients smaller than predicted by existing models of oxygen diffusion. They found that during exercise the principal resistance to oxygen transport resides in the capillary and extracellular space.

In the recent past the modeling approaches have included the diffusion resistance within the capillary and have taken into account the presence of rbc's. (3,7,23,38,39,50,51,59). Artigue and Bruley (3) developed a model which lumps radial diffusion resistances into mass transfer coefficients which are obtained from experiments. Baxley (7) considered the rbc to be cylindrical slugs and included radial diffusion and reaction within the rbc and also included diffusion in the layer of plasma between the rbc and the capillary wall, in his model. He also took into account the effective flux from the rbc's, due to the presence of alternate plasma gaps between them. Clark et al (23) studied the mass transfer from the rbc's alone. Federspiel and Sarelius (38) investigated the effect of rbc spacing on the ability of the capillary blood to supply a uniform flux of oxygen at the capillary wall. Federspiel and Popel (39) developed a model for small capillaries taking rbc spacing, rbc velocity and rbc clearance as parameters. They considered their rbc's to be spheres and found an increased resistance due to the discrete nature of blood over Hb solutions. Groebe and
Thews (50) developed a model similar to Baxley's model which considered diffusion in the rbc and the plasma film. However they also included axial diffusion within the rbc. Hideyuki and Sugihara (59) proposed a lumped parameter two phase model taking into account the difference in average velocities of the rbc and the plasma and used mass transfer coefficients to lump the resistances.

About 25-35% of the microcirculatory O2 transport occurs in the arterioles and larger vessels (66, 92, 97, 101), 10-100 μ in diameter. Hence it is important that we be able to predict O2 transport processes in larger vessels as well as in capillaries. Also, membrane oxygenators used in cardiopulmonary bypass surgery and in membrane lungs involves O2 transport from relatively large conduits (about 100 μ). The mass transfer resistance attributable to the blood phase is a significant fraction of the total resistance for O2 transport in most devices. A basic understanding of gas transport in blood from large vessels therefore provides guidance in the understanding of microcirculatory O2 transport, aids in the interpretation of membrane lung function, and is a prerequisite for a rational theoretical analysis and design of such devices.

The flow and mass transfer characteristics in the large capillaries are known to be different from those in the small capillaries (18). In the large capillaries there are
Fig. 1.1: Flow of red blood cells in large capillaries (taken from Exempla Haemorheologica, Vol. 2, by Schmid-Schonbein, Grunau and Brauer, Hoechst publication)
many rbc's at any cross section (Fig 1.1), and the flow is complex. The flow is different in the smaller capillaries, where the conduit is smaller than the maximum dimension of the rbc. For the rbc's to pass through the small capillary, it folds into a parachute or a slipper shaped object and flows in a single file (Fig 1.2). The mechanism of oxygen transport from small capillaries is different from that in large capillaries. The steps involved are the same but the distribution of resistances and the important mechanism are different in the two cases. As mentioned before, several workers have studied and modeled O₂ transport from small vessels. These models would be inappropriate for large vessels. For transport from large vessels, blood has often been treated as if it were a homogeneous solution of Hb. Some other small capillary models which consider the presence of rbc's, may be used for large capillaries (3,100).

Due to the complex physical situation various assumptions have to be made to make the model for O₂ transport mathematically tractable. However, in most cases these assumptions have not been validated by an experiment.

There are great difficulties in designing and executing experiments that will serve to critically test a mathematical model for O₂ transport in the microcirculation. As a result, there have been few - if any - critical tests, and there is no uniformity in the models used by various workers.
Fig.1.2: Flow of red blood cells in small capillaries (taken from Exempla Haemorheologica, Vol. 2, by Schmid-Schonbein, Grunau and Brauer, Hoechst publication)
in the field. By way of illustration, consider the models used by different research workers who are currently active in the field, and who have considered the resistance in blood. Fletcher (41) has used a model in which: 1) the continuum approach is used, 2) the diffusional resistance in blood is either neglected or lumped into a capillary wall permeability coefficient, and 3) the resistance due to the chemical reaction in the blood is taken into account. Bruley and his co-workers (3) are using a different approach: 1) the rbc's are treated as a separate phase uniformly distributed in the plasma; 2) diffusional resistance between the cells and the plasma is taken into account by means of a mass transfer coefficient; and 3) the resistance due to chemical reaction rate is neglected. (They assume local chemical equilibrium). Thus, we see that some of the most active workers in the field are using very different set of assumptions. This point emphasizes the need for experimental measurements which can provide a critical test of the models. A test of this general type was carried out by Schubert, Fletcher and Reneau (106). They compared histograms of experimentally determined $O_2$ tension distributions in a perfused heart with predictions from three mathematical models. They found that the calculations and the experiments did not agree. Agreement was improved only after the
introduction of anomalously large values of the tissue diffusion coefficients into the model.

An in-vitro capillary system has been developed by Boland et al (13). The capillaries are 27 μm in diameter (size of a typical arteriolar vessel). The data obtained from this capillary is analyzed and used to develop a validated mathematical model for large capillaries.

1.1 Objectives

The Objectives of this work are:

1) To develop a mathematical model for the simulation of oxygen transport from large capillaries. This model will be critically tested by comparing the results with data obtained from experiments performed by Boland (13), Lemon (79), and Stathopoulos (114), which cover a wide range of conditions.

2) To develop a mathematical model for small capillaries and compare with previous models.

3) To develop predictive methods of practical utility from the validated mathematical results.

4) To apply the mathematical methodologies to understanding normal and pathological processes in the human microcirculation.
1.2 Outline of approach

The experimental system (artificial silicone rubber capillary) is described in Ch 2 together with the experimental methodology used by Boland et al (13), Lemon, et al (79), and Stathopoulos, et al (114). In Ch 3 the results for oxygen transport are given for the capillary perfused with hemoglobin solutions. A detailed mathematical simulation of the experimental measurements for Hb solutions is developed in Ch 3 and shown to give results in agreement with the observed $O_2$ saturation values over a wide range of parameters. This mathematical simulation serves as a validation for the experimental system because the mathematics for $O_2$ transport from Hb solutions is fairly well developed. The same experimental system is used to study $O_2$ transport from rbc suspensions flowing through large bore capillaries (Ch 4). A mathematical model for large bore capillaries is developed in Ch 4 and validated by comparison with experimental results. In Ch 5 a mathematical model is developed for small bore capillaries. The model is applied to certain in vivo situations of interest and compared to models proposed by others. Ch 6 suggests work to be done in the future, and lists the conclusions of this work.
CHAPTER 2

EXPERIMENTAL METHODOLOGY

2.1 Introduction

Mathematical analysis of oxygen transport in the microcirculation normally requires the introduction of a number of simplifying assumptions to reduce the complicated physical situation to a form that is tractable. Experimental verification of the various proposed models requires accurate, simultaneous measurement of all of the key mass transfer parameters. Although in vivo $O_2$ transport has been examined carefully by Duling and co-workers (32, 74, 93, 94, 95, 102), the exact capillary wall boundary conditions and dimensions have not been well-defined experimentally. These difficulties led to the development of an in vitro system which both simulates the physiological situation and permits accurate measurement of transport and flow characteristics. This system was developed by Unno, Boland, Hellums and Olson. The experimental work discussed in this thesis was performed by Boland, Lemon and Stathopoulos and many of the results have been reported (13,79). This thesis project involved the mathematical analysis of the experimental results and planning of the experiments. The building of the
apparatus and performing of the experiments are not part of this thesis work. However, since the apparatus and its results are crucial to this thesis work and for the sake of completeness it is reviewed here.

In this system, the artificial capillary lumen and surrounding silicone rubber film dimensions are determined precisely by microscopy; the flow rate is carefully regulated; the inlet concentration of red cells or hemoglobin is controlled independently; the oxygen saturation of hemoglobin is measured spectrophotometrically; and the boundary conditions in the silicone rubber capillary can be computed by established mathematical techniques. Accurate measurement of these variables allows us to test and validate several mathematical schemes used for simulation of microcirculatory oxygen transport.

Heineken et al. (54), originally developed an in vitro system by fabricating artificial capillaries in a silicone rubber film which had one free surface for oxygen exchange. They also made substantial progress in demonstrating the applicability of these capillaries for studying gas transport using oxygen microelectrodes. In this experimental system their approach has been extended in two ways. Here, the silicone rubber films have two free surfaces for oxygen transport, and oxygen binding to hemoglobin is measured directly by dual wavelength microspectrophotometry. The
detection system represents an adaptation of previous work by Sinha (111) with stationary red cells and by Pittman and Duling (93, 94, 95) with red cells flowing through microvessels. The artificial capillary is placed on the stage of a microscope, and the transmitted light is diverted to photomultipliers for absorbance measurements. The exact operational details of the apparatus and its applicability to \( O_2 \) transport studies with human hemoglobin solutions and red blood cell suspensions are presented in this chapter.

2.2 The Experimental System

The experimental system consists of the four parts shown schematically in Figs. 2.1-2.3. (1) The capillary is a small cylindrical conduit cast in a film of silicone rubber which was chosen because of its high oxygen permeability, low optical density, and structural stability. (2) The flow system pumps, meters, and maintains in suspension the fluid-cell mixture which passes through the capillary. (3) The environmental system controls separately the gas composition in the space which surrounds the capillary and in the area above the feed reservoir containing the perfusate; it also regulates the temperature of the apparatus. (4) The detector system consists of a microspectrophotometer which allows repetitive absorbance measurements at various axial positions along the length of the capillary.
Fig. 2.1: Side view of the capillary molding apparatus (shown disassembled). Center section of the 3-section mold is capillary holder during subsequent perfusion experiments. Above structure is mounted on fixed stand with attached micromanipulators to ensure precise positioning of lumen within silicone film.
Fig. 2.2: Cross section of capillary and associated silicone rubber film. Typical dimensions are shown.
Fig. 2.3: Capillary and environmental gas chamber assembly. C, glass covers; CG, capillary gas space; EG, external gas space; EP, end piece; MM, micromanipulator; MS, microscope stage; OL, objective lens; R, perfusate reservoir; S, silicone rubber film; P, syringe pump.
2.2.1 Artificial Capillary Fabrication

The procedure for casting the artificial capillary can be followed by reference to Fig.2.1. The mold serves both to determine the size and shape of the silicone rubber film during fabrication and to hold the film in place during perfusion. The center mold piece is grooved on the inner face of each end to provide support for the silicone rubber film after the bottom and top pieces have been removed. The artificial capillary is cast directly in the mold by pouring degassed silicone rubber (Sylgard 184 silicone, Dow-Corning Co.) around a thin strand of tungsten wire (24 μm in diameter) which was positioned with micromanipulators in the center of the film (Fig.2.1). The silicone was allowed to polymerize for four days before removal of the tungsten wire. A typical film is shown schematically in Fig.2.2. The silicone films used in the experiments reported here were 160 to 180 μm thick, 1 cm wide, and 5 mm long in the direction of the flow. The lumen of the capillaries averaged 27.5 μm in diameter. Dimensions were determined, after use, by sectioning the silicone sheet and measuring their geometrical parameters on a Leitz microscope with a digital micrometer attachment.
2.2.2 The Flow and Environmental Systems

The flow and environmental systems are illustrated schematically in Fig.2.3. The assembly is mounted on a Leitz Diavert microscope. The central part of the drawing represents the silicone rubber film surrounding the capillary lumen. The space between the film and the glass cover pieces is designated the capillary gas space and suffused with either pure nitrogen in the case of deoxygenation experiments or oxygen-nitrogen mixtures in the case of $O_2$ uptake measurements. The area outside the glass cover pieces is designated the reservoir gas space and is suffused separately and independently. This external gas is in contact with the perfusate in the feed reservoir, and its composition is regulated to produce the desired inlet oxygen concentration of the hemoglobin solution or red cell suspension. The temperature of the system is controlled with a heat curtain. Fluid is drawn from the feed reservoir through the capillary by a syringe pump (Sage model 302) using a 50 μl or 100 μl gas tight syringe (Hamilton).

2.2.3 The Microspectrophotometer

The dual wavelength spectrophotometric system is outlined in Fig.2.4. Light from a xenon arc lamp (75 W) is transmitted through a low band pass filter which removes light at wavelengths above 540 nm and then directed to the capillary
Fig. 2.4: Schematic of microspectrophotometric apparatus. D, rectangular diaphragm; EC, capillary environmental chamber (Fig. 2.3); LG, fiber optic light guidebeam splitter; M, microscope (Leitz Diavert); MM, micromanipulator; MS, microscope stage; P, syringe pump; PM, photomultiplier tube; XL, xenon lamp.
chamber. The image is brought to focus by a long-working-distance lens (Leitz ACH L32/0.40), and its size is regulated by a rectangular diaphragm which is adjusted to allow only light passing through the capillary to be incident upon the fiber optic beam splitter. The field of view is normally 0.025 mm in the transverse direction and 0.035 mm in the axial direction. The dual beams are conducted to separate photomultiplier tubes where they are passed through an interference filter (either 414 or 430 nm) housed immediately anterior to the cathode window. Each photometer output is amplified and either displayed on a chart recorder or digitized and stored in an IBM System 9000 laboratory computer.

2.2.4 Absorbance Measurements in the Capillary

The extent of oxygenation of the hemoglobin solution was monitored by changes in light transmittance. Because of the path length (≤ 30μm) of the absorbing solution, measurements were made at the Soret region wavelength maxima for oxy-(414 nm) and deoxyhemoglobin (430 nm). The dual wavelength technique used has been described by Olson (90) for rapid mixing experiments with intact red cells. Sample transmittance traces are shown in Fig.2.5. for O2 release measurements at a position 2 mm from the capillary entrance. Initially, the capillary was perfused with an oxygenated
Fig. 2.5: Typical output from photomultiplier tube amplifiers at 430 and 415 nm when going from 100% saturated hemoglobin (100% O₂ in both gas spaces) to some intermediate level of saturation when 100% N₂ is introduced into capillary gas space.
hemoglobin solution, and the sample entering the capillary was kept fully saturated by maintaining a 100 percent O₂ atmosphere in both the reservoir and capillary gas spaces. The addition of 100 percent N₂ to the internal capillary gas space caused the release of oxygen from the fluid as is passed through the capillary. There was a decrease in transmittance at 430 nm (i.e., an increase in absorbance due to deoxyhemoglobin formation) and an increase at 414 nm. All light intensity measurements were made after the steady state condition was reached at the same flow condition. The change in absorbance at each wavelength, \( \Delta A_\lambda \), was calculated from the logarithm of the ratio of the transmittance voltage of the sample under the O₂ transport condition to that for the fully oxygenated sample. The \( \Delta A_\lambda \) values at each wavelength were then subtracted to reduce light scattering artifacts and to enhance the resultant signal since the absorbance changes are in opposite directions:

\[ \Delta A_{\text{obs}} = \Delta A_{430} - \Delta A_{414}. \]

Light transmittance through the completely deoxygenated sample was also measured at each position along the capillary. The total change in absorbance in passing from the fully oxygenated state to the fully deoxygenated state, \( \Delta A_{100-0 \text{ percent}} \), represents the maximum possible signal and was used to normalize the \( \Delta A_{\text{obs}} \) values and to compute the fractional degree of saturation of the hemoglobin molecules:
\[ Y = 1 - \frac{\Delta A_{\text{obs}}}{\Delta A_{\text{100-0 percent}}} \quad \text{[3.1]} \]

The calculation of oxygen saturation described above is based on the Lambert-Beer Law for the absorption of light by solutions. Light scattering by erythrocytes is the most important mechanism for deviation from the Lambert-Beer Law, but several other mechanisms can be important in some circumstances. The "sieving effect" occurs in erythrocyte suspensions due to light passing through variable amounts of encapsulated hemoglobin at various positions in the field of view of the detector. "Glare" and "stray light" effects occur when light reaches the detector which has not passed through the specimen. Still other deviations from the Lambert-Beer Law are associated with the fact that optical filters do not yield purely monochromatic light. More through discussions of these effects have been presented by Burkhard and Barnikol (17), Pittman and Duling (93), and Boland et al. (14).

These deviations from the idealized Lambert-Beer Law are dealt with in the spectrophotometric method of this work in a way that is both practical and on a theoretically sound basis. Scattering effects are the most important. They are minimized by using differences between simultaneous absorption determinations at 414 and 430 nm. Since
scattering is wavelength dependent in this range, there will be a small effect even after subtraction of the changes at 430 and 414 nm. Compensation for this residual scattering effect is made by using absorption differences from the fully saturated condition at the same wavelength. Both of these differences are indicated in the expression for the hemoglobin oxygen saturation, Equation [3.1]. Use of the latter differences assumes that the hematocrit is the same for the two measurements. This assumption has caused little problems in our experiments since the same sample is used for all measurements. In addition, the transmittance is a sensitive indicator of hematocrit, thus any significant change in hematocrit is quite apparent.

The other deviations from the Lambert-Beer Law also are minimized by measuring absorption differences from the fully saturated condition. Equation [3.1] can be regarded as an interpolation formula between the two known conditions of complete oxygenation and complete deoxygenation. The theory of the "Glare" and "Sieve" effects admits the possibility that the relationship between oxygen saturation and the absorbance differences could deviate from the linear relationship of Equation [3.1]. An important advantage of our in-vitro system is that the oxygen saturation of the suspension in the capillary can be manipulated to known, constant, and intermediate levels. This capability was used in a series
of calibration experiments with normal human red cells and erythrocytes from sickle cell anemia patients. The oxygen saturation determined from the microspectrophotometer via Equation [3.1] was compared to that measured independently (111). The linear relationship between \( Y \) and \( \Delta A_{\text{obs}} \) in Equation [3.1] was confirmed to within the accuracy of the artificial capillary measurements for both types of erythrocytes, although much more scatter was observed for the sickle cells.

2.3 Experimental Procedure

2.3.1 Sample Preparation

Hemoglobin solutions were prepared as follows. Human blood specimens were drawn into heparin (10 USP units/ml), washed three times with saline, and lysed by stirring for 90 minutes with an equal volume of distilled water. Cell debris was removed by adjusting the salt concentration of the lysate to 3 M NaCl followed by centrifugation at 10,000 x g for two hours. The supernatant was dialyzed extensively against either 10 mM Hepes, 0.150 M NaCl, or 77.5 mM NaCl, 58 mM Na phosphate (work in Lemon et al (79)), both at pH 7.4. Identical results were obtained with either buffer system when \( P_{50} \) differences were taken into account. Red cell suspensions were prepared from washed, packed cells by
resuspension in 1 BSA, 10 mM Hepes, 0.15 M NaCl at pH 7.4. For most of the experiments presented in this work, the free hemoglobin concentration was adjusted to 4.0 mM heme. The erythrocyte suspensions were adjusted to a hematocrit of 20 percent to yield an equivalent heme concentration.

2.3.2 Procedure

In a typical experiment, a 4 ml sample was filtered (0.45 μm pore size for hemoglobin solutions; 10 μm for red cell suspensions) and deoxygenated with 100 percent N₂ in a tonometer. During this procedure, the capillary chamber was brought to the desired temperature and equilibrated with 100 percent N₂ in both the internal capillary and external reservoir gas spaces. Two ml's of the deoxygenated solution was transferred from the tonometer to the reservoir of the capillary apparatus, and flow was initiated by the syringe pump. The cell samples were stirred continuously to prevent settling and hematocrit changes. After steady state flow was reached, transmittance readings for the deoxygenated state were made at eight or nine different axial positions. For oxygen release experiments, the next step was to switch both gas spaces to 100 percent O₂ or air, wait 15 minutes to allow complete saturation of the specimen in the reservoir, and make the reading for 100 percent saturation at the first axial position. Then the gas flowing to the internal gas
space was switched to the desired composition for the transport experiment (usually 100 percent \( N_2 \)) and the intermediate light intensity was measured. The capillary was then moved to the second axial position and the procedure repeated, alternating 100 percent \( O_2 \) or air and 100 percent \( N_2 \) in the internal capillary gas space. For oxygen uptake experiments, the procedure was similar; however, in this case the intermediate light intensities and those for the completely deoxygenated sample were measured at each axial position as the capillary was moved across the microscopic stage. Then both gas spaces were filled with pure \( O_2 \) to obtain the 100\% oxygenation readings at the end of the experiment.

2.3.3 Measurement of Silicone Rubber Permeability

The permeability coefficient of silicone rubber, \( K \), as reported in literature seems to be highly variable. Thus, the permeability is measured directly by following the mass transfer of oxygen into a plexiglass cell which has been fitted with a film of silicone rubber. The films are constructed in the manner used to prepare the capillary films, except that no lumen is formed. An \( O_2 \) electrode is used to measure the appearance of \( O_2 \) in the well-stirred saline solution which fills the cell.
2.3.4 Oxygen Affinity Measurements

Solution of the differential equations for simulation of oxygen transport requires accurate information on the equilibrium relationship between $O_2$ and oxyhemoglobin. The equilibrium curves are affected by the procedures of preparation of the cell suspensions. Furthermore, the equilibrium curves change with time. Thus, it was found to be important that the equilibrium curves be determined in the individual specimens at the same time as the specimens were studied in the artificial capillary.

Equilibrium curves of each red cell suspension are obtained at 25°C and at 37°C by use of a Hem-O-Scan $O_2$ Dissociation Analyzer (SLM/AMINCO, SLM Instruments Inc., Urbana, IL.) This instrument requires only 2μl of sample to produce a complete, continuous oxygen equilibrium curve. The sample is spread as a thin layer and exposed to varying $O_2$ partial pressures monitored by a Clark $O_2$ electrode while the $O_2$ saturation of the sample is monitored spectrophotometrically. The gas mixtures used are pure $N_2$ and 25 percent $O_2$, balance nitrogen. A series of preliminary studies carried out confirm the validity of the Hem-O-Scan instruments, and are described in reference (114).
2.4 Discussion

The apparatus developed in this work is intended to be of direct applicability in studies on microcirculatory physiology. Some such studies in vivo may be found in references, 69, 70, 74. For example, a flow rate of 9.4 μl/hr corresponds to an average axial velocity of 4.6 mm/s and a residence time at the end of the capillary of ≈ 1 s. Since the capillary dimensions, flow parameters, hematocrit, and hemoglobin fractional saturation are either controlled or measured accurately, the resultant experimental data can be analyzed rigorously.

The key features of the in vitro capillary are the low optical density and high oxygen permeability of the silicone rubber film. Light transmittance through the capillary walls allows direct measurement of the extent of chemical combination between O₂ and the hemoglobin sample. Analysis of the radial distribution of free oxygen in both the lumen and the surrounding silicone film indicates that only about 50 percent of the total resistance to transport occurs in the walls even though their mean thickness is ≈ 60μm compared to an intracapillary radius of ≈14 μm (see Fig.3.8, Ch.3). Thus, at least half of the resistance to transport resides in the fluid flowing through the capillary and is readily evaluated. This conclusion is demonstrated qualitatively in Fig.4.13 where O₂ uptake curves for a hemoglobin solution
and an equivalent red blood cell suspension are compared. If diffusion through the silicone rubber were very slow and rate limiting, then no differences between the transport properties of the hemoglobin solution and those of the cell suspension would have been observed. The marked difference between the $O_2$ uptake rates of erythrocytes and free hemoglobin demonstrates the importance of intracapillary resistance in determining the overall efficiency of transport.

A great advantage of this in vitro system is that it is a relatively simple matter to vary the conditions (capillary dimensions, flow rates, hematocrit and oxygen flux etc.), over very wide ranges. Hence models with two or more adjustable parameters can be critically tested.
CHAPTER 3

OXYGEN TRANSPORT IN HEMOGLOBIN SOLUTIONS

In this chapter, the artificial capillary system described in Ch 2, is tested for its applicability in studying oxygen transport from capillaries, by comparing the results obtained from it with that predicted by a well developed mathematical model for hemoglobin solutions. The effects of various physiological parameters on the efficiency of oxygen transport from Hb solutions is also studied. The model is used to analyse quantitatively the mass transport properties of the concentrated hemoglobin solutions flowing through the 27 μm capillary. The work in this chapter was done in cooperation with Doug Lemon and J.S. Olson.

3.1 Mathematical model

3.1.1 Transport equations

The capillary is described mathematically as a cylinder of radius $r_c$. The mass balance equations including radial diffusion, axial convection and chemical reaction within the capillary are described by:
\[ v_z \frac{\partial C}{\partial z} = \frac{D_{O2}}{r} \frac{\partial}{\partial r} \left[ r \frac{\partial C}{\partial r} \right] + C_H f(C, y) \]  
[3.1a]

\[ v_z \frac{\partial y}{\partial z} = \frac{D_{HbO2}}{r} \frac{\partial}{\partial r} \left[ r \frac{\partial y}{\partial r} \right] - f(C, y) \]  
[3.1b]

where \( v_z \) is the axial fluid velocity

- \( r \) is the radial coordinate
- \( z \) is the axial coordinate (distance from the capillary entrance)
- \( D_{O2} \) is the oxygen diffusivity
- \( D_{HbO2} \) is the oxyhemoglobin diffusivity
- \( C_H \) is the hemoglobin concentration in the solution
- \( C \) is the concentration of free oxygen in the Hb solution
- \( y \) is the fraction saturation of oxyhemoglobin molecules, the concentration of oxyhemoglobin divided by \( C_H \) (which includes both oxy and deoxyhemoglobin)

The dedimensionalized form of the equations is shown in the appendix, section A.3.1.
3.1.2 Boundary and initial conditions

The boundary conditions for the equations 3.1 a and b are

At \( r=0 \)

\[ \frac{\partial C}{\partial r} = 0 \quad [3.2] \]
\[ \frac{\partial y}{\partial r} = 0 \quad [3.3] \]

At \( r=r_c \)

\[ -D_{\text{HbO}_2} \frac{\partial y}{\partial r} = 0 \quad [3.4] \]
\[ -D_{\text{O}_2} \frac{\partial C}{\partial r} = \frac{\beta \left( C_{r=r_c} - \beta P_{\text{ext}} \right)}{r_c \ln \left( \frac{4a}{\pi r_c} \right)} \quad [3.5] \]

(This boundary condition is explained further in 3.1.4)

At \( z=0 \)

\[ C=C_{\text{in}} = \beta P_{\text{in}} \quad [3.6] \]
\[ y=f_{\text{eq}}(P_{\text{in}}) \quad [3.7] \]

where \( P_{\text{in}} \) is the inlet oxygen tension

\( K \) is the permeability of the Silicone rubber film

\( P_{\text{ext}} \) is the oxygen tension in the gas space surrounding the silicone rubber film

\( a \) is the half thickness of the silicone rubber film

\( f_{\text{eq}}(P) \) is oxygen saturation as a function of the oxygen tension at chemical equilibrium
3.1.3 Velocity distributions

The hemoglobin solution is approximately Newtonian and in the range of interest the flow is laminar. Hence, as described by Bird et al (11), the velocity distribution is parabolic:

\[ v_z(r) = \frac{20}{\pi r_c^2} \left[ 1 - \left( \frac{r}{r_c} \right)^2 \right] \]  \[\text{[3.8]}\]

where \( Q \) is the volumetric flow rate
\( r_c \) is the radius of the capillary

This expression for velocity is substituted into equations 3.1a,b.

3.1.4 Oxygen diffusion through the capillary walls

The mass balance for oxygen in the silicone rubber film is Laplace's equation.

\[ \nabla^2 C = 0 \]

The asymptotic solution to this equation is given by Balerzak and Raynor (6), for a circular inner boundary to all portions of an infinitely wide rectangular strip of half
thickness, a (Fig 2.3). From the solution, the flux at the circular inner boundary is obtained

$$\text{Flux} = \frac{K(P_r - P_{\text{ext}})}{r_c \ln \left( \frac{4a}{\pi r_c} \right)}$$

[3.9]

where $P_r$ is the oxygen tension at the inner circular boundary

$P_{\text{ext}}$ is the oxygen tension in the gas space surrounding the silicone film

Equation [3.9] is incorporated as a boundary condition at the capillary wall by applying the continuity of flux condition at the wall (Equation [3.5]).

The oxygen tension distributions in the capillary wall can be calculated from the integrated expression derived by Balcerzak and Raynor (6) (Fig 3.4a,b).
3.1.5 Kinetics and Equilibrium

3.1.5.1 Equilibrium -

The equilibrium curve between HbO₂ and O₂ is fitted by the Hill equation:

\[
y = \frac{\left[\frac{P}{P_{50}}\right]^n}{1 + \left[\frac{P}{P_{50}}\right]^n} \quad [3.10a]
\]

or

\[
y = \frac{\left[\frac{C}{K_H}\right]^n}{1 + \left[\frac{C}{K_H}\right]^n} \quad [3.10b]
\]

where \( n \) is the experimentally observed Hill coefficient

\( K_H \) the experimentally observed Hill equilibrium constant

\( P_{50} \) is the oxygen tension which would yield \( y = 0.5 \) at equilibrium

\( y \) is the fractional saturation as defined on pg 33

In most cases, oxygen equilibrium binding curves are measured directly for hemoglobin samples used in the capillary experiments, and \( n, K_H \) and \( P_{50} \) are determined by fitting the
results to the Hill equation (Table A.3.1). In the absence of equilibrium measurements, \( P_{50} \) and \( n \) values are taken from the data of Imai and Yonetani (67,68)

3.1.5.2 Kinetics -

Yap and Hellums (120) have shown that it is justifiable to use the simple one-step variable rate coefficient kinetic model, over the more complete Adair reaction scheme, to describe the reaction between \( O_2 \) and hemoglobin. For the purpose of this work the one-step model is used. Each hemoglobin molecule is made up of 4 heme molecules. In the one-step model each heme group is treated as if they were all the same and the reaction is represented as:

\[
\text{Hb} + O_2 \rightarrow \text{HbO}_2
\]

The rate of reaction is expressed as a rate of formation of oxygen per unit volume and given by:

\[
\text{Rate} = C_H f(C,y) = C_H (ky - k'(1-y)C) \tag{3.11}
\]

where \( k \) is the dissociation rate constant

\( k' \) is the association rate constant

One of the early one-step variable rate coefficient methods was developed by Moll (89). This method as modified by
Vandegriff and Olson (117) was used to simulate cooperative $O_2$ binding to hemoglobin. The association rate constant, $k'$, is assumed to be invariant with fractional saturation, whereas between $0.1 \leq y \leq 0.9$ the dissociation rate constant, $k$, for hemoglobin in a given volume element is given by:

$$k = k'(\beta P_{50'}) \left[ \frac{y}{(1-y)} \right]^{\frac{1}{n}-1} \quad [3.12a]$$

$$k = k'K_H^{1/n} \left[ \frac{y}{(1-y)} \right]^{\frac{1}{n}-1} \quad [3.12b]$$

where $\beta$ is the Bunsen solubility coefficient for $O_2$.

Equation [3.12b] is just an alternate form of [3.12a]. The values of $k$ at $y \leq 0.1$ and $y \geq 0.9$ are fixed at those computed for 10 percent and 90 percent saturation (117).

Clark et al (23) used a constant dissociation rate and varied the association rate.

$$k' = \left[ \frac{k}{[C]} \right] \left[ \frac{P}{P_{50}} \right]^n \quad [3.13]$$

where $k'$ is the association rate constant and $k$ is the dissociation rate constant whose value is 44 sec$^{-1}$.

Equations [3.11], and [3.13] are used as an alternate to
equations [3.11] and [3.12] for reaction kinetic expressions in the simulations. The results using the two kinetic expressions are then compared. When [3.12] is used it has to be divided into three regions. Hence, computationally [3.13] is more convenient.

3.1.6 Calculations

In this work, equations [3.1] - [3.7] are solved using the finite element method given by Madsen and Sincovec (85). The application of this method to this problem has been studied in detail by Baxley (7). The method gives concentration distributions as a function of r and z. Then fractional degree of saturation of the hemoglobin molecules at each axial position can be computed as a space average.

\[ \langle y \rangle = \frac{1}{\pi r_c^2} \int_0^{r_c} 2\pi r y dr \]  \hspace{1cm} [3.14]

The results are then compared with the experimental observations.
3.1.7 Summary of parameters

The various parameters that appear in the model can be placed into two categories:

A) Parameters from literature
   a) Physical properties: $D_{O2}$, $\beta$, $D_{HbO2}$
   b) Kinetic parameters: $k$, $k'$

B) Experimentally determined parameters
   a) Fixed parameters: $a$, $r_c$, $K$
   b) Experimentally varied parameters: $C_H$, $P_{50}$, $Q$, $P_{ext}$, $P_{in}$

3.2 Results

Each data point in Fig 3.1 - 3.7 represents the mean of 2 to 8 replicate observations. A standard deviation is calculated for each mean. The error bars in Fig 3.1 and 3.2 represent the standard deviations in fraction saturation. An average standard deviation ($\sigma_{data}$) is then calculated for each set of experimental conditions by taking the mean standard deviations of all the measured data points (i.e. all the axial positions). The lines in Figs 3.3-3.7 represent the theoretical calculations from the model; no parameters were fit to data. The root mean square deviation between measured data and the theoretical points ($\sigma_{rms}$) is calculated for each set of curves and is presented, along
with $\sigma_{\text{data}}$ in the figure legends. The value of $\sigma_{\text{data}}$ ranges from 0.01 to 0.06 fractional saturation and $\sigma_{\text{rms}}$ varies from 0.04 to 0.08 fractional saturation. Error bars are omitted in Figs 3.3-3.7 for clarity since multiple experimental and theoretical curves are presented in most of the figures. The correspondence in Fig 3.1-3.7 between the observed dependence of $y$ on axial position and that computed theoretically for O$_2$ uptake and release is good. Fractional O$_2$ saturation as a function of axial position is shown in Fig 3.1 for typical uptake and release experiments with free Hb solutions. Oxygenation occurs more rapidly than deoxygenation. The key parameter is the residence time of the solution element being examined. This time is determined by the bulk axial flow rate and the distance from the entrance to the capillary. For example, in the uptake result shown in Fig 3.1 the residence time required for 50 percent saturation of the hemoglobin solution is roughly 0.05 s, which corresponds to an axial position of about 0.5 mm downstream from the entrance at a velocity of 11.2 mm/sec. For release, the residence time for 50 percent deoxygenation is roughly 1 sec.
Fig.3.1: Typical oxygen release and uptake results for Hb solutions flowing in a 27 μm artificial capillary. Data points, means ± SD for 8 replicate experiments at 37°C, pH 7.4 with a 1.0mM hemoglobin solution used in perfusion. Parameters denote flow rate. Solid curves, theoretical simulation of experimental data.
Fig. 3.2a: Graph showing effect of flow rate on oxygen release for a hemoglobin solution having same characteristics as that of Fig 3.1. Flow rates are given, and solid lines represent theoretical simulation of experimental data.
Fig. 3.2b: Graph showing effect of flow rate on oxygen uptake for a hemoglobin solution having same characteristics as that of Fig 3.1. Flow rates are given, and solid lines represent theoretical simulation of experimental data.
Fig. 3.3: Dependence of O₂ uptake on O₂ tension. Symbols, experimental data (avg SD = 0.03) taken at varying O₂ tensions in the capillary gas space using 2 mM heme, pH 7.4, at a flow rate of 42 μl/hr in capillary 41. Triangles, 21% O₂; squares, 10% O₂; circles, 5% O₂ and diamonds, 2% O₂. Solid lines, theoretical uptake curves calculated for each O₂ tension (rms difference = 0.05).
Fig.3.4a: Dependence of O₂ release on heme concentration. Symbols, experimental data (avg SD = 0.04) for hemoglobin at pH 7.4 and flow rate of 3 μl/hr at heme concentrations of 2.3 mM (squares) and 4.6 mM (circles). Solid lines, corresponding theoretical release curves calculated for each heme concentration (rms difference = 0.06). The inlet O₂ tension was 159 mmHg. Capillary used # 24.
Fig. 3.4b: Dependence of O₂ uptake on heme concentration. Symbols, experimental data (avg SD = 0.02) for hemoglobin. Curves, theoretical simulations (rms difference = 0.08) at pH 7.4 and flow rate of 42 µl/hr at heme concentrations of 1 mM (triangles and dashed lines), 2 mM heme (circles and solid lines) and 3 mM heme (squares and dashed-dotted lines). The oxygen tension of the gas space surrounding the Silicone rubber film \( P_{\text{ext}} \) was 159 mmHg. Capillary used #41.
Fig. 3.5a: Dependence of $O_2$ release on $P_{50}$ (pH). Symbols, experimental data (avg SD = 0.03) and curves, theoretical simulations (rms difference = 0.04), at pH 6.6 (squares and dashed-dotted lines), pH 7.4 (circles and solid lines), pH 8.2 (triangles and dashed lines). Heme concentration is 2 mM, inlet oxygen tension is 760 mmHg and flow rate is 10μl/hr. Capillary used #24.
Fig. 3.5b: Dependence of $O_2$ uptake on $P_{50}$ (pH).
Symbols, experimental data (avg SD = 0.02) and curves, theoretical simulations (rms difference = 0.04), at pH 6.6 (squares and dashed-dotted lines), pH 7.4 (circles and solid lines), pH 8.2 (triangles and dashed lines). Heme concentration is 2 mM, the oxygen tension in the gas surrounding the Silicone rubber film is 159 mmHg, and the flow rate is 42 µl/hr. Capillary used #37.
Fig. 3.6a: Dependence of $O_2$ release on $P_{50}$ ($IP_6$). Symbols, experimental data (avg SD = 0.03) and curves, theoretical simulations (rms difference = 0.07), with $IP_6$ (squares and dashed-dotted lines), without $IP_6$ (circles and solid lines). The flow rate is 10 $\mu$l/hr. Heme concentration is 2 mM and inlet oxygen tension is 760 mmHg. Capillary used #45.
Fig. 3.6b: Dependence of $O_2$ uptake on $P_{50}$ (IP$_6$).
Symbols, experimental data (avg SD = 0.01) and curves, theoretical simulations (rms difference = 0.06), with IP$_6$ (squares and dashed-dotted lines), without IP$_6$ (circles and solid lines). The flow rate is 42 $\mu$I/hr. Heme concentration is 2 mM and the oxygen tension in the gas space surrounding the Silicone rubber film is 159 mmHg. Capillary used #37.
Fig.3.7a: Dependence of O₂ release on temperature
Symbols, experimental data (avg SD = 0.06) and curves, theoretical simulations (rms difference = 0.08), at 25°C (circles and solid lines), 37°C (squares and dashed lines). The flow rate is 6μl/hr, pH is 7.4, heme concentration is 5 mM, and inlet oxygen tension is 159 mmHg. Capillary used #41.
Fig.3.7b: Dependence of $O_2$ uptake on temperature
Symbols, experimental data (avg SD = 0.04) and curves, theoretical simulations (rms difference = 0.05), at 25°C (circles and solid lines), 37°C (squares and dashed lines). The flow rate is 23 μl/hr, pH is 7.4, heme concentration is 4 mM, and oxygen tension in the gas space surrounding the capillary is 159 mmHg. Capillary used #45.
3.2.1 Effect of the experimentally varied parameters

3.2.1.1 Effect of $Q$, $P_{ext}$, $P_{in}$, $C_H$, $P_{50}$ -

The effect of varying the flow conditions at 37 °C is shown in Fig 3.2a,b for both uptake and release. Increasing the rate of flow reduces the residence time in both cases and causes less fractional oxygenation or deoxygenation at a fixed axial position.

The observed rate of oxygen uptake is roughly proportional to the oxygen tension in the gas space surrounding the capillary walls (Fig 3.3). At the oxygen tension in air (160 mmHg) the transport process is very rapid. Over 50 percent of the hemoglobin molecules are saturated at an axial position 0.5 mm from the entrance of the capillary (Figs 3.3b, 3.4b, 3.5b).

The extent and rate of $O_2$ release exhibits little dependence on the initial oxygen tension of the hemoglobin solution which is entering the capillary as long as 100 percent saturation of the heme groups is maintained prior to deoxygenation. When the Hemoglobin samples are preequilibrated with 1 atm of $O_2$, both the observed and calculated curves show an initial lag in the change in $y$ with axial position (Figs 3.5a and 3.6a) whereas no lag is observed for air equilibrated samples (Fig 3.4a and 3.7).

As shown in Fig 3.4, axial distribution curves for
oxygenation and deoxygenation appear to depend markedly on
the total heme concentration of the capillary fluid. At
higher hemoglobin concentrations the sample must flow
further down the tube to reach the same fractional degree of
saturation as that observed at lower concentrations.

The equilibrium parameter \( P_{50} \) can be changed by changing
the \( \text{pH} \) or by addition of an organic phosphate like
inositol hexaphosphate. None of the other parameters are changed.
The equilibrium parameters exert a marked influence on the
\( \text{O}_2 \) release process (Figs 3.5a, 3.6a). In contrast to the
situation for release, the rate of oxygenation is roughly
independent of the equilibrium parameters for \( \text{O}_2 \) binding
(Figs 3.5b, 3.6b). The \( P_{50} \) values for solutions having a \( \text{pH} \)
of 8.2, 7.4 and 6.6, are 2, 5 and 12 mmHg respectively.
When inositol hexaphosphate is added to Hb solutions at \( \text{pH} \)
7.4, it causes the \( P_{50} \) to rise from 5-7 mmHg to 30-40 mmHg.

3.2.1.2 Effect of temperature -

The temperature affects some of the parameters listed in
3.1.7 as discussed in 3.2. The effects of temperature are
shown in Fig 3.7. There is an increased rate of deoxygena-
tion at the higher temperature (Fig 3.7a). The uptake
curves change very little with increasing temperature (Fig
3.7b).
3.2.2 Effect of the kinetic constants

The relative importance of the exact chemical reaction rate constants was also examined by increasing the absolute values of \( k' \) and \( k \) while maintaining the same equilibrium ratio. This had little effect on the theoretical curves for either uptake or release. Only when the absolute values of these rate constants were decreased by \( \Delta \) 4-fold did significant changes in the saturation distributions occur.

3.2.3 Oxygen tension profiles

Oxygen tension profiles through the silicone rubber film and within the artificial capillary are shown in Figs 3.8 a and b. These distributions are calculated at axial positions which yield either 50 percent oxygenation (\( \sim 1 \text{ mm from the entrance} \)) or deoxygenation (2-5 mm depending on pH) of the hemoglobin solution.

As shown in Fig 3.8, the \( O_2 \) gradients, both in the silicone wall and within the capillary itself, are roughly 10 times greater in uptake experiments than in release measurements.
Fig. 3.8a: Calculated radial oxygen tension profiles at 50% oxyhemoglobin saturation for release. Solid lines, oxygen tension profiles for pH 6.6 and 7.4 as indicated. Zero position on abscissa denotes capillary center. Short-dashed lines, capillary wall and long-dashed lines, outer wall of the silicone rubber slab.
Fig.3.8b: Calculated radial oxygen tension profiles at 50% oxyhemoglobin saturation for uptake. Solid lines, oxygen tension profiles for pH 6.6 and 7.4 as indicated. Zero position on abscissa denotes capillary center. Short-dashed lines, capillary wall and long-dashed lines, outer wall of the silicone rubber slab.
3.3 Discussion

Since all the parameters in the mathematical model are determined independently, the correspondence between the observed and calculated saturation curves in Figs 3.1-3.7 serves to validate both the mathematical model and the experimental system. This validation of the experimental system for transport in Hb solutions is especially significant for two reasons:

a) The experimental method is complex and unique and

b) The validation lends credence to measurements for red cell suspensions where such mathematical validation is not possible.

The absolute value of the oxygen concentration gradient between the capillary gas space and the lumen is roughly 20 times larger for uptake than for release (Fig 3.8 a,b). In both situations, the same total capacity for transport exists and is given by the heme concentration of the protein solution. However, the velocity of uptake is determined by a total oxygen gradient of \( \approx 2 \) mmHg/\( \mu \)m whereas the velocity of release is determined by a maximum gradient of \( \approx -0.2 \) mmHg/\( \mu \)m. Hence, oxygenation is faster than deoxygenation.

The large gradients which occur in the uptake experiments are determined almost exclusively by the external \( O_2 \) tension in the gas space surrounding the capillary bed. The exact \( O_2 \) tension in the capillary is very small and almost
negligible (Fig 3.8 b). The opposite situation occurs for release experiments: the internal capillary oxygen tension is the key factor controlling the rate of $O_2$ transport into the external gas spaces (Fig 3.8 a).

The oxygen tension profiles in Fig 3.8 also provide visual and quantitative estimates of the relative resistances in the fluid phase and the silicone walls. For both uptake and release, substantial gradients occur both in the lumen and in the silicone film and indicate roughly equal contributions to the overall resistance to mass transport by the capillary system.

Most of the oxygen present in the solution is bound to hemoglobin. For solutions equilibrated with air, the initial free oxygen concentration is 0.25 mM whereas the total heme concentration is in most cases 2-4 mM. Thus, even though there is a very rapid drop in the free concentration of $O_2$ as the hemoglobin solution enters the capillary, bulk transport does not occur until the $O_2$ tension has dropped to 20-10 mmHg and bound $O_2$ begins to be released from the protein. This drop in free $O_2$ concentration occurs quickly since the initial gradient, -2 mmHg/μm, is very large compared to that which occurs for the net removal of $O_2$ from the Hemoglobin molecules at 50 percent saturation, -0.2 mmHg/μm (Fig 3.8b). The lag represents the time required
for the free oxygen concentration to drop from 760 mmHg to the level where oxygen dissociates from hemoglobin.

The effect of Hb concentration suggests strongly that O₂ exchange in the capillary is limited by diffusional processes and not chemical reaction with the protein molecules. If chemical reaction were limiting, the half time or axial position for 50 percent change would be independent of the amount of protein in the solution since the probability of exchange would be proportional to the hemoglobin concentration (i.e., k'[C]_{H}(1-y)C or C_{H}y). At high protein concentrations, it takes longer for complete exchange since more O₂ molecules must be transported, and this is what is observed experimentally and predicted by the model (Fig 3.4). This is also illustrated by the fact that an increase in the kinetic constants have no effect on the theoretical curves for uptake or release.

Since the external oxygen tension determines the gradients and hence the flux into the capillary for uptake, the uptake rates are found to be approximately proportional to the external oxygen tensions as seen in Fig 3.3. The bulk of the oxygen that is stored in blood in the form of bound oxygen is taken up at oxygen tensions in the 10-20 mmHg range. Hence, if the external oxygen tension is ~150 mmHg, when the bulk of the uptake occurs, the internal oxygen tension has little effect on the total gradient.
across the silicone rubber film. This gradient determines the flux and hence a change in \( P_{50} \) has little effect on the uptake curves. However, in the case of release the internal oxygen tension determines the flux. Hence, changes in \( P_{50} \) drastically change the rate of deoxygenation.

Although increasing the temperature of the capillary system causes an increase in \( O_2 \) diffusivity in both the silicone bed and in the aqueous phase, there is an almost compensating decrease in the solubility of gas in both media. The net result is that the overall permeability is only increased by about 15 percent. The largest effect is a roughly 3-fold increase in the \( P_{50} \) for \( O_2 \) binding to hemoglobin in going from 25°C (about 6 mmHg) to 37°C (about 15 mmHg). Hence the temperature effect is similar to the \( P_{50} \) effect.

There is no difference in the results obtained by using the two different kinetic models in 3.2.5. As long as the kinetic expression reduces to the equilibrium expression at zero net reaction rate (109), the kinetic expression used has a negligible effect on the results. Hence, the kinetic model as suggested by Clark et al (23) is used for the other models for convenience of calculations.

Some of the basic conclusions derived from the studies of \( O_2 \) transport by homogeneous hemoglobin solutions also apply to the more physiological situations with red cell
suspensions. The major differences involve quantitation of the absolute rates of transport and the relative importance of the resistances exerted by the capillary wall and the fluid within the lumen.

Some of the basic conclusions drawn from this work can be applied to explain certain physiologically observed facts.

a) Since the absolute gradients for uptake are roughly ten times greater than those observed for release, much longer transit times are required for complete deoxygenation, and this explains the need for longer capillaries in aerobic muscle tissues (61).

b) The decrease in blood pH and elevation in temperature produced by heavy exercise enhances both the rate and extent of deoxygenation in the microcirculation (Figs 3.5a and 3.7a), whereas these changes in pH and temperature exert little or no effect on the rate of \( O_2 \) uptake in alveolar capillaries (Fig 3.5b). As a result, the overall efficiency of the \( O_2 \) transport from lungs to respiring tissues is enhanced.

c) Long range adaptation to high altitudes or continuous exercise by elevation of intracellular 2,3-DPG levels produces similar effects. The rate of deoxygenation is enhanced significantly with little or no effect on the already rapid rate of \( O_2 \) uptake (i.e., Fig 3.6).
CHAPTER 4

LARGE CAPILLARY OXYGEN TRANSPORT

4.1 Mathematical model

4.1.1 Physical problem and outline of approach

The flow of rbc's through large capillaries is more complex than the single file flow in the small capillaries of the microcirculation. The red cells more or less retain their disc shape in the large capillaries. The overall flow profile has been observed to be parabolic with a slight blunting at the center (96). Due to the shear field, the red cells tend to rotate and move away from the wall resulting in a relatively cell free layer close to the wall (8,12,18,40,48,58,116). Also this leads to a radial distribution of hematocrit with a higher hematocrit at the center and lower near the walls (18,40,49).

In the release of O2 from the suspension, O2 undergoes a dissociation reaction with Hb. It diffuses through the medium within the rbc, through the rbc membrane and passes through the surrounding plasma by convection and diffusion before leaving the capillary and diffusing through the silicone rubber medium in our system or through the tissue.
Figure 4.1: Schematic of the flow of rbc's in large capillaries. "A" shows the rbc and plasma velocity profiles and the hematocrit profile. "B" shows the basis for the calculation of the cell-free layer thickness.
in vivo. In case of uptake, the same process occurs in the reverse order (Fig 4.1). Our approach is to develop a mathematical model including the flow characteristics and the various diffusion steps, to simulate the experiment.

4.1.2 Cell free layer

As the cells flow through the capillary, there is a tendency for the cells to move away from the walls and concentrate to some degree in the core of the tube. The effect of this is to create a layer of suspending fluid very close to the tube wall that is depleted of cells—the cell free layer. This layer is not entirely free of cells, for the high core concentration and the agitated nature of the flow tend to push cells into this region, where they collide with the wall.

However even in the absence of flow, a cell free layer is formed for purely geometric reasons. The center of an rbc cannot go closer than half its smallest dimension, to the wall.

In flowing blood, the thickness of the cell free layer depends upon both flow rate and cell to tube radius ratio. In this work the cell free layer is taken as that due to geometric considerations alone. The effect of cell migration due to flow is included by the lower hematocrit close to the cell free layer, taken into account by the
hematocrit profile. Hence, the thickness of the cell free layer is (Fig 4.1)

\[ \delta = r_c + t_{rbc} - \sqrt{r_c^2 - r_{rbc}^2} \tag{4.1} \]

It should be noted that if \( r_c \gg r_{rbc} \), \( \delta \approx (t_{rbc})_{\text{max}} \).

where \( \delta \) is the cell free layer thickness

- \( r_c \) is the radius of the capillary
- \( r_{rbc} \) is the radius of the rbc disc
- \( t_{rbc} \) is the maximum half thickness of the rbc disc

4.1.3 Hematocrit profile

Due to the shear field the cells in the capillary tend to move away from the wall and migrate to the center (18,40,49). Thus there is a higher concentration of rbcs at the center than close to the wall. From observations of hematocrit profiles (18,49) it has been found that the radial hematocrit distribution can be expressed as

\[ h(r) = h_m \left[ 1 - \left( \frac{r}{r_r} \right)^{m} \right] \quad 0 \leq r \leq r_r \tag{4.2a} \]

\[ h(r) = 0 \quad r_r \leq r \leq r_c \tag{4.2b} \]
\[(h_m \geq 0, m \geq 0)\]

where \( r \) is the radial coordinate

\( h(r) \) is the hematocrit, the volume fraction rbc's at any radius \( r \)

\( r_r \) is the radius of the cell rich region

\( r_c \) is the radius of the capillary

\( h_m, m \) are constants

The distribution is similar in form to that suggested by Lih (40) (Fig 4.1). The difference is that the distribution is for the cell rich region. The cell free region as calculated in 4.3.2 is excluded. The parameters \( h_m \) and \( m \) have to be determined.

4.1.4 Velocity profiles

A different velocity profile is considered for the plasma and the rbc (Fig 4.1). The shape of both profiles are the same but differ by a constant - the slip. Both profiles are parabolic with a slight blunting in the center. The blunting is taken into account by a blunting factor (96).

\[ v'_{pl}(r) = A \left[ 1 - \left( \frac{r}{r_c} \right)^2 \right] \quad r_r \leq r \leq r_c \]  [4.3a]
\[ v_{pl}(r) = D \left[ 1 - B \left( \frac{r}{r_C} \right)^2 \right], \quad 0 \leq r \leq r_r \]  \[4.3b\]

\[ v_{rbc}(r) = D(1-slp) \left[ 1 - B \left( \frac{r}{r_C} \right)^2 \right], \quad 0 \leq r \leq r_c \]  \[4.3c\]

(\(0 \leq B \leq 1\)) and (\(0 \leq slp \leq 1\))

where \(B\) is the blunting factor based on Pittman's work (96)

\(A, D\) are constants to be determined as shown in 4.3.6

\(v_{pl}'\) is the plasma velocity at radius \(r\) in the cell

free region

\(v_{pl}(r)\) is the plasma velocity at radius \(r\) in the cell

rich region

\(slp\) is a "slip" constant based on Sinha's work (110)

\(v_{rbc}\) is the rbc velocity at radius \(r\) in the cell rich

region

The term "slip" is a misnomer. It is not a true slip in

that there is no slip between the plasma and the rbc. It is

the difference in velocity of the suspending fluid and the

particle at a particular point due to the finite size of the

particle. The velocity of a particle centered at a point is

less than the velocity the suspending fluid at that point,

would have had in the absence of the particle. The slip
term has been calculated for a single particle by Sinha (110). The slip is a function of the particle position and hematocrit. But for the sake of simplicity a constant slip has been assumed, and the sensitivity of the results to this assumption is checked.

The parameters $A$ and $D$ are determined as shown in section 4.1.6.

4.1.5 Tube hematocrit

The tube hematocrit is the space average hematocrit at any cross section in the tube. This is the hematocrit observed in most in situ spectrophotometric methods of hematocrit measurements (44,82). It is less than the mixed mean hematocrit. The different averages result from different weight being given to the radial distribution of the hematocrit and the velocity profile. Since there is a higher concentration of red cells at the center of the tube than at the wall, and the flow is faster at the center, the rbc move with a higher average velocity than the plasma. Hence, to have a balance of rbc mass, at any cross section at any fixed time, the volume fraction of rbc or tube hematocrit will be less than that in the feed. However, a disproportionately larger number of rbc compared to plasma, pass the cross section per sec, (due to the higher avg rbc velocity). Therefore in spite of the lower tube hematocrit, the volume
fraction of rbc's passing will be the same as the feed hematocrit. Mathematically,

\[ H_T = \frac{1}{\pi r_c^2} \int_0^{r_c} 2\pi r h(r) dr \quad [4.4] \]

\[ H_F = \frac{1}{\pi r_c^2 \langle v \rangle} \int_0^{r_c} 2\pi r h(r) v_{rbc}(r) dr \quad [4.5] \]

where \( H_T \) is the tube hematocrit
\( H_F \) is the feed hematocrit
\( \langle v \rangle \) is the average velocity as defined in [4.53]

This decrease in hematocrit in the tube from that in the feed is known as the Fahraeus effect. Gahtgens et al (45) have found from experiments, the tube hematocrit as a function of the feed hematocrit, tube diameter and flow rate. The values of the tube hematocrits used in this work for a given feed hematocrit, flow rate and tube diameter are obtained from Gahtgens et al (45). That work also gives a comparison with values of the tube hematocrit to those obtained by other workers.
4.1.6 Determination of profile parameters

The parameters $A, D, h_m$ and $m$ are obtained by simultaneous solution of the following equations.

Continuity of the plasma velocity profile

$$v'_p(l, r) = v_p(l, r) \quad [4.6]$$

Overall rbc mass balance

$$Q_{H_T} = \int_{0}^{r_c} 2\pi r v_{rbc}(r) h(r) dr \quad [4.7]$$

Overall plasma mass balance

$$Q(1-H_T) = \int_{0}^{r_c} 2\pi r v_p l(r)(1-h(r))dr + \int_{r_c}^{r} 2\pi r v'_p l(r) dr \quad [4.8]$$

Definition of tube hematocrit

$$H_T = \frac{1}{\pi r_c^2} \int_{0}^{r_c} 2\pi r h(r) dr \quad [4.9]$$

where $Q$ is the flow rate of the rbc suspension

Simultaneous solution yields (Details are given in the appendix A.4.1)

$$h_m = \frac{H_m(m+2)}{mb^2} \quad [4.10]$$
\[ D = \frac{2\theta H_F \left[ 1 + \frac{(1-H_F)}{H_F} (1-\text{slp}) \right]}{\pi r_c^2 (1-\text{slp}) \left[ 1 + b^2 (1-B) \right]} \]  
[4.11a]

\[ A = \frac{D\left[ 1 - Bb^2 \right]}{1 - b^2} \]  
[4.11b]

\[ m = \frac{2(2\phi - 1)}{1 - \phi} \]  
[4.12]

where \( b = \frac{r_r}{r_c} \)

\[ \phi = \frac{2}{Bb^2} \left[ 1 - \frac{(1+b^2(1-B))}{2H_T \left[ 1 + \frac{(1-H_F)}{H_F} (1-\text{slp}) \right]} \right] \]

(0.5 < \phi < 1)

4.1.7 Kinetics

The rate of reaction expressed as a rate of Oxygen formation per unit volume is given by the form of the VRC kinetic expression recommended by Clark (23) and described in 3.1.5.2 in equations [3.11] and [3.13].
4.1.8 Transport model

4.1.8.1 Mass balance equations -

The red cell suspension is considered as two phases: a red cell phase and a plasma phase. At any crosssection the plasma phase is continuous and the rbc phase is dispersed in it. In this model the geometric configuration of the rbc phase needs to be specified only for the purpose of estimation of the intracellular resistance to oxygen transport. As will be shown later this intracellular resistance is a very small fraction of the total resistance. Thus, it can be estimated with sufficient accuracy by treating the rbc phase geometry as being rectangular in cross section but constrained to have the surface to volume ratio appropriate for normal red blood cells.

By estimation of the various resistances in the plasma and in and around the rbc as described in section 4.1.11, it is found that most of the resistance lies in the plasma. Hence, it is important to consider the the radial variation of concentrations in the plasma, whereas within the rbc the concentrations can be averaged.

The mass transfer resistances within the rbc and in the plasma boundary layer close to the red cell wall are lumped into two mass transfer coefficients, $k_1$ and $k_2$. Transport due to bulk convection of the plasma and rbc, radial
diffusion in the plasma and reaction with Hb are taken into account.

Within the rbc there are three species. Hemoglobin (Hb), Oxyhemoglobin (HbO₂) and Oxygen (O₂). Since no Hb escapes from the rbc's the total heme content within the rbc remains constant. Therefore, [HbO₂] + [Hb] remains constant. Hence two independent mass balance equations can be written for O₂ transport within the rbc. The mass balance is written for an rbc at a radial position r and an axial position z in the capillary. The concentration C and the fraction saturation y are values averaged within the rbc, but varying with position of the rbc in the capillary. The rbc balance is written:

For oxygen
\[ \nu_{\text{rbc}}(r) \frac{\partial C}{\partial z} = - \text{flux} \left[ \frac{S}{V} \right]_{\text{rbc}} + C_H f(C,y) \] \[ \text{[4.13]} \]

For oxyhemoglobin
\[ \nu_{\text{rbc}}(r) \frac{\partial C_H^y}{\partial z} = - C_H f(C,y) \] \[ \text{[4.14]} \]

(since no Hb leaves the rbc there is no flux term in [4.14])

where \( C_H f(C,y) \) is the reaction rate as defined in Ch 3

\( C_H \) is the internal heme concentration in the rbc

\( C \) is the mean dissolved \( O_2 \) concentration in the rbc
y is the mean fraction $O_2$ saturation of the Hb molecules in the rbc

\[ \left[ \frac{S}{V} \right]_{rbc} \]

is the surface to volume ratio of the rbc

flux is the $O_2$ flux crossing the rbc wall

In the plasma there is only one species - dissolved oxygen. The mass balance for dissolved $O_2$ is written as:

\[
(1-h(r))v_{pl}(r) \frac{\partial C'}{\partial z} = \frac{D'_{O2}}{r} \frac{\partial}{\partial r} \left[ r \frac{\partial C'}{\partial r} \right] + \text{flux } h(r) \left[ \frac{S}{V} \right]_{rbc} \quad [4.15]
\]

(the $1-h(r)$ term appears since the basis is per unit volume of the plasma)

where $D'_{O2}$ is the diffusivity in the plasma

$C'$ is the dissolved $O_2$ concentration in the plasma

The plasma is divided into two regions - the rbc rich region and the cell free region. In the rbc free region, the flux term is zero and also $h(r)$ is zero. If the concentration in this region is denoted by $C''$, then the mass balance in the rbc free region reduces to

\[
v'_{pl}(r) \frac{\partial C''}{\partial z} = \frac{D'_{O2}}{r} \frac{\partial}{\partial r} \left[ r \frac{\partial C''}{\partial r} \right] \quad [4.16]
\]
The flux across the red cell may be written from the definition of the mass transfer coefficients:

\[
\text{flux} = k_1(C - C_{rw}) = k_2(C'_{rw} - C')
\]  \[4.17\]

where \(C_{rw}\) is the oxygen concentration at the red cell wall in the rbc
\(C'_{rw}\) is the oxygen concentration at the red cell wall in the plasma
\(k_1\) is the intracellular mass transfer coefficient
\(k_2\) is the extracellular mass transfer coefficient

Also, the oxygen tension is continuous at the rbc wall (since there is assumed to be no transport resistance at the rbc wall). Hence,

\[
\frac{C_{rw}}{\beta} = \frac{C'_{rw}}{\beta'}
\]  \[4.18\]

where \(\beta'\) is the Bunsen solubility coefficient in the plasma
\(\beta\) is the Bunsen solubility coefficient in the rbc

From [4.17] and [4.18], elimination of \(C_{rw}\) and \(C'_{rw}\) gives
flux = \frac{k_1k_2}{k_1 + k_2} (\frac{B'}{B}) (C - C') \quad [4.19]

Hence the mass balance equations can be written as

Mass balance for \(O_2\) within the rbc

\[ D(1-slp) \left[ 1 - B \left( \frac{r}{r_c} \right)^2 \right] \frac{\partial C}{\partial z} = C_Hf(C, y) \]

\[ - \frac{k_1k_2}{k_1 + k_2} \left( \frac{B'}{B} \right) \left[ \frac{S}{V} \right] rbc \left[ \frac{B'}{B} C - C' \right] \quad [4.20] \]

Mass balance for \(HbO_2\) within the rbc

\[ D(1-slp) \left[ 1 - B \left( \frac{r}{r_c} \right)^2 \right] \frac{\partial V}{\partial z} = - f(C, y) \quad [4.21] \]

In the plasma there is only one species - dissolved \(O_2\).

Mass balance for dissolved \(O_2\) in the cell rich region

\[ D \left[ 1 - B \left( \frac{r}{r_c} \right)^2 \right] \frac{\partial C'}{\partial z} = \frac{1}{(1-h(r))} \frac{D'_{O2}}{r} \frac{\partial}{\partial r} \left[ \frac{\partial C'}{\partial r} \right] \]

\[ + \frac{k_1k_2}{k_1 + k_2} \left( \frac{B'}{B} \right) \left[ \frac{S}{V} \right] rbc \left( \frac{h(r)}{(1-h(r))} \right) \left[ \frac{B'}{B} C - C' \right] \quad [4.22] \]

\[ 0 \leq r \leq r_r \]

Mass balance for dissolved oxygen in the cell free region
\[ A \left[ 1 - \left( \frac{r}{r_c} \right)^2 \right] \frac{\partial C''}{\partial z} = \frac{D'_0 2a}{r} \frac{\partial}{\partial r} \left[ r \frac{\partial C''}{\partial r} \right] \]  \hspace{1cm} [4.23]

\[ 0 \leq r \leq r_c \]

4.1.8.2 Boundary and initial conditions -

The fluxes and oxygen tensions are continuous at the rbc rich and rbc free region interface. Hence,

At \( r = r_r \)

\[ C' = C'' \]  \hspace{1cm} [4.24]

\[ -D'_0 \frac{\partial C'}{\partial r} = -D''_0 \frac{\partial C''}{\partial r} \]  \hspace{1cm} [4.25]

Using the symmetry condition at the center of the capillary,

At \( r = 0 \)

\[ \frac{\partial C'}{\partial r} = 0 \]  \hspace{1cm} [4.26]

The transport in the Silicone rubber phase is incorporated as a boundary condition at the capillary wall as shown in section 3.2.4.

At \( r = r_c \)
\[-D_0^2 \frac{\partial C''}{\partial r} = \frac{K}{\beta' r_c \ln\left(\frac{4a}{\pi r_c}\right)} (C'' - \beta' P_{ext}) \quad \text{[4.27]}\]

The initial conditions are given by:

At \( z = 0 \)

\[ C = \beta P_{in} \quad \text{[4.28]} \]
\[ C' = \beta' P_{in} \quad \text{[4.29]} \]
\[ C'' = \beta' P_{in} \quad \text{[4.30]} \]
\[ y = f_{eq}(P_{in}) \quad \text{[4.31]} \]

where \( f_{eq}(P) \) is the equilibrium expression for \( y \).

\( P_{in} \) is the inlet oxygen tension.

The dedimensionalized form of these equations is given in the Appendix A.4.2.

The equations [4.20]-[4.31] determine the oxygen transport variables \( C, C', C'', y \) for given values of the various parameters including \( k_1, k_2, r_c, P_{50}, n, C_H, H_F \) and \( Q \).

Methods of estimation of \( k_1 \) and \( k_2 \) are discussed below. The other parameters are measured independently or taken from the literature.
4.1.9 Mass transfer coefficients

4.1.9.1 The mass transfer coefficient within the rbc, $k_l$

The mass transfer coefficient within the rbc is obtained by solving the mass balance equations for oxygen transport within the rbc. In the large capillaries the rbcs are relatively undeformed (18). Since most of the surface area is the flat faces of the disc, most of the oxygen transport takes place through them. As an approximation the thin biconcave disc is treated as a one dimensional diffusion problem. The rbc is treated as being rectangular in cross section, but constrained to have the surface to volume ratio appropriate for normal red blood cells. Also as shall be seen later, the results are not sensitive to $k_l$. Hence, even an approximate estimate of $k_l$ would give accurate overall transport results. The transport equations within the rbc are written:

$$\frac{\partial C_r}{\partial t} = D_{O_2} \frac{\partial^2 C_r}{\partial x^2} + C_H f(C_r, y) \quad [4.32]$$

$$\frac{\partial y_r}{\partial t} = D_{HbO_2} \frac{\partial^2 y_r}{\partial x^2} - f(C_r, y) \quad [4.33]$$

Using the symmetry condition
At $x = 0$

$$\frac{\partial C_r}{\partial x} = 0 \quad [4.34]$$

$$\frac{\partial y_r}{\partial x} = 0 \quad [4.35]$$

For a prescribed $O_2$ flux at the rbc wall and no loss of Hb from the rbc,

At $x = x_r$

$$-D_{O2} \frac{\partial C_r}{\partial x} = \text{flux} \quad [4.36]$$

$$\frac{\partial y_r}{\partial x} = 0 \quad [4.37]$$

Initial conditions

At $t = 0$

$$C_r = C_{rin} \quad [4.38]$$

$$y_r = f_{eq}(C_{rin}) \quad [4.39]$$

where $C_{50} = \beta P_{50}$

$C_r$ is the dissolved oxygen concentration in the rbc

$y_r$ is the fraction $O_2$ saturation of Hb in the rbc

$t$ is the rbc retention time

$D_{O2}$ is the Oxygen diffusivity in the rbc
$D_{HbO2}$ is the oxyhemoglobin diffusivity in the rbc
$C_{in}$ is the inlet oxygen concentration
$x_r$ is the half thickness of the rbc

The equations are solved numerically using the finite element method given by Madsen and Sincovec (85). The mass transfer coefficient is then calculated as

$$k_1 = \frac{\text{flux}}{(\bar{C}_r - C_{rw})} \quad \text{[4.40]}$$

where $\bar{C}_r = \frac{1}{x_r} \int_0^{x_r} C_r \, dx$ is the avg. $O_2$ conc in the rbc

and $C_{rw} = C_r \bigg|_{x=x_r}$ is the $O_2$ conc at the rbc wall

4.1.9.2 Mass transfer coefficient in the plasma around the rbc, $k_2$ -

$k_2$ is obtained from Nusselt number correlations for mass transfer from discs to fluid flowing past it (87).

$$\frac{k_2 2x_r}{D_{O2}} = \frac{8}{\pi} + 0.6 \text{ Re}^{0.5} \text{ Sc}^{0.33} \quad \text{[4.41]}$$

where Re is the Reynolds number

Sc is the Schmidt number
The $8/\pi$ term is the asymptotic value of the Nusselt number for pure diffusion from the disc to a stationery medium around it. The $Re^{0.5}Sc^{0.33}$ term includes the effect of convection. Estimates of the cell Reynolds number and the Schmidt number indicate that the $8/\pi$ term in the equation [4.41] dominates.

4.1.10 Summary of model parameters

The various parameters that appear in the model can be distinguished into two types.

A) Parameters set from literature

a) Physical properties: $\beta', \beta, D_0', D_{02}'$

b) Rbc parameters: $[S]_{rbc}, C_H', k$

c) Flow parameters: $\delta, B, s1p, H_T$

d) Mass transfer coefficients: $k_1, k_2$

B) Experimentally determined parameters

a) System parameters: $a, r_c', K, P_{in}, P_{ext}, Q$

b) Sample parameters: $H_f, P_{50}, n$

The parameters $A, D, m, h_m$ are parameters calculated in
terms of the above parameters. The values of the parameters used in the simulations are given in the appendix A.4.6.

4.1.11 A highly simplified "Graetz" type model

As an approximation the resistance in the plasma may be lumped into a capillary wall resistance. The Graetz solution may be used to predict this resistance. For the values of the parameters of this work the Graetz solution predicts a constant Nusselt number of 4.0 (21). The resistances in and around the rbc are estimated from the mass transfer coefficients given in 4.1.9. Combining these resistances in series to get the overall resistance in blood and considering the reaction to be at equilibrium, the flux out of the system can be predicted for a given external and inlet oxygen tension. The results using this approximation are shown in 4.2 and discussed in 4.3.

4.1.12 Calculations

The equations [4.20]-[4.31] are solved numerically by finite element collocation using basis splines. The details of the method can be found in Baxley's thesis (7b).
4.1.12.1 Space average oxygen saturation -

The experiment measures the space average oxygen saturation of the Hb molecule at various axial positions along the capillary. From the numerical integration we get oxygen concentrations and saturations as functions of the radial and axial positions. The space average saturation is calculated as

\[ \langle y \rangle = \frac{1}{\pi r_c^2 H_T} \int_0^r c_2 \pi r h(r) y dr \] [4.42]

where \( \langle y \rangle \) is the space average fraction oxygen saturation. The simplification of this equation is given in A.4.3.

4.1.12.2 Overall Nusselt number for mass transfer -

The overall mass transfer Nusselt number for the capillary is calculated as

\[
Nu_o = \frac{k_o d c}{D_{O2}} = \frac{-\left[ \frac{\delta C''}{\delta r} \right]_{r=r_c} d c}{\left[ \frac{B'}{B} \langle C \rangle_{mmrbc} - C'' \right]}
\] [4.43]

where \( C'' \) \( r=r_c \) is the oxygen concentration at the capillary wall

\[ \langle C \rangle_{mmrbc} \] is the mixed mean oxygen concentration
in the rbc

\( \text{Nu}_0 \) is the Nusselt number in the capillary

\( k_o \) is the overall mass transfer coefficient in the capillary.

\( d_c \) is the capillary diameter (2\( r_c \))

The Nusselt number characterizes the resistance to oxygen transport. It is a dimensionless quantity inversely proportional to the resistance.

4.1.12.3 Mixed mean oxygen concentration in the rbc -

The mixed mean oxygen concentration is calculated as

\[
\langle C \rangle_{\text{mmrbc}} = \frac{1}{\pi r_c^2 H_c} \int_0^{r_c} 2\pi rh(r)v_{rbc}(r)C(r)dr 
\]

\[ [4.44a] \]

(Simplification in A.4.4)

\[
P_{\text{mmrbc}} = \frac{\langle C \rangle_{\text{mmrbc}}}{\beta} \]  \[ [4.44b] \]

\[
\langle v \rangle_{rbc} = \frac{1}{\pi r_c^2} \int_0^{r_c} 2\pi rv_{rbc}(r)dr = \frac{QH_F}{\pi r_c^2 H_c} 
\]

\[ [4.45] \]

where \( P_{\text{mmrbc}} \) is the mixed mean oxygen tension in the rbc.
\( \langle v \rangle_{\text{rbc}} \) is the average rbc velocity

4.1.12.4 Fractional resistances

The fractional resistances in the rbc, plasma and silicone rubber are calculated from the ratios of the oxygen tension difference at various points in the capillary.

\[
RS_{\text{rbc}}(r) = \frac{P_{\text{rbc}}(r) - P_{\text{rcw}}(r)}{P_{\text{rbc}}(r) - P_{\text{ext}}} \tag{4.46}
\]

\[
RS_{\text{pl}}(r) = \frac{P_{\text{rcw}}(r) - P_{\text{capw}}}{P_{\text{rbc}}(r) - P_{\text{ext}}} \tag{4.47}
\]

\[
RS'_{\text{rbc}} = \frac{1}{r_c} \int_{r_c}^{r} c_{S} RS_{\text{rbc}}(r) dr \tag{4.48}
\]

\[
RS'_{\text{pl}} = \frac{1}{r_c} \int_{r_c}^{r} c_{S} RS_{\text{pl}}(r) dr \tag{4.49}
\]

\[
RS'_{\text{si}} = 1 - RS'_{\text{rbc}} - RS'_{\text{pl}} \tag{4.50a}
\]

where \( RS_{\text{rbc}}(r) \) is the fractional resistance in the rbc at radius \( r \)

\( RS_{\text{pl}}(r) \) is the fractional resistance in the plasma at radius \( r \)
$P_{rbc}(r)$ is the oxygen tension in the rbc
$P_{rbcw}(r)$ is the oxygen tension at the rbc wall
$P_{capw}$ is the oxygen tension at the capillary wall
$RS'_{rbc}$ is the average fraction resistance in the rbc
$RS'_{pl}$ is the average fraction resistance in the plasma
$RS''_{Si}$ is the resistance in the Silicone rubber

The resistance in the silicone rubber calculated in the manner shown here takes a mean of the resistances at various radial positions. In order to directly compare with resistances calculated by Hellums (55) and Baxley (7), the resistance in the silicone rubber is also calculated using the oxygen tension in the rbc at the center of the capillary:

$$RS''_{Si} = \frac{P_{capw} - P_{ext}}{P_{rbc}(0) - P_{ext}} \quad [4.50b]$$

where $RS''_{Si}$ is the fraction resistance in the silicone rubber

$P_{rbc}(0)$ is the oxygen tension in the rbc at the center of the capillary
4.1.12.5 Simulation of data from capillary deoxygenator

The data obtained from Schmuckler and Shu Chien's hollow fiber deoxygenator is predicted using this model. To compare with their results (105), the mixed mean oxygen tension of blood at the capillary outlet is required. The mixed mean oxygen concentration in blood is calculated as

\[
\langle C' \rangle_{mm} = \frac{1}{\pi r_c^2} \left[ \int_0^{r_c} 2\pi r h(r) v_{rbc}(r) C(r) \, dr \right. \\
+ \left. \int_0^{r_c} 2\pi r (1 - h(r)) v_{pl}(r) C'(r) \, dr \right. \\
+ \left. \int_{r_c}^r 2\pi r v_{pl}(r) C''(r) \, dr \right] \\

\text{[4.51]}
\]

\[
P_{mm} = \frac{\langle C' \rangle_{mm}}{\beta'} \\
\text{[4.52]}
\]

(Simplifications in appendix A.3.5)

\[
\langle v \rangle = \frac{0}{\pi r_c^2} \\
\text{[4.53]}
\]

where \( \langle C' \rangle_{mm} \) is the average overall mixed mean oxygen concentration in the capillary

\( \langle v \rangle \) is the average velocity in the capillary
\( P_{mm} \) is the mixed mean oxygen tension

The permeability of the polypropylene fibers used in the deoxygenator is calculated from the data for hemoglobin solutions obtained from the same system. The calculated permeability is used in the simulation of the rbc suspension data.

4.2 Results

4.2.1 Comparison with experimental data

Figures 4.2 - 4.10 show the experimentally obtained data on fraction saturation of Hb and the fraction saturation saturation curve predicted by theory, for uptake and release of oxygen into and from the capillary. The parameters \( P_{50} \), hematocrit, and flow rate have been varied. It is observed that the theory predicts the experimental results closely. Figs 4.11 a,b compare the experimental results of O\(_2\) release from sickle and normal red blood cells from large capillaries. From the theory it is found that a difference in the \( P_{50} \) explains the difference in the observed release characteristics, between normal and sickle cells.
Fig. 4.2: Oxygen uptake results for red blood cell suspensions flowing at 23 μl/hr in a 27 μ artificial capillary. Data points, means ± S.D. for 8 replicate experiments at 37 °C, pH 7.4 with a 21% hematocrit suspension having a P_{50} of 20 mmHg used in perfusion. Solid curves, theoretical simulation of experiments.
Fig. 4.3: Oxygen release results for red blood cell suspensions flowing at 12 μl/hr in a 27 μ artificial capillary. Data points, means ± S.D. for 8 replicate experiments at 37 °C, pH 7.4 with a 21% hematocrit suspension having a P50 of 20 mmHg used in perfusion. Solid curves, theoretical simulation of experiments.
Fig. 4.4: Oxygen release results for red blood cell suspensions flowing at 6 μl/hr in a 27 μ artificial capillary. Data points, means ± S.D. for 8 replicate experiments at 37 °C, pH 7.3 with a 30 % hematocrit suspension having a P50 of 27 mmHg used in perfusion. Solid curves, theoretical simulation of experiments.
Fig. 4.5: Oxygen release results for red blood cell suspensions flowing at 12 μl/hr in a 27 μ artificial capillary. Data points, means ± S.D. for 8 replicate experiments at 37 °C, pH 7.3 with a 30% hematocrit suspension having a P50 of 27 mmHg used in perfusion. Solid curves, theoretical simulation of experiments.
Fig. 4.6: Oxygen uptake results for red blood cell suspensions flowing at 12 µl/hr in a 27 µ artificial capillary. Data points, means ± S.D. for 8 replicate experiments at 37 °C, pH 7.3 with a 30% hematocrit suspension having a P50 of 27 mmHg used in perfusion. Solid curves, theoretical simulation of experiments.
Fig. 4.7: Oxygen uptake results for red blood cell suspensions flowing at 23 μl/hr in a 27 μ artificial capillary. Data points, means ± S.D. for 8 replicate experiments at 37 °C, pH 7.3 with a 30% hematocrit suspension having a P_{50} of 27 mmHg used in perfusion. Solid curves, theoretical simulation of experiments.
Fig. 4.8: Oxygen release results for red blood cell suspensions flowing at 12 μl/hr in a 27 μ artificial capillary. Data points, means ± S.D. for 8 replicate experiments at 37 °C, pH 7.3 with a 20% hematocrit suspension having a $P_{50}$ of 25 mmHg used in perfusion. Solid curves, theoretical simulation of experiments.
Fig. 4.9: Oxygen uptake results for red blood cell suspensions flowing at 12 μl/hr in a 27 μ artificial capillary. Data points, means ± S.D. for 8 replicate experiments at 37 °C, pH 7.3 with a 22% hematocrit suspension having a P50 of 25 mmHg used in perfusion. Solid curves, theoretical simulation of experiments.
Fig. 4.10: Oxygen uptake results for red blood cell suspensions flowing at 23 μl/hr in a 27 μ artificial capillary. Data points, means ± S.D. for 8 replicate experiments at 37 °C, pH 7.3 with a 23% hematocrit suspension having a P₅₀ of 27 mmHg used in perfusion solid curves, theoretical simulation of experiments.
Fig 4.11: Comparison of oxygen saturation changes of normal and sickle cell suspensions flowing at the same rate in 27μm artificial capillary. In all cases, the pH was 7.36 and the temperature was 25°C. The points denote the means ± SD for 3 to 10 replicate experiments. The curves are theoretical simulations. Results are given for two flow rates: 9.4μl/hr (A), and 16.0μl/hr (B).
4.2.2 Comparison with deoxygenator data

Fig 4.12 compares the theoretically predicted values of the oxygen tension to the experimentally obtained data for rbc suspensions from the deoxygenator experiments of Schmukler and ShuChien (105). The model accurately predicts the data. The permeability obtained from the Hb solution calculations using the data in the same paper is $1 \times 10^{-11} \frac{M \cdot cm^2}{sec \cdot mmHg}$. The $P_{50}$ was taken to be 27 mmHg which is a typical value for a pH of 7.4 as used in the experiments. The wall thickness is taken to be 15 μ as estimated from the photomicrograph of the fiber in the paper. The solution is not very sensitive to it. Hence, an approximate value is all that is required.

4.2.3 Experimental comparison between rbc suspensions and Hb solutions

Comparison of the transport curves for $O_2$ release and uptake by rbc suspensions with those for homogeneous hemoglobin solutions are shown in Fig 4.13 a,b. In the case of uptake, the rate of oxygenation of the red blood cell sample was roughly 5 times smaller than that of an equivalent concentration of free hemoglobin flowing through the capillary at the same fluid velocity (fig 4.13b). The residence time required for 50 percent oxygenation of the Hb sample was
Fig. 4.12: Oxygen release results for red blood cell suspensions flowing in 100μ microporous polypropylene hollow fibers. Data points, mean of experiments from Schmukler and Shu Chien's paper (105). A wall thickness of 15 μ, a P50 of 27 mmHg, and a wall permeability of 1x10^-11 (M·cm²)/(sec·mmHg) was used in the simulation. Solid curves, theoretical simulation of experiments.
Fig. 4.13a: Comparison of oxygen release results for hemoglobin solutions with red cell suspensions of same hemoglobin content. Conditions are same as those of Fig 3.1. Circles, experimental results for hemoglobin solutions \([P_{50} = 13 \text{ mmHg}]:\) solid curves theoretical simulation curves for same conditions. Triangles and broken lines, experimental findings on red cell suspensions when \(P_{50} = 20 \text{ mmHg}.\) Dashed-dotted line, plot of theoretical curve for hemoglobin solution with a \(P_{50}\) of 20 mmHg.
Fig. 4.13b: Comparison of oxygen uptake results for hemoglobin solutions with red cell suspensions of same hemoglobin content. Conditions are same as those of Fig 3.1. Circles, experimental results for hemoglobin solutions \([P_{50} = 13 \text{ mmHg}]\); solid curves theoretical simulation curves for same conditions. Triangles and broken lines, experimental findings on red cell suspensions when \(P_{50} = 20 \text{ mmHg}\). Dashed-dotted line, plot of theoretical curve for hemoglobin solution with a \(P_{50}\) of 20 mmHg.
roughly 0.05 secs whereas that for 50 percent oxygenation of the cell suspension was approximately 0.25 secs.

In oxygen release experiments (Fig 4.13 a), the difference between the transport curves for rbc suspensions and that for free hemoglobin is much smaller than the difference observed between the corresponding curves for uptake (Fig 4.13 b). However, in the case of release experiments, direct comparison between the data for the cell suspension and the free hemoglobin is difficult due to the affinity differences. The cell suspension exhibited a $P_{50}$ of 20 mmHg compared to 13 mmHg for the Hb solution. As described in Ch 3, the rate of deoxygenation in the capillary is roughly proportional to the $P_{50}$ of the Hb sample. Consequently, the higher $P_{50}$ of the rbc suspension partly compensates for the extra resistance in the rbc suspensions. The dashed-dotted line represents a theoretical curve for a free Hb sample with a $P_{50}$ equal to that of the cell suspension. Thus, for release experiments, one should compare the experimental results for red cells (the triangles and upper, broken curve in Fig 4.13a) for a Hb solution exhibiting the same $P_{50}$ value. Results from similar calculations for uptake experiments are shown in Fig 4.13b (dash-dotted line). The $P_{50}$ value of the sample has a little effect on the oxygenation curve. Thus measurements of $O_2$ uptake allow a more direct
experimental evaluation of the extra resistance to transport caused by using cell suspensions.

4.2.4 Comparison of models

Figures 4.14 and 4.15 compare experimental data on release and uptake from rbc suspensions to the large capillary model and to other models used in the past. The large capillary model predicts the experimental data most accurately as compared to the other models. Of the other models the Artigue and Bruley model shows the closest fit. The models which totally neglect resistance in the capillary, the "Krogh" type model (97,101), deviate the most.

4.2.5 Effect of model parameters on O₂ transport

Figures marked "a" denote the effect of a parameter on release and those marked "b" denote the effect on uptake. In all these cases only the parameter shown is varied. All other parameters are kept constant unless mentioned.

Figs 4.16 - 4.18 show the effect of the variation of the sample parameters $H_F$, $P_{50}$ and $n$ on oxygen transport. Figs 4.19 - 4.24 show the effect of the system parameters $d_c$, $Q_a$, $K_a$, $P_{ext}$, $P_{in}$. When $d_c$ is changed the flowrate is also changed so as to keep the residence time of the rbc's in the
Fig. 4.14: Comparison of models for O$_2$ release for red blood cell suspensions flowing at 12 μl/hr in a 27μ artificial capillary. Data points, means ± S.D. for experiments at 37°C, with a 21 % hct suspension having a $P_{50}$ of 20 mmHg used in perfusion. Curves: (-----) Large capillary model, (----) Reneau model (------) Hemoglobin solution, (-----) Artigue model (-----) Krogh type model
Fig. 4.15: Comparison of models for O$_2$ uptake for red blood cell suspensions flowing at 12 $\mu$l/hr in a 27 $\mu$m artificial capillary. Data points, means $\pm$ S.D. for experiments at 37°C, with a 30% hct suspension having a $P_{50}$ of 27 mmHg used in perfusion. Curves:

(-----) Large capillary model, (-----) Reneau model
(-----) Hemoglobin solution, (-----) Artigue model
(-----) Krogh type model
capillary the same. Figs 4.25 - 4.28 show the effect of flow parameters $\delta$, slp, $E$, $\frac{H_m}{H_F}$. Figs 4.29 - 4.31 show the effect of the rbc parameters and physical properties $C_H$, $D'_{O2}$, $\beta'$. The behaviour of the curves in these figures is discussed in 4.5.

Variation of the reaction kinetic constant, 'k', was found to have a negligible effect. For example there is only a 1% change in the fraction saturation in the extreme case when "k" is decreased by an order of magnitude. Variation in $\frac{S}{V}_{rbc}$ also has a negligible effect. There is only a 2% change in the fraction saturation when $\frac{S}{V}_{rbc}$ changes from 1 to 3. This range of variation is many times that of the physiologically significant range. Similarly, variation in the mass transfer coefficients, $k_1$ and $k_2$, have negligible effects on the mass transfer from the rbc suspensions. Hence, the results of variations of these parameters are not reported here.

4.2.6 Nusselt number for mass transfer

The overall Nusselt number Nu, is plotted as a function of the space average fraction $O_2$ saturation $\langle y \rangle$, for release and uptake. The Nusselt number can be used to predict fluxes into and out of the capillary. The flux and the Nusselt number depend on the space average fraction
Fig. 4.16a: Effect of feed hematocrit on oxygen release from red blood cell suspensions with a $P_{50}$ of 27 mmHg flowing at 6 $\mu$l/hr in a 27 $\mu$m artificial capillary. Curves are theoretical simulations. Parameters shown are values of feed hematocrit. The tube hematocrits corresponding to these feed hematocrits are 17%, 21%, 25%, 29%, and 33%.
Fig. 4.16b: Effect of feed hematocrit on oxygen uptake by red blood cell suspensions with a $P_{50}$ of 27 mmHg flowing at 12 μl/hr in a 27 μm artificial capillary. Curves are theoretical simulations. Parameters shown are values of feed hematocrit. The tube hematocrits corresponding to these feed hematocrits are 17%, 21%, 25%, 29%, and 33%.
Fig. 4.17a: Effect of oxygen affinity as indicated by \( P_{50} \) on oxygen release from red blood cell suspensions with a feed hematocrit of 30% flowing at 6 \( \mu l/hr \) in a 27 \( \mu m \) artificial capillary. Curves are theoretical simulations. Parameters shown are values of \( P_{50} \) in mmHg.
Fig. 4.17b: Effect of oxygen affinity as indicated by $P_{50}$ on oxygen uptake by red blood cell suspensions with a feed hematocrit of 30% flowing at 12 μl/hr in a 27 μm artificial capillary. Curves are theoretical simulations. Parameters shown are values of $P_{50}$ in mmHg.
Fig. 4.18a: Effect of the Hill equation parameter, 'n', on oxygen release from red blood cell suspensions with a feed hematocrit of 30% and a $P_{50}$ of 27 mmHg flowing at 6 $\mu$L/hr in a 27 $\mu$m artificial capillary. Curves are theoretical simulations. Parameters shown are values of n.
Fig. 4.18b: Effect of the Hill equation parameter, 'n', on oxygen uptake by red blood cell suspensions with a feed hematocrit of 30% and a P50 of 27 mmHg flowing at 12 μl/hr in a 27 μm artificial capillary. Curves are theoretical simulations. Parameters shown are values of n.
Fig. 4.19a: Effect of capillary diameter, \( d_c \), on oxygen release from red blood cell suspensions with a feed hematocrit of 30% and a \( P_{50} \) of 27 mmHg, flowing with an average axial velocity of 0.3 cm/sec in artificial capillaries. Curves are theoretical simulations. Parameters shown are values of the capillary diameter in \( \mu m \).
Fig. 4.19b: Effect of capillary diameter, $d_c$, on oxygen uptake by red blood cell suspensions with a feed hematocrit of 30% and a $P_{50}$ of 27 mmHg, flowing with an average axial velocity of 0.6 cm/sec in artificial capillaries. Curves are theoretical simulations. Parameters shown are values of the capillary diameter in $\mu$m.
Fig. 4.20a: Effect of flow rate, $Q$, on oxygen release from red blood cell suspensions with a feed hematocrit of 30% and a $P_{50}$ of 27 mmHg flowing in a 27 μm artificial capillary. Curves are theoretical simulations. Parameters shown are values of the flow rate in μl/hr.
Fig. 4.20b: Effect of flow rate, $Q$, on oxygen uptake by red blood cell suspensions with a feed hematocrit of 30% and a $P_{50}$ of 27 mmHg flowing in a 27 μm artificial capillary. Curves are theoretical simulations. Parameters shown values of the flow rate in μl/hr.
Fig. 4.21a: Effect of silicone rubber film half-thickness, 'a', on oxygen release from red blood cell suspensions with a feed hematocrit of 30% and a P₁₀₀ of 27 mmHg, flowing at 6 μl/hr in a 27 μm artificial capillary. Curves are theoretical simulations. Parameters shown are values of 'a' in μm.
Fig. 4.21b: Effect of silicone rubber film half-thickness, 'a', on oxygen uptake by red blood cell suspensions with a feed hematocrit of 30% and a $P_{50}$ of 27 mmHg, flowing at 6 $\mu$l/hr in a 27 $\mu$m artificial capillary. Curves are theoretical simulations. Parameters shown are values of 'a' in $\mu$m.
Fig. 4.22a: Effect of silicone rubber oxygen permeability 'K', on oxygen release from red blood cell suspensions with a feed hematocrit of 30% and a P50 of 27 mmHg, flowing at 6 μl/hr in a 27 μm artificial capillary. Curves are theoretical simulations. Parameters shown are values of 'K' in M cm²/sec mmHg.
Fig. 4.22b: Effect of silicone rubber oxygen permeability 'K', on oxygen uptake by red blood cell suspensions with a feed hematocrit of 30% and a \( P_{50} \) of 27 mmHg, flowing at 12 \( \mu l/hr \) in a 27 \( \mu m \) artificial capillary. Curves are theoretical simulations. Parameters shown are values of 'K' in \( \frac{M \text{ cm}^2}{\text{sec mmHg}} \).
Fig. 4.23a: Effect of oxygen tension external to the Silicone rubber capillary, $P_{ext}$, on oxygen release from red blood cell suspensions with a feed hematocrit of 30% and a $P_{50}$ of 27 mmHg, flowing at 6 μl/hr in a 27 μm artificial capillary. Curves are theoretical simulations. Parameters shown are values of $P_{ext}$ in mmHg.
Fig. 4.23b: Effect of oxygen tension external to the silicone rubber capillary, $P_{ext}$, on oxygen uptake by red blood cell suspensions with a feed hematocrit of 30% and a $P_{50}$ of 27 mmHg, flowing at 12 $\mu$l/hr in a 27 $\mu$m artificial capillary. Curves are theoretical simulations. Parameters shown are values of $P_{ext}$ in mmHg.
Fig.4.24a: Effect of the feed oxygen tension, $P_{in}$, on oxygen release from red blood cell suspensions with a feed hematocrit of 30% and a $P_{50}$ of 27 mmHg flowing at 6 µl/hr in a 27 µm artificial capillary. Curves are theoretical simulations. Parameters shown are values of $P_{in}$ in mmHg.
Fig. 4.24b: Effect of the feed oxygen tension, $P_{in}$, on oxygen uptake by red blood cell suspensions with a feed hematocrit of 30% and a $P_{50}$ of 27 mmHg flowing at 12 μl/hr in a 27 μm artificial capillary. Curves are theoretical simulations. Parameters shown are values of $P_{in}$ in mmHg.
Fig. 4.25a: Effect of cell free layer thickness adjacent to the capillary wall, \( \delta \), on oxygen release from red blood cell suspensions with a feed hematocrit of 30\% and a \( P_{50} \) of 27 mmHg, flowing at 6 \( \mu \)l/hr in a 27 \( \mu \)m artificial capillary. Curves are theoretical simulations. Parameters shown are values of \( \delta \) in \( \mu \)m.
Fig. 4.25b: Effect of cell free layer thickness adjacent to the capillary wall, $\delta$, on oxygen uptake by red blood cell suspensions with a feed hematocrit of 30% and a P$_{50}$ of 27 mmHg, flowing at 12 µl/hr in a 27 µm artificial capillary. Curves are theoretical simulations. Parameters shown are values of $\delta$ in µm.
Fig. 4.26a: Effect of slip parameter (equation 4.3c), $slp$, on oxygen release from red blood cell suspensions, with a feed hematocrit of 30% and a $P_{50}$ of 27 mmHg, flowing at 6 $\mu$l/hr in a 27 $\mu$m artificial capillary. Curves are theoretical simulations. Parameters shown are values of $slp$. 

\[ \text{AXIAL POSITION mm} \]

\[ \text{OXYGEN SATURATION} \]

0.0 0.2 0.4 0.6 0.8 1.0

0.0 1.0 2.0 3.0 4.0 5.0

0.2
0.1
0.0
Fig. 4.26b: Effect of slip parameter (equation 4.3c), slp, on oxygen uptake by red blood cell suspensions, with a feed hematocrit of 30% and a P_{50} of 27 mmHg, flowing at 12 μl/hr in a 27 μm artificial capillary. Curves are theoretical simulations. Parameters shown are values of slp.
Fig. 4.27a: Effect of Blunting factor (equation 4.3), 'B' on oxygen release from red blood cell suspensions, with a feed hematocrit of 30% and a \( P_{50} \) of 27 mmHg, flowing at 6 \( \mu l/hr \) in a 27 \( \mu m \) artificial capillary. Curves are theoretical simulations. Parameters shown are values of B.
Fig. 4.27b: Effect of Blunting factor (equation 4.3), 'B' on oxygen uptake by red blood cell suspensions, with a feed hematocrit of 30% and a $P_{50}$ of 27 mmHg, flowing at 12 $\mu$l/hr in a 27 $\mu$m artificial capillary. Curves are theoretical simulations. Parameters shown are values of B.
Fig. 4.28a: Sensitivity of the solution (oxygen saturation vs axial position) for release, to the value of the tube hematocrit, $H_T$, taken for a given feed hematocrit, flow rate and tube diameter in the range observed by various workers (45). A feed hematocrit of 30%, a $P_{50}$ of 27 mmHg, a flow rate of 6 µl/hr, and a tube diameter of 27 µm are used in the simulations. Parameters shown are values of $H_T$. 
Fig. 4.28b: Sensitivity of the solution (oxygen saturation vs axial position) for uptake, to the value of the tube hematocrit, $H_T$, taken for a given feed hematocrit, flow rate and tube diameter in the range observed by various workers (45). A feed hematocrit of 30%, a $P_{50}$ of 27 mmHg, a flow rate of 12 μl/hr, and a tube diameter of 27 μm are used in the simulations. Parameters shown are values of $H_T$. 
Fig. 4.29a: Effect of internal heme concentration, \( C_H \), on oxygen release from red blood cell suspensions with a feed hematocrit of 30% and a \( P_{50} \) of 27 mmHg flowing at 6 \( \mu l/hr \) in a 27\( \mu m \) artificial capillary. Curves are theoretical simulations. Parameters shown are values of \( C_H \) in mM.
Fig. 4.29b: Effect of internal heme concentration, $C_H$, on oxygen uptake by red blood cell suspensions with a feed hematocrit of 30% and a $P_{50}$ of 27 mmHg flowing at 12 µl/hr in a 27 µm artificial capillary. Curves are theoretical simulations. Parameters shown are values of $C_H$ in mM.
Fig. 4.30a: Effect of plasma oxygen diffusivity, $D_{O_2}$, on oxygen release from red blood cell suspensions with a feed hematocrit of 30% and a $P_{50}$ of 27 mmHg flowing at 6 μl/hr in a 27μm artificial capillary. Curves are theoretical simulations. Parameters shown are values of $D_{O_2}$ in cm$^2$/sec.
Fig. 4.30b: Effect of plasma oxygen diffusivity, $D_{O2}$, on oxygen uptake by red blood cell suspensions with a feed hematocrit of 30% and a $P_50$ of 27 mmHg flowing at 12μl/hr in a 27μm artificial capillary. Curves are theoretical simulations. Parameters shown are values of $D_{O2}$ in cm$^2$/sec.
Fig. 4.31a: Effect of plasma oxygen solubility, 'β', on oxygen release from red blood cell suspensions with a feed hematocrit of 30% and a $P_{50}$ of 27 mmHg flowing at 6 μl/hr in a 27μm artificial capillary. Curves are theoretical simulations. Parameters shown are values of 'β' in M/mmHg.
Fig. 4.31b: Effect of plasma oxygen solubility, $\beta^\prime$, on oxygen uptake by red blood cell suspensions with a feed hematocrit of 30% and a $P_{50}$ of 27 mmHg flowing at 12 μl/hr in a 27 μm artificial capillary. Curves are theoretical simulations. Parameters shown are values of $\beta'$ in M/mmHg.
saturation, which is a relatively easily measured quantity. Hence, the flux can be determined, knowing the fraction saturation at any point in the capillary from figures of Nu vs \langle y \rangle. The effect of Nu on some parameters of interest is shown. Figs 4.32 a,b show the effect of $H_F$ on Nu. Figs 4.33 a,b show the effect of tube diameter on Nu, and Figs 4.34 a,b show the effect of the average capillary wall oxygen tension. Figs 4.35 shows the effect of $P_{50}$ for uptake. The corresponding figure for effect of $P_{50}$ on the Nu for release is not shown since there is a negligible effect not observable on the plot.

The Nu increases with increasing \langle y \rangle for release. For uptake, Nu decreases with increasing y and increases at very high \langle y \rangle (\langle y \rangle > 0.9). The Nusselt number varies over a larger range for uptake than for release. Nu increases slightly with increasing hematocrit (Fig 4.32) and appreciably with tube diameter (Fig 4.33). The Nusselt number also depends on the wall oxygen tension. In Fig 4.34 a,b the Nusselt number is plotted vs \langle y \rangle for various average wall oxygen tensions. In the calculations the wall oxygen tension is not fixed. It is a calculated parameter and is found to vary from inlet to outlet by about ± 5 mmHg for release and by about ± 10 mmHg for uptake, from the average wall tension value. For release, as the wall oxygen tension increases, Nu decreases for the same "attainable" \langle y \rangle. For
Fig. 4.32a: Nusselt number as a function of percent space average saturation for release from large capillaries. Effect of hematocrit ($H_F$). When the $P_{50}$ is 25mmHg, capillary diameter is 30μm, average capillary wall oxygen tension is 10 mmHg. Parameters shown are values of the feed hematocrit. The corresponding values of the tube hematocrit ($H_T$) are 17%, 25%, 33%, and 42% (45).
Fig. 4.32b: Nusselt number as a function of percent space average saturation for uptake by large capillaries. Effect of hematocrit (Hc). When the P50 is 25 mmHg, capillary diameter is 30 μm, average capillary wall oxygen tension is 110 mmHg. Parameters shown are values of the feed hematocrit (H_F) are 17%, 25%, 33%, and 42% (45).
Fig. 4.33a: Nusselt number as a function of percent saturation for release from large capillaries. Effect of capillary diameter ($d_c$), when the $P_{50}$ is 25 mmHg, hematocrit is 30%, and the average oxygen tension at the capillary wall is 10 mmHg. Parameters shown are the capillary diameters in $\mu$m.
Fig. 4.33b: Nusselt number as a function of percent saturation for uptake from large capillaries. Effect of capillary diameter ($d_c$), when the $P_{50}$ is 25 mmHg, hematocrit is 30 %, and the average oxygen tension at the capillary wall is 110 mmHg. Parameters shown are the capillary diameters in $\mu$m.
Fig. 4.34a: Nusselt number as a function of percent saturation for release from large capillaries. Effect of capillary wall O$_2$ tension ($P_{\text{Wall}}$). When the $P_{50}$ is 25 mmHg, the capillary diameter is 30 μ, and the hematocrit is 30%. Parameters shown are the average wall O$_2$ tensions in mmHg.
Fig. 4.34b: Nusselt number as a function of percent saturation for uptake from large capillaries. Effect of capillary wall $O_2$ tension ($P_{\text{wall}}$). When the $P_{50}$ is 25 mmHg, the capillary diameter is 30 $\mu$, and the hematocrit is 30%. Parameters shown are the average wall $O_2$ tensions in mmHg.
Fig. 4.35: Nusselt number as a function of percent saturation for uptake from large capillaries. Effect of $P_{50}$. When the capillary diameter is 30 μ, hematocrit is 30 %, and the average capillary wall oxygen tension is 110 mmHg. Parameters shown are the $P_{50}$s in mmHg.
uptake, the Nusselt number is higher for higher wall tensions, at lower \( y \). At higher \( y \), the order is reversed. The \( P_{50} \) has a small effect for uptake as seen in Fig 4.35. The flow rate has no effect on the Nusselt number.

4.2.7 Distribution of resistances

About 25 percent of the resistance to oxygen transport lies in the Silicone rubber film. The rest of the resistance is in the rbc suspension. Within the suspension, about 2 percent of the resistance lies in the rbc and 98 percent of the resistance lies in the plasma for the 27 \( \mu \) capillary. In the 15 \( \mu \) capillary 3 percent of the resistance lies in the rbc and the rest in the plasma. In the 100 \( \mu \) capillary only 0.2 percent of the resistance lies in the rbc. All these resistance figures are for a 40 percent hematocrit. However, the distribution of resistances is not very sensitive to the hematocrit in the range of interest. Of the resistance in the plasma only 2 percent of that resistance lies in the plasma boundary layer close to the red cell wall.

The resistance in the silicone rubber calculated using the centerline rbc oxygen tension as in equation (4.50 b) is 15%.
4.2.8 Results from the highly simplified "Graetz" type model

Figures 4.36 a,b and 4.37 a,b show the simulation using values of the capillary wall resistance estimated from the Graetz solution and rbc resistances as in section 4.1.9. The shortcomings of using the Graetz solution to estimate the plasma resistance are discussed in 4.3.1.

4.3 Discussion and Conclusions

4.3.1 Discussion of the results

The model developed in this work determines transport rates by entirely theoretical means. Application of this model to a given condition of flow rate, capillary dimensions etc. yields the oxygen concentration distribution directly. All the constants in the model are either physical properties or are determined in ways independent of the capillary experiment. There is no fitting to data. The model predicts the variations due to changes in flow rate, $P_{50}$ and $H_T$ accurately as seen from the comparison with experimental data in Figs 4.2 - 4.12.

The model also accurately predicts the data observed by Schmukler and Shu Chien (105) in the 100 $\mu$m diameter
Fig. 4.36a: Oxygen release results for red blood cell suspensions flowing at 12 μl/hr in a 27 μ artificial capillary. Data points, means ± S.D. for 8 replicate experiments at 37 °C, pH 7.3 with a 21 % hematocrit suspension having a P<sub>50</sub> of 20 mmHg used in perfusion Solid curves, Graetz type simulation of experiments.
Fig. 4.36b: Oxygen uptake results for red blood cell suspensions flowing at 23 \( \mu l/hr \) in a 27 \( \mu \) artificial capillary. Data points, means \pm \text{S.D.} for 8 replicate experiments at 37 °C, pH 7.3 with a 21% hematocrit suspension having a \( P_{50} \) of 20 mmHg used in perfusion. Solid curves, Graetz type simulation of experiments.
Fig. 4.37a: Oxygen release results for red blood cell suspensions flowing at 12 μl/hr in a 27 μ artificial capillary. Data points, means ± S.D. for 8 replicate experiments at 37 °C, pH 7.3 with a 30% hematocrit suspension having a P<sub>50</sub> of 27 mmHg used in perfusion. Solid curves, Graetz type simulation of experiments.
Fig. 4.37b: Oxygen uptake results for red blood cell suspensions flowing at 12 μl/hr in a 27 μ artificial capillary. Data points, means ± S.D. for 8 replicate experiments at 37 °C, pH 7.3 with a 30% hematocrit suspension having a P50 of 27 mmHg used in perfusion. Solid curves, Graetz type simulation of experiments.
capillaries of a deoxygenator. These accurate predictions give credibility to the model for large capillaries.

The most commonly used models for large capillaries have been (1) the model (97), which neglects all diffusion resistance within the capillary and, (2) the hemoglobin solution model, which treats blood as a solution of hemoglobin. The resistance to $O_2$ transport in the capillary is underestimated by considering blood to be Hb solution. This is borne out by experiments as shown in Figs 4.13 a,b and also shown by the theoretical model (Fig 4.14 a,b).

The results in Fig 4.13 support two ideas developed by Hellums and co-workers in previous theoretical work(7,55). The first idea is that the resistance to Oxygen transport in the blood itself is a significant fraction of the total resistance in the microcirculation and is much higher than suggested by a number of investigators (55). Unfortunately, it is difficult to determine experimentally the capillary and tissue resistances in-vivo. For the in-vitro system described in Ch 2, quantitative analysis can be carried out, and the resistance in the transport fluid is observed to be greater than 50 percent of the total, even when hemoglobin solutions are used (Ch 3), despite the fact that the capillary wall thickness is about 6 times greater than the capillary lumen. The second idea is that the continuum model, which approximates blood as an isotropic solution of
hemoglobin with an equivalent heme concentration, seriously underestimates the resistance to oxygen transport in capillaries. As shown in Fig 4.13, the rate of oxygen uptake is reduced 5-7 fold when Hb is encapsulated in rbc's. A similar effect is observed for $O_2$ release when the differences between the oxygen affinities of the cell suspension and Hb solution are taken into account. These results provide direct evidence that the continuum approximation is not adequate for a rigorous analysis of $O_2$ transport by intact red blood cells flowing through a vessel the size of an arteriole (about 30 $\mu$ in diameter).

In the past, some models have been developed for small capillaries, which could be applied to large capillaries. These models also underestimate the resistance as seen in Figs 4.14 and 4.15. The Reneau model (100) considers blood as Hb solution but does not take into account facilitated diffusion due to Hb$O_2$. Neglect of facilitated diffusion fortuitously predicts a higher resistance and results in a closer fit to the experimental results. However, as shown in Figs 4.14 and 4.15 the agreement is not good. The Ar-tigue and Bruley model takes into account the discrete nature of blood. This model lumps the radial resistances in the plasma and the rbc as mass transfer coefficients, and does not take into account the radial variations in flow and hematocrit. This model can be made to fit data by adjusting
the mass transfer coefficients. The mass transfer coefficients will vary as a function of various parameters such as hematocrit and tube radius, and will have to be empirically found by fitting to available data. In the large capillary model developed here, these mass transfer coefficients are predicted by the model, and the agreement with experiment is excellent without empirical parameters.

It is found that most of the resistance to mass transfer from large capillaries lies in the plasma. Very little of this resistance lies in and around the rbc's. If these resistances were to be lumped and the resistance in the plasma considered as a resistance in the boundary layer close to the capillary wall, as mentioned in 4.1.11, the wall mass transfer coefficient would be most important. The Graetz solution was considered as an approximation for the plasma resistance. Due to the presence of the rbc's and due to their radial distribution the actual resistance will be different from that predicted by the Graetz solution, which is for non-reactive single phase fluids. However, the Graetz solution gives an order of magnitude estimate of the relative resistances between the rbc and the plasma. From such a preliminary analysis it is found that the plasma resistance is far greater than the rbc resistance. Hence when developing the model (equations [4.13] - [4.16]) the rbc resistance can be safely lumped as a mass transfer
coefficient ([4.13], [4.14]), whereas the convection and diffusion equation is solved in the plasma ([4.15], [4.16]).

The approach using the Graetz solution predicts the experimental results more closely at lower hematocrits (Fig 4.36 a,b) than at higher hematocrits (Fig 4.37 a,b). This is expected, as seen from the results of the effect of hematocrit on resistance (Nusselt number) in Fig 4.32 a,b. At the lower hematocrit, the value of the Nusselt number in the initial portion of the tube is closer to that predicted by the Graetz solution, than at the higher hematocrit.

The large resistance in the plasma explains the result of effect of \( P_{50} \) with sickle cells (114). In this paper it was observed that the difference in \( P_{50} \) accounted for the difference in the \( O_2 \) release characteristics between sickle and normal cells flowing in 27 \( \mu \) capillaries. The shape of the cells and presumably the intracellular oxygen diffusivity changes in sickling rbc's (1). From this work it is clear that the shape of the cell and the diffusivity in the rbc has very little effect on oxygen delivery in the large capillaries. The resistance in the rbc is a small fraction of the total. This conclusion may not be true in smaller capillaries where the rbc resistance becomes more important.

The oxygen saturation curves depend markedly on the hematocrit for both uptake and release. At higher hematocrit the sample must flow further down the tube to reach a given
fractional degree of saturation than is the case at the lower hematocrit. For a doubling in hematocrit it takes somewhat less than twice the time to oxygenate or deoxygenate to a given oxygen saturation level. Higher hematocrit yields a decrease in mass transfer resistance, due to the presence of more rbcs close to the capillary wall. The effect of $P_{50}$ is similar to that with Hb solutions (Ch 3). The Hill coefficient varies between 2 and 3 and there is not much of an effect in this range. With an increase in capillary radius for the same hematocrit and transit time, the oxygen saturation change is slower due to the decreased surface to volume ratio of the capillary, even though there is a higher Nusselt number in larger tubes (Fig 4.33 a,b). The flow rate does not affect the mass transfer resistance, in the range of interest, as indicated by the Nusselt number. Changes in flow serve to change the transit time of the rbcs in the capillary, and change the bulk convective transport of oxygen into the system.

A decrease in the cell free layer thickness, $\delta$, from that used has little effect on the oxygen transport. However, a larger cell free layer could affect the results. However, even in 100 $\mu$ tubes cell free layers of up to only 2 $\mu$ have been reported (18), and the solution of the model is not very sensitive to $\delta$ in this region. The slip parameter is taken to be 0.1 which is based on a single particle flowing
through a tube down the center. The presence of more particles and also positions closer to the wall will lower this value. But, due to the absence of any rigorous theory to predict the slip in these cases, the higher value has been taken. However, in the range from 0 to 0.1 between which the "true" slip lies, the solution is insensitive to the value of slip. There is a greater effect of blunting factor on uptake than on release. In other words the type of flow profile is important in uptake. This is the same as observed for Hb solutions as reported in section 3.2.2. In this model it should be noted that the blunting factor cannot be varied from 0 to 1 keeping all other parameters the same, without inconsistencies (appendix A.4.1).

From reference 45 we find that the tube hematocrit observed by various workers, for a fixed feed hematocrit, tube diameter and flow rate, lies in a certain range. For a typical case as shown in Fig 4.28, where the feed hematocrit is 30 %, flow rate is 6 μl/hr, and tube radius is 27 μm, the tube hematocrit has been reported to lie in the 25 % to 22 % range by various workers. This lies within the "consistent" range of the model. Most of the workers report values close to 25 %. The sensitivity of the calculated oxygen saturations to the value of $H_T$, used is shown in Fig 4.28 a,b. A change in the value of $H_T$, keeping $H_F$ fixed, changes the
hematocrit profiles of the model as can be seen from equation [4.10].

As the internal heme concentration increases the extent of oxygen desaturation or saturation decreases. This is because increasing the internal heme concentration increases the amount of oxygen in the suspension, but does not change the mass transfer characteristics. This is because an increase in internal heme concentration does not affect the external plasma mass transfer rate. Also the change in diffusivity within the rbc due to a change in the heme concentration does not affect the overall mass transfer rate since the rbc offers only a small fraction of the resistance. The kinetic constant $k$ has negligible effect on the solution since the rate is mass transfer limited. The $\frac{S}{V}_{rbc}$ has only a small effect in large capillaries. This is again due to the small fraction resistance in the rbc. The solution is sensitive to diffusivity and solubility in the plasma. However, over the range of values of diffusivities and solubilities reported in literature the resulting fraction saturations do not vary by more than 10%. The solution is insensitive to the mass transfer coefficients in and around the rbc again due to the low resistance contribution from this region.

Only 25 percent of the total resistance lies in the
Silicone rubber. Hence, the system can be effectively used to study the transport mechanism within the capillary lumen.

The Nusselt number is higher at higher hematocrit since there are more rbcs close to the capillary wall. Since, the rbcs carry most of the oxygen, they maintain a higher $P_O$, near the wall at higher hematocrits. This results in a larger flux out of the capillary. However, the mixed mean oxygen tension does not change very much. The result is a higher Nu and a lower resistance. The Nusselt number increases with tube radius for much the same reason: at higher tube radii the rbcs can move closer to the wall. Beyond a certain increase in the tube radii there is no change in the Nu since a further increase has little effect on the distance the rbc can approach the wall.

The Nusselt number for hemoglobin solutions having the same Hb content as the corresponding rbc suspension is about twice as high (3.5 for the rbc suspension vs 7 for the equivalent Hb solution for a typical case). The resistance to oxygen transport offered by Hb solutions is lower than rbc suspensions. The difference is related to the spatial distribution of the Hb molecules. In the case of Hb solutions, there are HbO molecules close to the wall which enhance the $O_2$ transport towards or from the wall. In the case of rbc suspensions, the HbO is confined to the rbc and cannot move as close to the wall.
The method developed in this work for simulation of $O_2$ transport in rbc suspensions has been tested against and shown to agree with results of well defined experiments. It is particularly significant that all the parameters in the model are determined independently - not by adjustable parameters. Thus, we have a predictive model of practical utility which has been critically tested for capillaries of 27 $\mu$m and 100 $\mu$m diameters.

4.3.2 Prediction of fluxes from large capillaries

Figs 4.32 - 4.35 may be used to predict the fluxes to and from large capillaries. Knowing the capillary wall oxygen tension the flux can be calculated at a particular space average fractional saturation for a certain radius and hematocrit.

$$\text{Flux} = \text{Nu} \left( \frac{D_{O_2}^B}{d_c} \right) (P_{\text{mm rbc}} - P_{\text{wall}})$$  \hspace{1cm} [4.54]

$P_{\text{mm rbc}}$ is the mixed mean oxygen tension in the rbc. The mixed mean oxygen tension is defined as in equation [4.44b]. However, it can be easily obtained from the plots of $P_{\text{mm rbc}}$ vs $P_{eq}$ in Figs 4.38, 4.39. $P_{eq}$ is the oxygen tension at equilibrium with $\langle y \rangle$ which may be obtained from the
Fig. 4.38: Mixed mean oxygen tension as a function of the oxygen tension, which is in equilibrium with the space average oxygen saturation for release from large capillaries.
Fig. 4.39: Mixed mean oxygen tension as a function of the oxygen tension, which is in equilibrium with the space average oxygen saturation for uptake from large capillaries.
equilibrium curve or from the Hill equation. Knowing the $P_{50}$ and the Hill parameter $n$,

$$P_{eq} = \left[ \frac{\langle y \rangle}{(1-\langle y \rangle)} \right]^{1/n} P_{50}$$  \hspace{1cm} [4.55]

For large capillaries it is found from Figs 4.38 - 4.39 that $P_{mm\text{rbc}}$ is always greater than the $P_{eq}$. $P_{mm\text{rbc}}$ would have been equal to $P_{eq}$ if the velocity and fraction saturation profiles were flat and the reaction were at equilibrium. The relationship between $P_{mm\text{rbc}}$ and $P_{eq}$ does not change appreciably with the various parameters, $d_c$, $P_{50}$, $H_F$, and $P_{wall}$. There is less than 5% variation in the $P_{mm\text{rbc}}$ vs $P_{eq}$ curves with these parameters. The Nusselt number may be obtained from Figs 4.32 - 4.35, depending on the conditions at which the flux needs to be calculated.

Fig 4.40 and fig 4.41 show the relationship between the mixed mean fraction saturation and the space average fraction saturation for release and uptake. This figure together with figures 4.32 - 4.39, may be used in the design of oxygenators. The space average fraction saturation is defined in equation [4.42]. The mixed mean oxygen saturation is defined as,

$$\langle y \rangle_{mm} = \frac{1}{\pi r_c^2 H_F \langle y \rangle} \int_0^r 2 \pi r v_{rbc}(r) h(r) y dr$$  \hspace{1cm} [4.56]
where \( \langle y \rangle_{mm} \) is the mixed mean oxygen saturation
Fig. 4.40a: Mixed mean oxygen saturation as a function of the space average oxygen saturation for release from large capillaries.
Fig.4.40b: Mixed mean oxygen saturation as a function of the space average oxygen saturation for uptake by large capillaries
CHAPTER 5

SMALL CAPILLARY OXYGEN TRANSPORT

A model is developed for blood flowing in a single file in small capillaries. This model incorporates the parameters such as flow rate, tube hematocrit, \( P_{50} \), and cell clearance which control \( O_2 \) transport to tissue in vivo. Since the rbc's flow in a single file as slipper shaped objects, the rbc's in the model are taken as cylinders, which more closely approximates the slipper shape than spheres (56).

The model is used to examine the supply of \( O_2 \) to a Krogh type model of tissue. A finite thickness of endothelial cells and extravascular space is also included as observed in tissue cross sections (Fig 5.1). The rate of release of \( O_2 \) from red cells covered by endothelium is about the same as the rate when red cells are covered by a plasma layer of equal thickness (111). There has been some disagreement on this point, which is discussed in Ch 6. In this model these layers have been included as plasma layers through which \( O_2 \) diffuses as done by Sinha (111), Groebe and Thews (50), and Honig (62) in their analyses. The model is also used to examine the uptake of oxygen from the alveoli in the lungs. The effects of various parameters on \( O_2 \) transport are
Fig. 5.1: This electron micrograph shows a muscle capillary cut in cross section and containing an erythrocyte (EC). Its wall is made of an endothelial cell (EN) which contains a nucleus (N) and numerous vesicles (V), and forms a tortuous intercellular junction (J). It is enwrapped by a basement membrane (BM) which is associated with a pericyte process (P). Scale marker: 1 μm. (From Weibel (113)).
studied. The resistance breakup within the capillary and the overall Nusselt number are calculated and compared with that of previous models.

It should be noted that as yet none of these small capillary models have been validated by experiment.

5.1 Physical problem and outline of approach

The small capillaries in the microcirculation, range from 3 to 7 μm in diameter. When an 8 μm diameter rbc passes through them it folds into a slipper shaped or parachute shaped structure depending on the flow rate and size of the tube. The rbc's flow in a single file with plasma gaps between them. The length of the plasma gap or the cell spacing changes depending on the tissue oxygen demand, thereby changing the tube hematocrit. Between the rbc and the capillary wall, is a layer of plasma - the plasma film. The rbc's move faster than the plasma on an average.

The capillaries supply the tissue with O₂. Each tissue region is supplied by several capillaries. Around each capillary is a layer of endothelial cells about 1 μm thick. Around the endothelial cells is the extravascular space which is of the order of 2 μm thick. This space is in turn surrounded by the tissue (Fig 5.1).

In the case of oxygen uptake in the lungs the capillary surroundings are different. The capillary is surrounded by
Fig. 5.2: Alveolar capillary from human lung showing how $O_2$ and $CO_2$ are exchanged between alveolar air (A) and capillary blood with erythrocytes (EC) in plasma (P), across a tissue barrier (T) of variable thickness. Scale marker: 2$\mu$m.
tissue about 0.6 μm thick. External to this is the alveolar air (Fig 5.2).

In the release of O₂ from blood, O₂ undergoes a dissociation reaction with the Hb. It diffuses through the medium within the rbc, through the rbc wall into the plasma film and plasma gap. Due to the difference in velocities between the rbc and the plasma film the oxygen is convected away from the rbc wall in the film and also diffuses out through the capillary wall. The oxygen in the plasma gap also diffuses out through the capillary wall.

In the case of uptake, O₂ diffuses from the alveolar air through the tissue into the plasma film and the plasma gap. From the surrounding plasma it then diffuses into the rbc where it undergoes an association reaction with the hemo-
globin molecule.

5.2 Mathematical model

5.2.1 Model geometry

The rbc's are treated as cylindrical shaped slugs of radius r_w and length L_f. The rbc is surrounded by a plasma film between the rbc wall and the capillary wall. The capillary wall has a radius r_c. Adjacent to the rbc's are the two plasma gaps of length L_p. The difference in oxygen
tension between two consecutive rbc's is negligible compared to the drop in tension across the length of the capillary. Hence, the oxygen tensions in the adjacent plasma gaps are considered to be the same (Fig 5.3).

Surrounding the capillary are two concentric cylinders of radii \( r_{en} \) and \( r_{ex} \) (not shown on Fig 5.3) which represent the endothelium and the extravascular space. Another concentric cylinder of radius \( r_t \), the tissue, surrounds the extravascular space.

5.2.2 Mass transfer coefficients

The various resistances in the capillary are lumped as resistances in layers close to the walls, characterized by Nusselt numbers or mass transfer coefficients. These coefficients are calculated separately by solution of steady state diffusion equations in each of the regions over which the mass balance is written. The details of these solutions are given in the appendix (A.5.1 - A.5.4). The mass transfer coefficients are expressed as dimensionless Nusselt numbers.
Figure 5.3: Schematic of model geometry for single file flow in small capillaries.
5.2.2.1 Nusselt numbers in the plasma film -

The Nusselt number in the plasma resistance layer close to the rbc wall is (appendix A.5.1)

\[ \text{Nu}_{rf} = \frac{k_{rf} d_w}{D'_{02}} = \frac{4}{\left[2\gamma_{cw} \ln \gamma_{cw}^2 - 1\right] \left[\gamma_{cw}^2 - 1\right]} \quad [5.1] \]

The Nusselt number in the plasma boundary layer close to the capillary wall is (appendix A.5.1)

\[ \text{Nu}_{cf} = \frac{k_{cf} d_c}{D'_{02}} = \frac{4}{\left[1 - \frac{2 \ln \gamma_{cw}^2}{\gamma_{cw}^2 - 1}\right]} \quad [5.2] \]

where \( \text{Nu}_{rf} \) is the Nusselt number in the plasma film at the rbc wall

\( k_{rf} \) is the mass transfer coefficient in the plasma film at the rbc wall

\( d_w \) is the diameter of the rbc cylinder

\( D'_{02} \) is the diffusivity in the plasma

\( \gamma_{cw} \) is the ratio of the capillary radius to the rbc cylinder radius

\( \text{Nu}_{cf} \) is the nusselt number in the plasma film at the capillary wall
\( k_{cf} \) is the mass transfer coefficient in the plasma film at the capillary wall

\( d_c \) is the capillary diameter

5.2.2.2 Nusselt numbers in the plasma gap -

The Nusselt numbers in the plasma gap are obtained by solving the two dimensional steady state diffusion equations in the plasma gap. Convection can be neglected as seen from the work of Aroesty and Gross (2). The details of the solution are given in the appendix (A.5.2). Although it is possible that a solution to the 2 dimensional diffusion problem that needs to be solved for these Nusselt numbers is available in literature, it was not found in the readily available literature. Therefore, it was solved using Linear operator theory (98) as shown in the appendix, section A.5.2. The Nusselt number in the plasma boundary layer close to the capillary wall in the plasma gap is

\[
Nu_{cg} = \frac{k_{cg}d_c}{D_{O2}} = \frac{N_1}{D_1 - D_2}
\]  

[5.3]

The Nusselt number in the plasma boundary layer close to the lateral rbc wall adjacent to the plasma gap is as given in the appendix, section A.5.2.
\[ \text{Nu}_{zg} = \frac{k_{zg} L_p}{D_{02}} = \frac{N_2}{D_1} \]  \[ \text{[5.4]} \]

where
\[ d = \left[ \frac{\lambda_i}{\int_0^{\sqrt{\lambda_i}} \eta J_0^2(\eta) d\eta} \right]^{0.5} \]

\[ N_1 = -2 \gamma \sum_i \sqrt{\lambda_i} J_1(\sqrt{\lambda_i}) \frac{F(E(e^{g}+e^{-g_{-2}})-(g+1-e^{g}))}{g} \]

\[ D_1 = \gamma \sum_i ((g+1-e^{g})-E(e^{g}+e^{-g_{-2}})) \frac{F}{g} \frac{d}{\sqrt{\lambda_i}} \int_0^{\sqrt{\lambda_i}} J_0(\eta) d\eta \]

\[ D_2 = \gamma \sum_i J_0(\sqrt{\lambda_i}) \frac{F}{g} ((g+1-e^{g})-E(e^{g}-e^{-g_{-2}})) \]

\[ N_2 = \gamma \sum_i Fg(2E+1) \frac{d}{\sqrt{\lambda_i}} \int_0^{\sqrt{\lambda_i}} J_0(\eta) d\eta \]

\[ g = \sqrt{a \lambda_i} \]

\[ a = \left[ \frac{L_p}{r_c} \right]^2 \]

\[ H = \frac{k_{zg} r_c}{D_{02}} \]

\[ F = \frac{c}{g^2} \]
\[ E = \frac{e^{g-1}}{e^{-g-e^{g}}} \]
\[ u_e = \frac{C_{ext}-C_r}{C_r} \]

If the boundary condition at the capillary wall is of the form

\[-D_{02}^\frac{\partial C}{\partial r} = k_e (C - C_{ext}) \]

then

\[ c = -\alpha D_{02} J_0(\sqrt{\lambda_i}) \frac{k_{er} D_{02}}{C_r} \]

and \( \sqrt{\lambda_i} \) is the solution of

\[ J_0(\sqrt{\lambda_i}) = \left[ \frac{\sqrt{\lambda_i} D_{02}}{k_{er} C_r} \right] J_1(\sqrt{\lambda_i}) \]

If the boundary condition at the capillary wall is of the form

\[-D_{02}^\frac{\partial C}{\partial r} = q \]

then

\[ c = -\alpha D_{02} J_0(\sqrt{\lambda_i}) \frac{q D_{02}}{C_r} \]

and \( \sqrt{\lambda_i} \) is the solution of

\[ J_1(\sqrt{\lambda_i}) = 0 \]

where \( Nu_{cg} \) is the nusselt number at the capillary wall in the plasma gap

\( k_{cg} \) is the mass transfer coefficient at the capillary
wall in the plasma gap

$\text{Nu}_{zg}$ is the Nusselt number in the plasma gap at the rbc wall

$k_{zg}$ is the mass transfer coefficient in the plasma gap at the rbc wall

$L_p$ is the length of the plasma gap

$r_c$ is the radius of the capillary

$k_c$ is the external mass transfer coefficient

$C_{ext}$ is the external oxygen concentration

$C_r$ is the rbc wall oxygen concentration

$q$ is the constant flux out of the system

5.2.2.3 Nusselt number in the rbc on the lateral wall adjacent to the plasma gap -

The resistance due to axial diffusion in the rbc is lumped at the lateral walls and is characterized by the Nusselt number at the lateral walls. We are interested in the radial oxygen tension distribution for resistance calculations. Inclusion of axial diffusion, makes a 5% difference in the results (50). Hence, the average oxygen concentration and fraction saturation in the rbc is averaged axially and the axial diffusion term is lumped as a resistance at the lateral wall. The Nusselt number in the rbc is the same as the Nusselt number for a sheet of hemoglobin solution. From one dimensional diffusion calculations in Hb solution
as in 4.3.9.1 it is found that this Nusselt number is approximately constant:

\[ \text{Nu}_{\text{zr}} = \frac{k_{\text{zr}} L_r}{D_{02}} = 7.5 \]  \hspace{1cm} [5.5]

where \( \text{Nu}_{\text{zr}} \) is the Nusselt number in the rbc at the side walls adjacent to the plasma gap

\( k_{\text{zr}} \) is the mass transfer coefficient in the rbc at the side walls adjacent to the plasma gap

\( L_r \) is the length of the rbc

\( D_{02} \) is the \( O_2 \) diffusivity in the rbc

5.2.2.4 Nusselt number in the plasma film at the lateral walls adjacent – to the plasma gap

The resistance due to axial diffusion in the plasma film is lumped at the lateral ends and is characterized by the Nusselt number at the lateral ends of the plasma film adjacent to the plasma gap. This Nusselt number is found to be (appendix A.5.3)

\[ \text{Nu}_{\text{zf}} = \frac{k_{\text{zf}} L_k}{D_{02}} = 4 \]  \hspace{1cm} [5.6]

where \( \text{Nu}_{\text{zf}} \) is the Nusselt number in the plasma film at the
boundary adjacent to the plasma gap

$k_{zf}$ is the mass transfer coefficient in the plasma film at the boundary adjacent to the plasma gap

5.2.2.5 Nusselt numbers in the endothelium and extravascular space -

The overall resistance in the endothelium and the extravascular space which are concentric cylinders around the capillary is expressed as Nusselt numbers (appendix A.5.4)

$$\text{Nu}_{en} = \frac{k_{en} d_{en}}{D_{02en}} = \frac{2}{\ln \left[ \frac{d_{en}}{d_t} \right]}$$  \[5.7\]

$$\text{Nu}_{ex} = \frac{k_{ex} d_{ex}}{D_{02ex}} = \frac{2}{\ln \left[ \frac{d_{ex}}{d_{en}} \right]}$$  \[5.8\]

where $\text{Nu}_{en}$ is the Nusselt number in the endothelium

$k_{en}$ is the mass transfer coefficient in the endothelium

$\text{Nu}_{ex}$ is the Nusselt number in the extravascular space

$k_{ex}$ is the mass transfer coefficient in the extravascular space

$d_{en}$ is the outer diameter of the endothelium
\( d_{ex} \) is the outer diameter of the extravascular space
\( D_{O2en} \) is the oxygen diffusivity in the endothelium
\( D_{O2ex} \) is the oxygen diffusivity in the extravascular space
\( d_c \) is the diameter of the capillary

5.2.3 Flux out of the capillary for release

For an oxygen consumption of \( R_0 \) mols cc sec by the tissue the flux out of the capillary by a simple mass balance is

\[
F_c = \frac{R_0 r_{ex}^2}{2r_c} \left[ \frac{2}{\gamma_{tex}} - 1 \right]
\]

[5.9]

where \( \gamma_{tex} = \frac{r_t}{r_{ex}} \)

\( r_t \) is the outer radius of the tissue cylinder
\( r_{ex} \) is the outer radius of the extravascular space
\( F_c \) is the flux at the capillary wall
\( R_0 \) is the oxygen consumption by the tissue in mols cc sec
5.2.4 Tube Hematocrit

The tube hematocrit is related to the rbc size and the cell separation

\[ H_T = \frac{\pi r_w^2 L_r}{\pi r_c^2 (L_r + L_p)} \]  \hspace{1cm} [5.10a]

which can be simplified to give

\[ H_T = \left[ \frac{r_w}{r_c} \right]^2 \left[ \frac{L_r}{L_r + L_p} \right] \]  \hspace{1cm} [5.10b]

The tube hematocrit is lower than the feed hematocrit due to the higher average velocity of the rbc over the plasma. The ratio \( \frac{H_T}{H_F} \) has been observed by Fahreus et al (80).

where \( r_w \) is the radius of the rbc

\( r_c \) is the radius of the capillary
5.2.5 Average velocities

The average rbc and plasma velocities are related to the flow rate and hematocrits by an overall mass balance

\[ v'' = \frac{Q}{\pi r_c^2} \frac{H_F}{H_T} \] \hspace{1cm} [5.11]

\[ \frac{v'}{v''} = \frac{1-H_F}{H_F} \frac{H_T}{1-H_T} \] \hspace{1cm} [5.12]

where \( v'' \) is the average velocity of the rbc

\( v' \) is the average velocity of the plasma

\( H_T \) is the tube hematocrit

\( H_F \) is the feed hematocrit

\( Q \) is the flowrate in the capillary

5.2.6 Transport equations

The rbc with the plasma film and the plasma gap is taken as the control volume (unit) over which the mass balance is written. This "unit" flows down the tube and gives out or takes in oxygen by diffusion and bulk convection as a function of time. To write the mass balance equations this unit is split into three regions which are interconnected - the
rbc, the plasma film and the plasma gap. A mass balance of the independent species in each of these regions is written. The mass balance equations are slightly different for release and uptake due to the different boundary conditions.

5.2.6.1 Transport equations for release

From previous work (23, 39, 50, 55) it is expected that most of the resistance to oxygen transport within the capillary lies in the rbc and the contribution from the plasma is less than 20%. Also most of the oxygen transport is expected to take place from the rbc and plasma film region (7). The leak of oxygen into the plasma gap would serve as a small correction of about 5-10%. Hence, lumping the resistances in the plasma gap both radially and axially would give sufficiently accurate results while simplifying the mathematics considerably. Since the transport in the rbc is the most important step, the radial diffusion and reaction have to be taken into account. Even though the plasma film diffusion is not the major resistance it is not negligible. Hence, it is taken into account as lumped resistances. Also, since axial diffusion in the rbc was found to make less than 5% difference (50), it is treated as a lumped resistance. The difference in this model from Baxley's (7) or Groebe and Thews model (50) is that it includes the "leak" of oxygen due to convection (relative motion between the plasma film
and the rbc) and the "leak" into the plasma gap. The transport equations are:

In the rbc

**Oxygen mass balance**

\[
\frac{\partial C}{\partial t} = \frac{D_0}{r} \frac{\partial}{\partial r} \left[ r \frac{\partial C}{\partial r} \right] + C_{_{H}} f(C, y) - k_{_{gr}} L_{_{r}} \left[ \frac{C_{_{r}}}{\beta} - C'' \right] \quad \text{[5.13]}
\]

**Oxyhemoglobin mass balance**

\[
\frac{\partial y}{\partial t} = \frac{D_{_{HbO2a}}}{r} \frac{\partial}{\partial r} \left[ r \frac{\partial y}{\partial r} \right] - f(C, y) \quad \text{[5.14]}
\]

In the plasma film

\[
\frac{dC'}{dt} = \left( (v'' - v') + 2k_{fg} \right) \left( \frac{r_c^2 - r_w^2}{r_c^2 L_r} \right) \left( C'' - C' \right) + k_{_{rf}} \frac{2\pi r_w L_r}{V_p} \left( \frac{C_{_{r}}}{\beta} - C' \right) - \frac{F_c 2\pi r_c L_r}{V_p} \quad \text{[5.15]}
\]

In the plasma gap

\[
\frac{dC''}{dt} = \left( (v'' - v') + 2k_{fg} \right) \left( \frac{r_c^2 - r_w^2}{r_c^2 L_p} \right) \left( C' - C'' \right) + k_{_{rg}} \frac{2\pi r_c^2 L_p}{V_{_{c'}}} \left( \frac{C_{_{r}}}{\beta} - C'' \right) - \frac{F_{_{c'}}}{r_{c'}} \quad \text{[5.16]}
\]

where \( k_{fg} = \frac{k_{zf} k_{zg}}{k_{zf} + k_{zg}} \)

\[ k_{gr} = \frac{k_{zr}k_{zg}}{k_{zr} + k_{zg}\left[\frac{\beta'}{\beta}\right]} \]

C is the oxygen concentration in the rbc

\( f(C,y) \) is the reaction rate

\( C'' \) is the \( O_2 \) concentration in the plasma gap

\( C' \) is the \( O_2 \) concentration in the plasma film

\( y \) is the fraction \( O_2 \) saturation in the rbc

\( C_H \) is the internal heme concentration in the rbc

\( \beta' \) is the bunsen solubility coefficient in the plasma

\( \beta \) is the bunsen solubility coefficient in the rbc

\( V_p' \) is the volume of the plasma film

\( F_c \) is as given in equation [5.9] or as given in section 5.2.6.2

\( k_{fg} \) is the overall mass transfer coefficient between the plasma film and the plasma gap

\( k_{gr} \) is the overall mass transfer coefficient between the rbc and the plasma gap on the lateral rbc wall

Equation [5.13] includes radial diffusion in the rbc, the reaction kinetics and the term for the leak of oxygen from the laterl walls into the plasma gap. \( k_{gr} \) is an overall mass transfer coefficient obtained by combining \( k_{zr} \) and \( k_{zg} \) as shown above, from continuity of flux condition at the lateral rbc wall. Equation [5.14] includes the diffusion of oxyhemoglobin and the reaction kinetics.
In equation [5.15] the first term on the right hand side is the bulk convection term. It includes the input of oxygen from the plasma gap from one end and output into the plasma gap at the other end due to the plasma motion relative to the rbc. The second term is the input of oxygen from the rbc into the plasma film and the third term is the output of oxygen from the plasma film to the tissue.

In equation [5.16] the first term on the right hand side is the bulk convection term for input and output of oxygen due to bulk plasma motion from and to the plasma film. The second term is the input of oxygen from the rbc and the third term, the output of oxygen out of the capillary at the wall.

5.2.6.1.1 Boundary conditions -

At the rbc wall the flux is specified by the $k_{rf}$ and the drop in oxygen tension from the rbc wall to the plasma film. Also, since no Hb escapes from the rbc, the flux of Hbo$_2$ vanishes at the rbc wall. Hence,

At $r=r_w$

\[-D_0 \frac{\partial C}{\partial y} = k_{rf} \left( \frac{C^B}{B} - C' \right) \]  \hspace{1cm} [5.17]

\[-D_{HbO2} \frac{\partial y}{\partial r} = 0 \]  \hspace{1cm} [5.18]

Applying the symmetry conditions at the center,
At $r=0$

$$\frac{\partial C}{\partial r} = 0$$  \hspace{1cm} (5.19)

$$\frac{\partial y}{\partial y} = 0$$  \hspace{1cm} (5.20)

Initial conditions,

At $t=0$

$$C = \beta P_{in}$$  \hspace{1cm} (5.21)

$$C' = \beta' P_{in}$$  \hspace{1cm} (5.22)

$$C'' = \beta' P_{in}$$  \hspace{1cm} (5.23)

where $P_{in}$ is the inlet $O_2$ tension

The dedimensionalized equations are shown in appendix A.5.5

5.2.6.2 Transport equations for uptake in vivo and for in vitro studies -

The Oxygen mass balance and the oxyhemoglobin mass balance in the rbc are the same as (5.13) and (5.14) The Oxygen mass balance in the plasma film and plasma gap are the same except that the expression for the flux $F_C$ is not that given in (5.9). The expression for $F_C$ for the plasma film balance (5.15) is

$$F_C = k_C (C' - C_{cw})$$  \hspace{1cm} (5.24)
The expression for $F_c$ for the plasma gap mass balance \([5.16] \) is

$$F_c = k_{cg}(C"-C_{cw})$$ \[5.25\]

where $C_{cw}$ is the capillary wall $O_2$ concentration in the plasma film

$C_{cw}$ is the capillary wall $O_2$ concentration in the plasma gap

These wall oxygen concentrations can be calculated from the mass transfer coefficients and the oxygen concentration in the plasma,

$$C'_{cw} = \frac{k_{cf}}{k_s+k_{cf}} \cdot \frac{(C'+C'\prime)}{2} + \frac{k_s}{k_s+k_{cf}} \cdot \beta'P_{ext}$$ \[5.26\]

$$C''_{cw} = \frac{k_{cg}}{k_s+k_{cg}} \cdot \frac{(C''+C''\prime)}{2} + \frac{k_s}{k_s+k_{cg}} \cdot \beta'P_{ext}$$ \[5.27\]

where $k_s$ is the mass transfer coefficient of the medium external to the capillary.

For in vivo simulations (Uptake in lungs)
\[
\frac{k_s d_t}{D_{02t}} = \frac{2}{\ln \left( \frac{r_t}{r_c} \right)} \quad [5.28]
\]

For in vitro simulations in the Silicone rubber capillary

\[
\frac{k_s d_c}{D'_{02}} = \frac{2K}{D_{02} B' \ln \left( \frac{4a_l}{\pi r_c} \right)} \quad [5.29]
\]

The dedimensionalized equations are shown in the appendix A.5.5

5.2.7 Solution

The equations are solved numerically by finite element collocation using basis splines (85). The values of the parameters used are shown in the figures and given in the appendix A.5.6.
5.2.8 Oxygen tension drops in tissue, endothelium and the extravascular space

The tissue is treated as if it consumes oxygen uniformly at \( R_0 \text{ mols cc sec}^{-1} \). The simplest model for estimation of the drop in \( O_2 \) tension across the tissue given by (78),

\[
P_t - P_{ex} = \frac{R_0r^2}{4BD_{02t}}(\gamma_{tex}^2 - 1 - \gamma_{tex}ln\gamma_{tex}^2)
\]  

[5.30]

where \( P_t \) is the \( O_2 \) tension at the outer radius of the tissue

\( P_{ex} \) is the \( O_2 \) tension at the outer radius of the extravascular space

\( D_{02t} \) is the \( O_2 \) diffusivity in tissue

The oxygen tension drop over the endothelium is

\[
P_{en} - P_c = \frac{F_{en}}{k_{en}^\beta_{en}}
\]  

[5.31]

The oxygen tension drop over the extravascular space is

\[
P_{ex} - P_{en} = \frac{F_{ex}}{k_{ex}^\beta_{ex}}
\]  

[5.32]
where $F_{en}$ and $F_{ex}$ are the fluxes out of the endothelium and the extravascular space respectively.

$P_{en}$, $P_{c}$ are the oxygen tensions at the outer boundary of the endothelium and at the capillary wall.

$F_{en}$ and $F_{ex}$ are calculated from $F_{c}$,

$$F_{en} = F_{c} \frac{r_{c}}{r_{en}} \quad [5.33]$$

$$F_{ex} = F_{c} \frac{r_{c}}{r_{en}} \quad [5.34]$$

5.2.9 Capillary wall oxygen tension for in vivo release

The capillary wall oxygen tension adjacent to the plasma film $P'_{cw}$ is given by

$$P'_{cw} = P' \frac{F_{c}}{k_{cf} \beta'} \quad [5.35]$$

where $P'$ is the average oxygen tension in the plasma film.

The capillary wall oxygen tension adjacent to the plasma gap $P''_{cw}$ is given by
\[ P_{cw}'' = P'' - \frac{F_c}{k_{cg} \beta'} \]  
\[ \text{[5.36]} \]

where \( P'' \) is the average oxygen tension in the plasma gap

5.2.10 Fractional resistances

The fractional resistance in the rbc, plasma, endothelium, extravascular space and tissue are

\[ RS_t = \frac{P_t - P_{ex}}{P_o - P_t} \]  
\[ \text{[5.37]} \]

\[ RS_{ex} = \frac{P_{ex} - P_{en}}{P_o - P_t} \]  
\[ \text{[5.38]} \]

\[ RS_t = \frac{P_{en} - P_{cw}}{P_o - P_t} \]  
\[ \text{[5.39]} \]

\[ RS_c = \frac{P_{ro} - P_{cw}}{P_o - P_t} \]  
\[ \text{[5.40]} \]

\[ RS_p = \frac{P_{rw} - P_{cw}}{P_o - P_t} \]  
\[ \text{[5.41]} \]

\[ RS_r = \frac{P_{ro} - P_{rw}}{P_o - P_t} \]  
\[ \text{[5.42]} \]

where \( RS_t \) is the fraction resistance in the tissue

\( RS_{ex} \) is the fraction resistance in the extra-
vascular space

$R_{en}$ is the fraction resistance in the endothelium

$R_{c}$ is the fraction resistance in the capillary

$R_{p}$ is the fraction resistance in the plasma

$R_{r}$ is the fraction resistance in the rbc

$P_{rc}$ is the oxygen tension at the center of the rbc

$P_{rw}$ is the oxygen tension at the rbc wall

$P_{cw}$ is the oxygen tension at the capillary wall in the plasma film region

Since it is observed that most of the oxygen is transported in the radial direction, the oxygen tension drops are considered in that direction for calculation of fraction resistances.

5.2.11 Overall Nusselt number

The overall Nusselt number is calculated using the average concentration at the wall.

$$Nu = \frac{q_{avg}2r_c}{\left[\frac{E' \cdot C' - C_{wavg}}{E' \cdot C' - C_{wavg}}\right] D_{02}} \quad [5.43]$$

where $C'_r$ is the mixed mean intracellular oxygen concentration
q_{avg} \text{ is the average oxygen flux through the capillary wall}

In the case of uptake and in vitro simulations

\[ q_{avg} = \frac{f1'L_r + f1''L_p}{L_r + L_p} \quad [5.44] \]

\[ f1' = k_s(C'_c - B'P_{ext}) \quad [5.45] \]

\[ f1'' = k_s(C''_c - B'P_{ext}) \quad [5.46] \]

where \( f1' \) is the flux out of the plasma film region

\( f1'' \) is the flux out of the plasma gap region

In case of in vivo release

\[ q_{avg} = F_c \quad [5.47] \]

In both cases

\[ C_{wavg} = \frac{C'_c L_r + C''_c L_p}{L_r + L_p} \quad [5.48] \]

\[ C'_r = \frac{1}{\pi r_w^2} \int_0^{r_w} 2\pi r C(r) dr \quad [5.49] \]

The mixed mean intracellular oxygen tension is given by
\[ P'_r = \frac{C'_r}{\beta'} \]  

[5.50]

where \( P'_r \) is the mixed mean rbc oxygen tension

5.3 Results

Equations [5.24]-[5.28] have been used for calculation of \( F_c \) for all uptake results. These boundary conditions correspond to passive diffusion in the tissue, like that present in the lungs. Equations [5.24]-[5.27] and [5.29] have been used for calculation of \( F_c \) for most release calculations. These boundary conditions correspond to passive diffusion in the silicone rubber film surrounding the capillary like that in the in vitro experimental set up described in Ch. 2. Equation [5.9] has been used for some release calculations. This boundary condition corresponds to diffusion and consumption in the tissue which is modelled as a Krogh cylinder. The equations used for release will be indicated when describing the results.
5.3.1 In vivo release and uptake

Fig 5.4 shows the calculated release of oxygen from a 5 μm capillary under typical rest conditions in a human skeletal muscle in vivo (119). Equation [5.9] was used for calculation of $F_c$. The oxygen tension goes down from 90 mmHg to 40 mmHg. It also shows the release of oxygen into tissue during exercise with an increase in tissue oxygen consumption without changes in any of the other parameters, and also in the presence of the oxygen supply enhancement techniques of increased flow rate, increased $P_{50}$, decreased cell spacing, and increased capillary density. In the absence of the oxygen enhancement factors, the oxygen tension goes to 0 mmHg very close to the entrance of the capillary. In the presence of all the enhancement factors, the capillary oxygen tension drops from 90 mmHg to 68 mmHg.

Fig 5.5 shows the uptake of oxygen in the lungs (human) under typical rest conditions in vivo. Blood is completely saturated in less than 0.1 secs in less than 30% of the capillary length. It also shows the uptake under typical exercise conditions. It takes 0.2 secs for complete saturation and almost the whole length of the capillary is required.
Fig. 5.4: Release of oxygen from 5 μm capillaries. The solid curve shows the average RBC oxygen tension (P₀') as predicted by the small capillary model when Hᵣ=20%, P₅₀=25 mmHg, residence time is 1 sec, rₛ=30μm, and R₀=7x10⁻⁹ mols/cc-s. The dashed line shows the P₀' in the capillary with an increase in oxygen consumption to 140x10⁻⁹ mols/cc-sec. The dotted line shows the change when R₀=140x10⁻⁹ mols/cc-sec and residence time=0.3 sec, P₅₀=32 mmHg, Hᵣ=40%, rₛ=10μm.
Fig. 5.5: Uptake of oxygen in 5 μm capillaries. The solid curve shows the average rbc oxygen tension ($P'_r$) as predicted by the small capillary model under rest conditions, when $H_T = 20\%$, $P_{50} = 25$ mmHg and residence time is 0.6 secs. The dashed line shows the $P'_r$ in the capillary under conditions of exercise, when $H_T = 40\%$, $P_{50} = 32$ mmHg, and the residence time is 0.2 secs.
5.3.2 Comparison with other models

Figs 5.6a,b show a comparison of the small capillary model (SCM) developed here with other models for release and uptake. The SCM predicts a greater resistance than Reneau's model or the Hb solution model, but a lower resistance than the plasma film model as used by Baxley.

The Groebe and Thews model (50) is very similar to Baxley's plasma model except for the fact that it takes axial diffusion in the rbc into account. Axial diffusion makes less than 5% difference in the overall saturation change. Hence, the results from their work are not very different from the model in this work. If their results were plotted in Fig 5.6 a,b the curve would lie between Baxley's curve and the curve predicted by this work.

Equations [5.24]-[5.27] and [5.29] have been used for $F_c$ in the above comparisons.

Two other groups have reported models in which the red cell resistance is taken into account by means of lumped mass transfer coefficients: Artigue and Bruley (3), and Hideyuki and Sugihara (59). In each case results were reported for oxygen saturation trends for the constant flux condition equation ([5.9]). Comparisons of the oxygen saturation changes between models which employ the constant flux boundary condition are not meaningful. The boundary condition itself determines the oxygen saturation change.
Fig. 5.6a: Comparison of models for $O_2$ release from red blood cell suspensions with a 22% tube hematocrit, having a $P_{50}$ of 25 mmHg and flowing at 0.08 $\mu$l/hr in a 6 $\mu$ artificial capillary. The models used for the simulations are shown next to the curves.
Fig. 5.6b: Comparison of models for O$_2$ uptake from red blood cell suspensions with a 22% tube hematocrit, having a $P_{50}$ of 25 mmHg and flowing at 0.08 μl/hr in a 6 μ artificial capillary. The models used for the simulations are shown next to the curves.
Thus, a comparison with these models was prepared in which the intracapillary oxygen tension drop calculated by the method of the present work was compared to that calculated in the prior work. These comparisons require adjustment of the parameters of the present work to yield the same values as in the prior work. These comparisons are given in Tables 5.1 and 5.2. The differences between the results are explained in section 5.4.2.

Federspiel and Popel (39) have reported the Nusselt numbers as a function of the parameters, cell clearance and cell spacing. The results from this work are qualitatively in agreement with the results obtained by them. Comparing specific results with those of Federspiel and Popel (39), we find $\text{Nu}_{SCM} = 1.18$, $\text{Nu}_{Fed} = 0.75$ ($L_p/L_r=1, r_c/r_w=1.25, r_c=2.5$). Taking another point of comparison $\text{Nu}_{SCM} = 0.37$, $\text{Nu}_{Fed} = 0.2$ ($L_p/L_r=4, r_c/r_w=1.5, r_c=3$). The significance of these results and the reason for the difference is explained in the discussion section 5.4.2.

5.3.3 Effect of parameters, $Q$, $P_{50}$, $n$, $r_c$, $L_p$, $r_w$, $L_r$, $C_H$.

To compare the effect of these parameters on oxygen release, by comparing the saturation curves, equations [5.24]-[5.27] and [5.29] are used for $F_c$.

Fig 5.7 a,b show the effect of flow rate on release and
TABLE 5.1. Comparison of Intracapillary Oxygen Tension Distribution with that of Artique and Bruley (3).

Parameter values:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue Oxygen Consumption (as in [5.9])</td>
<td>$3.75 \times 10^{-8}$ gmols/cm³·sec</td>
</tr>
<tr>
<td>Krogh Cylinder Radius</td>
<td>30 μm</td>
</tr>
<tr>
<td>Capillary diameter</td>
<td>5 μm</td>
</tr>
<tr>
<td>Rbc Mean Oxygen Tension</td>
<td>50 mmHg</td>
</tr>
<tr>
<td>Parameters of this work</td>
<td>$r_c/r_w = 1.1, L_r = 9.1 μm, L_p = 7.7 μm</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Artique and Bruley</th>
<th>This work</th>
</tr>
</thead>
<tbody>
<tr>
<td>plasma gap $P_O_2$</td>
<td>-</td>
<td>39 mmHg</td>
</tr>
<tr>
<td>plasma film $P_O_2$</td>
<td>-</td>
<td>48 mmHg</td>
</tr>
<tr>
<td>Average plasma $P_O_2$</td>
<td>36 mmHg</td>
<td>41 mmHg</td>
</tr>
<tr>
<td>Tissue wall $P_O_2$</td>
<td>26 mmHg</td>
<td>33 mmHg</td>
</tr>
</tbody>
</table>

TABLE 5.2. Comparison of Intracapillary Oxygen Tension Distribution with that of Hideyuki and Sugihara (59).

Parameter values:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue Oxygen Consumption (as in [5.9])</td>
<td>$1.47 \times 10^{-7}$ gmols/cm³·sec</td>
</tr>
<tr>
<td>Krogh Cylinder radius</td>
<td>9.5 μm</td>
</tr>
<tr>
<td>Capillary Diameter</td>
<td>8 μm</td>
</tr>
<tr>
<td>Rbc Mean Oxygen Tension</td>
<td>50 mmHg</td>
</tr>
<tr>
<td>Parameters of this work</td>
<td>$r_c/r_w = 1.1, L_r = 11.7 μm, L_p = 36.6 μm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Hideyuki and Sugihara</th>
<th>This work</th>
</tr>
</thead>
<tbody>
<tr>
<td>plasma gap $P_O_2$</td>
<td>-</td>
<td>20 mmHg</td>
</tr>
<tr>
<td>plasma film $P_O_2$</td>
<td>-</td>
<td>48 mmHg</td>
</tr>
<tr>
<td>Average plasma $P_O_2$</td>
<td>43 mmHg</td>
<td>22 mmHg</td>
</tr>
<tr>
<td>Tissue wall $P_O_2$</td>
<td>39 mmHg</td>
<td>20 mmHg</td>
</tr>
</tbody>
</table>
Fig. 5.7a: Effect of flowrate, Q, on oxygen release from red blood cell suspensions flowing in a single file with a cell spacing of one red cell length through a 5 μm capillary. The P_{50} is 25 mmHg. Curves are theoretical simulations. Parameters shown are values of Q in μl/hr.
Fig. 5.7b: Effect of flowrate, $Q$, on oxygen uptake by red blood cell suspensions flowing in a single file with a cell spacing of one red cell length through a 5 μm capillary. The $P_{50}$ is 25 mmHg. Curves are theoretical simulations. Parameters shown are values of $Q$ in μl/hr.
uptake. The overall Nusselt numbers are exactly the same for all flow rates.

Fig 5.8 a,b show the effect of $P_{50}$ on release and uptake. An increase in $P_{50}$ helps release more oxygen to tissue. An increase in $P_{50}$ does not affect the uptake characteristics as much as release.

Fig 5.9 a,b show the effect of the Hill equation parameter, $n$, on release and uptake. In the normal range of values of $n$, 2-3, there is not much of an effect. Close to $n=1$ when the Hill equation becomes hyperbolic, the effect is great due to the incorrect equilibrium curve (109).

Figs 5.10 a,b show the effect of the capillary radius on release and uptake. The residence time, the $r_c/r_w$ ratio and the hematocrit are kept the same. With increase in radius there is a decrease in $O_2$ saturation change.

Figs 5.11 a,b show that the cell spacing (tube hematocrit) has a greater effect on release than on uptake.

Figs 5.12 a,b and Fig 5.13 a,b show the effects of some of the model parameters: $r_w$, $L_r$ on the oxygen transport. Figs 5.12 a,b show the effect of a change in the radius of the rbc, $r_w$, keeping the rbc length the same (change in $S/V$ and cell-capillary wall clearance). Fig 5.13 a,b show the effect of changing the length of the rbc (change in $S/V$) keeping the rbc radius and tube hematocrit constant. In all four cases the effects are small, although $r_w$ has a small
Fig. 5.8a: Effect of oxygen affinity of the hemoglobin molecule as indicated by the \( P_{50} \), on oxygen release from red blood cell suspensions flowing in a single file with a cell spacing of one red cell length through a 5 \( \mu \text{m} \) capillary. Curves are theoretical simulations. Parameters shown are values of \( P_{50} \) in mmHg.
Fig. 5.8b: Effect of oxygen affinity of the hemoglobin molecule as indicated by the $P_{50}$ on oxygen release from red blood cell suspensions flowing in a single file with a cell spacing of one red cell length through a 5 μm capillary. Curves are theoretical simulations. Parameters shown are values of $P_{50}$ in mmHg.
Fig. 5.9a: Effect of Hill parameter, $n$, on $O_2$ release from red blood cell suspensions flowing in a single file with a cell spacing of one red cell length through a 5 $\mu$m capillary. The $P_{50}$ is 25 mmHg. Curves are theoretical simulations. Parameters shown are values of $n$. 
Fig. 5.9b: Effect of Hill parameter, \( n \), on \( O_2 \) uptake by red blood cell suspensions flowing in a single file with a cell spacing of one red cell length through a 5 \( \mu m \) capillary. The \( P_{50} \) is 25 mmHg. Curves are theoretical simulations. Parameters shown are values of \( n \).
Fig. 5.10a: Effect of capillary radius, $r_c$, on $O_2$ release from red blood cell suspensions flowing in a single file with a cell spacing of one red cell length through small capillaries. The $P_{50}$ is 25 mmHg. Curves are theoretical simulations. Parameters shown are values of $r_c$ in $\mu$m.
Fig. 5.10b: Effect of capillary radius, $r_c$, on O$_2$ uptake from red blood cell suspensions flowing in a single file with a cell spacing of one red cell length through small capillaries. The $P_{50}$ is 25 mmHg. Curves are theoretical simulations. Parameters shown are values of $r_c$ in μm.
Fig. 5.11a: Effect of cell spacing, $L_p$, on oxygen release from red blood cell suspensions flowing in a single file through a 5 $\mu$m capillary. The $P_{50}$ is 25 mmHg. Curves are theoretical simulations. Parameters shown are values of cell spacing in rbc lengths.
Fig. 5.11b: Effect of cell spacing, \( L_p \), on oxygen uptake by red blood cell suspensions flowing in a single file through a 5 \( \mu \)m capillary. The \( P_{50} \) is 25 mmHg. Curves are theoretical simulations. Parameters shown are values of cell spacing in rbc lengths.
Fig. 5.12a: Effect of rbc radius, $r_W$, on $O_2$ release from red blood cell suspensions flowing in a single file with a cell spacing of one red cell length through a 5 μm capillary. The $P_{50}$ is 25 mmHg. Curves are theoretical simulations. Parameters shown are values of $r_C/r_W$. 
Fig. 5.12b: Effect of rbc radius, $r^*_W$, on $O_{2}$ uptake by red blood cell suspensions flowing in a single file with a cell spacing of one red cell length through a 5 $\mu$m capillary. The $P_{50}$ is 25 mmHg. Curves are theoretical simulations. Parameters shown are values of $r^*_C/r^*_W$. 
Fig. 5.13a: Effect of rbc length, $L_r$, on $O_2$ release from red blood cell suspensions flowing in a single file with a cell spacing of one red cell length through a 5 $\mu$m capillary. The $P_{50}$ is 25 mmHg. Curves are theoretical simulations. Parameters shown are values of $L_r$ in $\mu$m.
Fig. 5.13b: Effect of rbc length, \( L_r \), on \( O_2 \) uptake by red blood cell suspensions flowing in a single file with a cell spacing of one red cell length through a 5 \( \mu \text{m} \) capillary. The \( P_{50} \) is 25 mmHg. Curves are theoretical simulations. Parameters shown are values of \( L_r \) in \( \mu \text{m} \).
but significant effect on release. There is more release at smaller $r_w$, corresponding to an increase in $\left[ \frac{S}{V} \right]_{rbc}$.

$C_H$ has an effect on both uptake and release (Fig 5.14 a,b). The time taken for a given $O_2$ saturation change is approximately directly proportional to the heme concentration in the rbc, just as for hemoglobin solutions as seen in Ch 3.

5.3.4 Effect of the Nusselt numbers used in the model

$(\text{Nu}_{rf}, \text{Nu}_{cf}, \text{Nu}_{zr}, \text{Nu}_{zg}, \text{Nu}_{cg}, \text{Nu}_{zf})$.

The Nusselt numbers in the plasma film ($\text{Nu}_{rf}, \text{Nu}_{cf}$) affect the results the most of all the Nusselt numbers. The effects of doubling and halving of the Nusselt number from its calculated value is studied. $\text{Nu}_{rf}$ has a less than 5 % effect on the oxygen saturations. $\text{Nu}_{cf}$ has a 10 % effect. $\text{Nu}_{zr}$ has less than 5 % effect. The rest of the Nusselt numbers have a less than 1 % effect on the saturations. Again for all these calculations equations [5.24]-[5.27] and [5.29] are used for the calculation of $F_c$. 
Fig. 5.14a: Effect of the internal heme concentration, $C_H$, on $O_2$ release from RBC suspensions flowing in a single file with a cell spacing of one red cell length, through a 5-μm capillary. The $P_{50}$ is 25 mmHg. Curves are theoretical simulations. Parameters shown are values of $C_H$ in mM.
Fig. 5.14b: Effect of the internal heme concentration, $C_H$, on $O_2$ uptake by rbc suspensions flowing in a single file with a cell spacing of one red cell length, through a 5 $\mu$m capillary. The $P_{50}$ is 25 mmHg. Curves are theoretical simulations. Parameters shown are values of $C_H$ in mM.
5.3.5 Effect of the kinetic constant, $k$ and physical properties, $D_{O2}$, $D_{HbO2}$, and $\beta$.

The kinetic constant has a less than 1% effect on both release and uptake for values twice as much and half that of the value used.

Oxygen diffusivity has a small effect when changed in the range of values for the plasma and hemoglobin solutions with pertinent concentrations (less than 3%). Hemoglobin diffusivity has a small effect on both uptake and release (less than 5%), even in the extreme case of an order of magnitude change. The solubility has a small effect (less than 5%) when changed in the range of values for the plasma and hemoglobin solutions with pertinent concentrations.

5.3.6 Distribution of resistances

The distribution of resistances in the various regions within the capillary for uptake and release are shown in Table 5.3
<table>
<thead>
<tr>
<th>Type of Transport and state of the tissue</th>
<th>Rbc</th>
<th>Plasma</th>
<th>Endothelium</th>
<th>Extravascular space</th>
<th>Tissue</th>
<th>Inlet - Exit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Release at rest</td>
<td>25 - 11</td>
<td>3.5 - 2</td>
<td>10.5 - 13</td>
<td>16 - 19</td>
<td>45 - 55</td>
<td></td>
</tr>
<tr>
<td>Release during exercise</td>
<td>37 - 23</td>
<td>4 - 3.6</td>
<td>16 - 19.4</td>
<td>24 - 30</td>
<td>19 - 24</td>
<td></td>
</tr>
<tr>
<td>Uptake at rest</td>
<td>67 - 89</td>
<td>19 - 6</td>
<td>-</td>
<td>-</td>
<td>14 - 5</td>
<td></td>
</tr>
<tr>
<td>Uptake during exercise</td>
<td>48 - 68</td>
<td>29 - 16</td>
<td>-</td>
<td>-</td>
<td>23 - 16</td>
<td></td>
</tr>
</tbody>
</table>
5.3.7 Overall Nusselt numbers.

Figs 5.15 to 5.19 a and b show the effects of various parameters on the Nusselt number. The Nusselt number is plotted as a function the space average saturation \( \langle y \rangle \) in these figures. In this case, the mixed mean saturation is the same as the space average saturation. The Nusselt number does not vary with \( \langle y \rangle \) for release. For uptake however, the Nusselt number decreases with increasing \( \langle y \rangle \).

For release the Nusselt number increases with increasing radius of the rbc (Fig 5.15 a) or decreasing \( r_c/r_w \) values. The Nusselt number increases with decreasing cell spacing for release (Fig 5.16 a). There is a slight decrease in Nusselt number with increase in rbc length (Fig 5.17 a). As the radius of the capillary is increased keeping \( r_w/r_c \) the same, the Nusselt number increases for release (Fig 5.19 a).

There is an increase in Nusselt number for an increase in the oxygen consumption in the tissue up to a certain level, after which it remains the same (Fig 5.18 a). For uptake, the variations are different. For higher \( \langle y \rangle \)'s the Nu increases slightly with decreasing tube diameter. For lower \( \langle y \rangle \)'s the behaviour is reversed (Fig 5.19 b). The behaviour is similar with \( P_{\text{ext}} \) (Fig 5.18 b). At lower \( \langle y \rangle \) the Nu decreases with decreasing \( P_{\text{ext}} \) with a reversal at higher \( \langle y \rangle \). The Nusselt number increases with increasing cell spacing (decreasing hematocrit) (Fig 5.16 b), for uptake, which is
Fig. 5.15a: Nusselt number vs mixed mean saturation for release from 5μm capillaries. Effect of rbc radius, when cell spacing is 8 μm, cell length is 8 μm and the tissue oxygen consumption is 3.75x10^{-8} mols/cc sec. Parameters shown are values of $r_C/r_W$. 
Fig. 5.15b: Nusselt number vs mixed mean saturation for uptake by 5 μm capillaries. Effect of rbc radius, when cell spacing is 8 μm, cell length is 8 μm and the oxygen tension in the alveolar gas is 100mmHg. Parameters shown are values of $r_c/r_w$. 


Fig. 5.16a: Nusselt number vs mixed mean saturation for release from 5 μm capillaries. Effect of cell spacing, $r_C/r_W$ is 1.1, cell length is 8 μm, and the tissue oxygen consumption is $3.75 \times 10^{-8}$ mols/cc sec. Parameters shown are values of $L_p$ in μm.
Fig. 5.16b: Nusselt number vs mixed mean saturation for uptake by 5 μm capillaries. Effect of cell spacing, $r_c/r_w$ is 1.1, cell length is 8 μm, and the oxygen tension in the alveolar gas is 100 mmHg. Parameters shown are values of $L_D$ in μm.
Fig. 5.17a: Nusselt number vs mixed mean saturation for release from 5μm capillaries. Effect of red cell length, when $r_c/r_w$ is 1.1, cell spacing is 8 μm, and the tissue oxygen consumption is $3.75 \times 10^{-8}$ mols/cc sec. Parameters shown are values of $L_R$ in μm.
Fig. 5.17b: Nusselt number vs mixed mean saturation for uptake by 5μm capillaries. Effect of red cell length, when r_c/r_w is 1.1, cell spacing is 8 μm, and the alveolar gas tension is 100 mmHg. Parameters shown are values L_P in μm.
Fig. 5.18a: Nusselt number vs mixed mean saturation for release from 5 µm capillaries. Effect of tissue $O_2$ consumption when $r_c/r_w$ is 1.1, cell spacing is 8 µm, and the cell length is 8 µm. Parameters shown are values of the tissue oxygen consumption in mols/cc sec.
Fig. 5.18b: Nusselt number vs mixed mean saturation for uptake by 5μm capillaries. Effect of O₂ tension in the alveolar gas, when $r_c/r_w$ is 1.1, cell spacing is 8 μm, and the cell length is 8 μm. Parameters shown are values of the external gas tension in mmHg.
Fig. 5.19a: Nusselt number vs mixed mean saturation for release from small capillaries. Effect of tube diameter, when $r_c/r_w$ is 1.1, cell spacing is 8 µm, cell length is 8 µm, and the tissue oxygen consumption is $3.75 \times 10^{-8}$ moles/cc sec. Parameters shown are values of the diameter in µm.
Fig. 5.19b: Nusselt number vs mixed mean saturation for uptake by small capillaries. Effect of tube diameter, when \( r_c/r_w \) is 1.1, cell spacing is 8 \( \mu m \), cell length is 8 \( \mu m \), and the alveolar gas tension is 100 mmHg. Parameters shown are values of the diameter in \( \mu m \).
opposite to the effect of cell spacing for release. The rbc length has a very small effect on the nusselt number for uptake (Fig 5.17 b). The rbc radius has a great effect on the Nusselt number for uptake. For most of the region of \( \langle y \rangle \)'s, the Nu decreases with decreasing \( r_w \). The behaviour reverses only at high \( \langle y \rangle \)'s. The \( P_{50} \) has a negligible effect and flow rate has no effect on the Nusselt numbers for either release or uptake.

The Nusselt number for an equivalent solution of Hb flowing through the capillary under similar conditions is about 4 as compared to about 1 for rbc suspensions.

5.4 Discussion and conclusions

5.4.1 In vivo release and uptake

In the tissue there is up to a 20 fold increase in oxygen consumption per unit mass of tissue with exercise (119). The Figs 5.4 and 5.5 illustrate that the capillary can more than compensate for this increased flux by adjustment in its flow rate, \( P_{50} \), Hct and capillary density. For Fig 5.4 the maximum observed changes in each of these quantities has been used with a 20 fold increase in \( O_2 \) consumption. In actuality not all parameters change. One or more of them
may change to provide the tissue with enough oxygen. If all
the parameters do not work in unison the saturation may fall
to 25 percent at the exit as observed in vivo (119). If
none of these parameters are changed the saturation falls to
0 percent very close to the inlet which would result in
hypoxia. When all the oxygen supply enhancement factors are
changed simultaneously the saturation is still 68 percent at
exit, showing that the healthy capillaries can easily supply
the tissue with the required oxygen. An increase in
flowrate increases the amount of oxygen supplied to the tis-
sue by increasing the convective inflow of blood carrying
\( O_2 \). The reduction in the residence time helps keep the sa-
turation from falling excessively, thus maintaining a suffi-
ciently high \( P_{O2} \) in the blood. The increase in \( P_{50} \) with
exercise helps release more \( O_2 \) by decreasing the \( O_2 \) affinity
of Hb. An increase in hematocrit or a decrease in red cell
spacing tends to keep the \( O_2 \) tension in the plasma gap from
falling. Increasing the hematocrit increases the amount of
bound \( O_2 \) in the system, taking it longer for it to reach the
same saturation since more \( O_2 \) has to be transported.

In the case of uptake an increase in flowrate helps in-
crease the rate at which \( O_2 \) is picked up. However, the in-
crease in \( P_{50} \) and flowrate require a longer residence time
before the blood is completely saturated. The capillaries
in the lungs are overdesigned, as far as the resting
condition is concerned. Hence, at rest only a small fraction of the length of the capillary is made use of for uptake. The rest of the length is made use of during exercise, when it takes a longer length before the blood approaches complete saturation as seen in Fig 5.5.

5.4.2 Comparison of models

As suggested by Hellums (55) and Popel and Gross (97) the presence of rbcs indeed introduces a resistance which is vastly underestimated by considering blood to be a solution of Hemoglobin. This is clearly illustrated in Figs 5.6a and b. The small capillary model in this work is also compared with some of the earlier models. The Reneau model and the Hb solution models essentially consider blood to be a single phase continuous fluid. They vastly underestimate the resistance. Most of the other models are similar to the plasma model suggested by Baxley. The SCM estimates a slightly lower resistance than these models, because it takes into account the oxygen transport from the rbc to the plasma gap. Also, it takes into account the difference in velocities between the plasma and the rbc (reduction in tube hematocrit from feed hematocrit) and convection due to the relative motion between the rbc and the plasma in the plasma film. In the plasma gap pure diffusion is considered since
it has been found by earlier studies (2), that the microconvection in the bolus flow in the plasma gap is negligible.

The difference in the plasma oxygen tensions between the model in this work and the Artigue and Bruley model, is due to the use of different mass transfer coefficients at the rbc wall in the two models. Artigue uses an overall mass transfer coefficient of 0.018 cm/sec compared to 0.34 cm/sec used by the SCM at the rbc plasma film boundary. Due to the higher resistance used by Artigue there is a larger drop. The mass transfer coefficient used by Artigue is from the work of Ono and Tazawa (91) who measured this resistance by \(O_2\) transport measurements to single rbc's on glass slides. The configuration and the flux in these single cell measurements are different from those in the capillary. Hence, the mass transfer coefficients are different. However, the mass transfer coefficient at the plasma gap-rbc wall boundary is 0.02 cm/sec, comparable to that used by Artigue. As a result, the oxygen tension in the plasma gap is comparable to that obtained by Artigue.

Hideyuki and Sugihara also lump the rbc and plasma resistance into a mass transfer coefficient. They used a value of 0.064 cm/sec as compared to 0.38 cm/sec at the rbc-plasma film boundary and 0.04 cm/sec at the rbc-plasma gap boundary as used by the SCM. Hence, the oxygen tension in the plasma film as predicted by the SCM is greater than the average
plasma oxygen tension predicted by Hideyuki and Sugihara and that in the plasma gap is less.

From Fig 5.15 a and 5.19 a we see that the Nusselt number is a function of both $r_c/r_w$ and $r_c$ and not just $r_c/r_w$ as in Federspiel's work. The Nusselt numbers predicted by Federspel's model are consistently lower than the small capillary model even though they follow the same trend. This difference is due to the fact that different geometries were used for the rbcs. As has been observed (Fig 5.15 a, 5.17 a) the dimensions and the shape of the rbc can make a difference in the Nusselt numbers. Also, due to the different geometries the tube hematocrit is different for the same $L_p$ and $r_c/r_w$. Federspiel's model calculates a lower hematocrit for the same $L_p$. A lower hematocrit would result in a lower Nusselt number. Also the flux is lower in the SCM for the same tissue oxygen consumption, due to the inclusion of the endothelium and extravascular space between the tissue and the capillary. As seen from Fig 5.18 a the Nusselt number is higher at lower fluxes.
5.4.3 Effects of parameters, $Q$, $P_{50}$, $n$, $r_c$, $L_p$, $r_w$, $L_r$, $C_H$.

The flow rate does not affect the mass transfer resistance as observed by unchanged Nusselt numbers with changes in flowrate. The flowrate changes the residence time and hence the release and uptake characteristics. The $P_{50}$ effect works to our advantage in that a rise in $P_{50}$ as observed during exercise aids release but does not affect uptake as much.

In Fig 5.10a, $r_c$ is increased by keeping the ratio of the rbc to capillary radius, the $L_p/L_r$ ratio and the surface area of the rbc the same. Hence, there is an increase in $r_c$ and a decrease in $L_r$ and $L_p$ all of which results in a higher Nusselt number (Fig 5.19 a, 5.16 a, 5.17 a). In other words there is a lower resistance for a higher radius tube. But the decrease in the S/V ratio of both the rbc and the capillary far outweighs the decrease in resistance leading to a smaller change in oxygen saturation. In case of uptake, the increase in $r_c$ and decrease in $L_p$ reduce the Nusselt number slightly (Fig 5.19 b, 5.16 b). Also the S/V ratio of the rbc and the capillary is reduced. However the effect of increasing $r_c$ on oxygen uptake is much less pronounced than release as seen in Figs 5.10 a,b. This seems to be consistent with the fact that there are smaller sized vessels in the skeletal muscles as compared to those in the lungs.

The change in cell spacing affects oxygen release. Hence
a decrease in spacing during exercise increases the O$_2$ flux into the tissue and also prevents the oxygen saturation from becoming too low. The cell spacing does not affect the capillary length required for complete saturation. Hence, even though the cell spacing decreases during exercise, blood does not require very much extra time to oxygenate.

The effect of decreasing the rbc radius, keeping the radius of the capillary constant, has a marked effect on release but a negligible effect on uptake. The surface to volume ratio of the rbc can be changed by changing the rbc radius or the rbc length.

\[
\frac{S}{V_{rbc}} = \frac{2}{L_r} + \frac{2}{r_w}
\]

Changing $L_r$ does not affect the S/V ratio as much as changing $r_w$. Hence, from Figs 5.12 a,b and 5.13 a,b we can deduce that the S/V ratio has an appreciable effect on release but a negligible effect on uptake. Also, changing $L_r$ has a small effect on the resistance for uptake (Fig 5.17 b), and release (Fig 5.17 a). The O$_2$ transport is not very different between the two cases where $L_r$ is the only difference. Changing the radius of the rbc has no effect on uptake since two opposing effects cancel each other. By decreasing $r_w$ the S/V is increased. However there is a marked increase in the resistance (Fig 5.15 b) which compensates for this increase in S/V. In the case of release the
increase in resistance is not as high as in uptake and the increase in S/V has an effect on the transport which is observed in Fig 5.12 a.

5.4.4 Mechanisms governing oxygen transport in small capillaries.

The sensitivity studies with the various Nusselt numbers used in the model shows the important mass transfer steps. Any good model for small capillaries should include radial diffusion in the rbc and plasma film. Axial diffusion in the rbc has a negligible effect. The S/V ratio has to be accurate especially for release calculations. The higher velocities of the rbc due to the decrease in the hematocrit with respect to the feed hematocrit has to be taken into account. Reaction kinetics are not very important. The internal heme concentration affects the oxygen transport characteristics. It takes twice the time to oxygenate or deoxygenate rbc with twice the heme concentration.
5.4.5 Overall Nusselt number - Effects of parameters on resistance to oxygen transport.

The marked decrease in the Nusselt numbers for uptake with an increase in the cell to capillary wall clearance (Fig 5.15 b) is related to the resistance to oxygen transport in the plasma (Table 5.1). Increasing the thickness of this plasma film increases the resistance. The percent resistance in the plasma film is smaller towards the end of the capillary at higher \( \langle y \rangle \). In this region the rbc resistance is high. Hence decreasing the rbc radius decreases the overall resistance at high \( \langle y \rangle \) (Fig 5.15 b). In the case of release the plasma resistance is low over the entire length of the capillary. Also the total fraction resistance within the capillary is smaller than for uptake (Table 5.1). Hence, the change in resistance with a change in clearance is less marked for release (Fig 5.15 a) than for uptake.

The rbc length has a negligible effect on the Nusselt number for both uptake and release (fig 5.17) since axial diffusion is not as important as radial diffusion. The cell spacing however has an effect. By increasing the spacing the average wall concentration decreases for release thereby resulting in a decrease in the Nusselt number. In case of uptake the average wall concentration increases, since in the plasma gap region \( O_2 \) tension tends to rise very fast as compared to the plasma film region due to its low
capacitance. Also, the plasma gap is not as close to the high capacitance region (the rbc) as the plasma film on an average.

As seen from Figs 5.15 a - 5.19 a, the Nusselt number depends on the ratio of the tube to cell radius, the cell spacing and the tube radius. The Nusselt number does not depend on \( r_c/r_r \) and \( L_p/L_r \) only. This can be clearly seen by comparing the Nusselt numbers when \( L_p = 6.4 \), \( L_r = 8 \) and when \( L_r = 10 \), \( L_p = 8 \). In both cases \( L_p/L_r = 0.8 \). However, the Nusselt numbers are 1.8 and 1.25 respectively, all other condition remaining the same. Also \( r_c \) has an effect even though \( r_c/r_w \) is unchanged. When \( r_c = 3, r_c/r_w = 1.1 \) \( Nu = 1.84 \). When \( r_c = 2.5 \), \( r_c/r_w = 1.1 \) \( Nu = 1.37 \), all other conditions remaining the same between the two cases being compared.

5.4.6 Distribution of resistances

From the distribution of resistances calculations it is found that for release a significant amount of the transport resistance lies in the capillary at rest and more so during exercise. For uptake, the resistance in blood is a major fraction in both rest and exercise. This result is due to the very thin layer of tissue separating the alveolar sacs and the blood. In release, however there is a significant amount of the resistance in the endothelium and
extravascular space. The resistance in this region would strongly depend on the dimensions of this space, which were taken to be 1 μm and 2 μm (119). There would be a sharp decrease in the transport resistance in this region with a decrease in thickness here. Such a decrease in thickness may happen in vivo due to the stretching of the muscles during exercise, which reduces the wall thickness and perhaps brings the tissue closer to the capillary wall.

These resistances were calculated using a simple Krogh cylinder as the tissue model. The inhomogeneous distribution of the mitochondria, the myoglobin facilitated diffusion in the tissue and the increase in capillary density at the venular end are not taken into account in the tissue model. The ΔP_{tissue} calculated using these tissue features would be closer to reality than that calculated for the Krogh cylinder. Some work has been done in this area (24, 40, 62, 119). The myoglobin facilitated diffusion could decrease the fraction resistance in the tissue by 10% in the range of P_{50} of myoglobin. The decrease in the tissue radius (increase in capillary density) at the venular end would decrease the fraction resistance at the venular end by about 10%. In the Krogh cylinder model, it is found that the tissue resistance is higher by about 10% at the venular end. Hence, the decrease in tissue radius at the venular
end is a natural adaptation for more efficient oxygen transport.

5.4.7 Prediction of capillary wall oxygen fluxes in small capillaries

The flux can be calculated as in Ch 4 equations 4.45 and 4.46. For the small capillaries \( P_{eq} = P'_r \) for release. For uptake the ratio of \( P'_r \) to \( P_{eq} \) is slightly greater than 1 in the 0 - 100 mmHg range and is shown in Fig 5.20. Again as in Ch 4 there is less than 5% variation in the \( P'_r \) vs \( P_{eq} \) curves with the various parameters.
Fig. 5.20: Mixed mean RBC oxygen tension, $P'_m$, as a function of the oxygen tension, which is in equilibrium with the mixed mean oxygen saturation for uptake by small capillaries.
CHAPTER 6

CONCLUSIONS AND FUTURE WORK

6.1 Conclusions from the large capillary work

1) The resistance to $O_2$ transport from red blood cell suspensions flowing through large capillaries is higher than that of the equivalent hemoglobin solution. Hence, oxygen transport in blood cannot be modelled accurately as if it were a solution of hemoglobin.

2) In the large capillaries, most of the resistance to oxygen transport lies in the plasma. In a 27 μm diameter capillary 98% of the resistance in blood lies in the plasma. In a 15 μm diameter capillary the plasma resistance is 97% and in a 100 μm diameter capillary it is 99.8%. This plasma resistance is distributed throughout the plasma. It is not concentrated in the boundary layer adjacent to the red cells.

3) The overall Nusselt number for mass transfer from the capillary varies from 5 to 3 for release, on an average, across the capillary length. For uptake, the variation is greater, from 2.5 to 6. The Nusselt number varies with hematocrit and diameter of the tube. The Nusselt number is
almost independent of $P_{50}$ and totally independent of flow rate.

4) The large capillary model developed here can be used with confidence for capillaries with diameters of 25 $\mu$m and larger. For the smaller sized vessels it could perhaps be used for vessels with diameters as small as 20 $\mu$m. Below diameters of 20 $\mu$m the resistance within the rbc becomes comparable to that in the plasma. We start getting deformation. In the smaller capillaries we also start getting single file flow. The large capillary model will not make accurate predictions in these smaller capillaries.

6.2 Conclusions from the small capillary work

1) In the small capillaries where the rbc's flow in a single file, the resistance in the rbc accounts for about 80% of the resistance in blood.

2) The diffusion of oxygen from the rbc to the plasma gap and the bulk convection in the plasma film enhance the oxygen transport rates by about 10%.

3) The resistance to oxygen transport from red blood cell suspensions flowing through the small capillaries is higher than that of the equivalent hemoglobin solution. Hence, oxygen transport in blood cannot be modelled accurately as if it were a solution of hemoglobin.

4) In release tissue at rest, at least 30% of the resistance to oxygen transport lies in the blood. During
exercise, this fraction increases to at least 40%. In uptake tissue, about 90% of the resistance lies in blood.

5) As the radius of the tube increases the resistance to oxygen transport decreases. However, there is a smaller change in oxygen saturation across the capillary length out of larger capillaries, due to the lower S/V ratio of the capillary. In the case of small capillaries, this effect of radius is more pronounced for release than for uptake. Hence the capillaries in the aerobic muscle tissues have a smaller diameter than in the lungs.

6) The overall Nusselt number for release from small capillaries is approximately constant across the capillary length and is about 1.5. For uptake, it varies from 1 to 10.

7) A decrease in cell spacing has an effect on release and a negligible effect on uptake. This helps during exercise, since the capillaries in the muscles can supply the tissue with more oxygen without becoming depleted of oxygen. At the same time the uptake times are not affected by the decreased cell spacing. Hence, more oxygen is taken in without requiring extra surface area (longer capillary lengths).

8) For small capillaries, the Nusselt number for mass transfer depends upon the cell clearance, the capillary
radius and the cell spacing. It does not depend appreciably on the \( P_{50} \) and flow rate.

9) The thickness of the endothelium and extravascular space for release tissue and the tissue separating the blood and the alveolar sacs in the lungs affects the oxygen transport rates. A decrease in thickness, as observed during exercise, increases the oxygen transported to tissue and the amount of oxygen taken up by the blood in the lungs.

6.3 General conclusions

1) Since the absolute gradients for uptake are roughly 10 times greater than those observed for release, much longer transit times are required for complete deoxygenation, and this explains the need for longer capillaries in aerobic muscle tissues.

2) An increase in the \( P_{50} \) of blood increases release rates but does not affect the uptake rates appreciably. This works in our favour since, there is an increase in \( P_{50} \) during exercise which helps release more oxygen to tissue without affecting the amount of oxygen taken up in the lungs.

3) The experimental system developed by Boland et al (13), has been validated with the help of the model for hemoglobin solutions and can be used for the study of oxygen transport in the microcirculation.
6.4 Future work

6.4.1 Critical testing of models over a range of diameters.

The small bore model is thought to be on a sound basis for small capillaries (10 μm diameter and smaller), but it has not been tested critically by comparison with experiment. The large bore model has been shown to agree with experimental data for large capillaries 27 μm in diameter. Its applicability to smaller diameters has to be tested.

The experimental methodology faces some important difficulties. One of these difficulties is addressed by means of a pilot study outlined below. A key question concerns the distribution of resistance to oxygen transport in the small capillaries. If the silicone rubber film thickness is too large in proportion to the lumen of the imbedded capillary, the method will have problems. The resistance to oxygen transport in the silicone rubber film could be of dominant importance. In that case, it would be impossible to determine the intracellular resistance accurately. As an example the oxygen tension distribution through a 90 μm film and the capillary is calculated. The calculations are for a 10 μm capillary perfused with 1.25 mM hemoglobin solution, at a flow rate in the physiological range of 9.0 μl/hr. The solution releases oxygen as it passes through the capillary in a way analogous to release experiments previously
described. It can be seen that the oxygen tension drop in the lumen is a substantial fraction of the overall drop. In fact, in this instance, 61% of the resistance to oxygen transport is in the capillary and 39% in the silicone film external to the capillary. Boland, Hellums and Olson have fabricated films of 90 \( \mu \text{m} \) thickness in a reproducible way. Calculations of the type discussed above using the small capillary model can serve to aid in the design of experiments.

In the intermediate range of diameters from about 8 \( \mu \text{m} \) to 20\( \mu \text{m} \) neither the large capillary model nor the small capillary model would work well. In this region various assumptions used in these models break down. In the larger capillary there is multifile flow and hence the small capillary model which is developed for single file flow cannot be applied. Also, in cases where there is single file flow but where the rbc's are relatively undeformed and move oriented perpendicular to the tube axis, the small capillary model would fail since axial diffusion in the rbc becomes important and it may not be accurate to lump resistances in the plasma. The large capillary model fails in this region because the radius of the cell rich layer is calculated assuming that the rbc is undeformed. This is an inaccurate assumption in these capillaries since the rbc's deform even in multifile flow at higher hematocrits, resulting in a
smaller cell free layer thickness than that calculated in the large capillary model.

In this range of intermediate diameters perhaps a new model would have to be developed or the models of this work have to be modified by introducing some empiricism into them. These can be validated by the experiments, the capillaries for which have been fabricated by Boland et al as mentioned earlier. It is interesting to note that in 100 μm capillaries the Nusselt number is about 5 for release. This decreases to about 4 for 30 μm capillaries. These are as predicted by the large capillary model. For the 5 μm capillaries the Nusselt number is 1.5 as predicted by the small capillary and this rises to about 2.0 for 6 μm capillaries. Hence, the Nusselt numbers in the intermediate range would be expected to be in the 2 - 4 range. The large capillary model predicts a Nusselt number of about 2.3 for 15 μm diameter tubes and 0.9 for 10 μm tubes. The small capillary model predicts Nusselt numbers of 7 for the 15 μm tube and 5 for the 10 μm tube. Hence, it seems as though the large capillary model overestimates the resistance in intermediate sized tubes, which is expected due to the overestimation of the cell free layer thickness. The small capillary model seems to underestimate the resistance in these intermediate sized vessels.
6.4.2 Cell size, shape and type

The models should be critically tested by examining the effect of cell shape and size experimentally. This could be done by altering osmotically, the shape of human cells and by measuring the rates of gas exchange of red blood cells from other species.

6.4.3 Pathological cases

The model should be applied to oxygen transport from blood in certain pathological cases. By observing the change in oxygen transport from experiments and analyzing the data obtained with the help of the model, the key parameters which are affected, which in turn affect the oxygen transport, can be identified. Effects of cell age can be examined. Red blood cells from patients with iron deficiency, thalassemia minor, red cell pyruvate kinase deficiency, and hereditary spherocytosis may be studied. It should also be interesting to study cells which have been subjected to sublethal damage by shear stress (as might occur through a prosthetic device) to determine if the oxygen transport function is impaired and if so why.
6.4.4 Effect of drugs on oxygen transport

The key parameters which are affected by drugs which in turn affect the oxygen transport could be studied by simulation with the model, of experiments using drugs. The experiments could be performed on the in-vitro system described in Ch 2.

6.4.5 Incorporation of CO₂ transport

A validated mathematical model of the transport processes with the additional species, additional chemical reactions, and modification of oxygen affinity needs to be developed. The feasibility of measuring CO₂ exchange in the artificial capillary system should also be examined.

6.4.6 Artificial red cells

A variety of workers have shown that liposome-encapsulated hemoglobin can serve as a red blood cell surrogate (28,43,63). These cells can be examined in the in vitro capillary system. The large capillary model could be used to predict oxygen transport from these artificial cells since the cell size is small compared to the capillary radius (~0.2 µm in diameter). This could be verified by the in vitro capillary system. Such a model could be of great utility when artificial red cells are used for oxygen transport.
6.4.7 Erythrocyte-associated transients

When small bore capillaries and low hematocrits are considered, it is essential that the erythrocyte be considered as discrete entities. It may also be important to consider the effects on the extracapillary medium (the tissue in-vivo, or the silicone film in the in-vitro system).

The treatment of the erythrocytes as discrete entities implies that it is necessary to consider transients in tissue mass flux caused by the erythrocytes. The term erythrocyte-associated transient is used here to distinguish such transients from longer term effects as might be due to flow pulsations, to changes in arterial oxygen tension, or to changes in metabolic rates.

The erythrocyte associated transients are of a time scale of about 0.02 secs, as compared to a tissue response time of 0.7 secs (55). Hence, the bulk of the tissue responds one order of magnitude more slowly than the cycle time of fluctuations imposed at the tissue-blood interface by the passing erythrocytes. Thus, as a first approximation, the response of the bulk of the tissue can be predicted with sufficient accuracy by using an average wall concentration or an average wall flux. This approach has been used in this work.

A more accurate quantitative assessment of the error from neglect of these and other transients can be obtained by
solution of a transient model. A periodic flux boundary condition should be imposed on the tissue (or silicone rubber film) diffusion model. The solution of the periodic model should then be compared directly to the steady-state solution based on the averaged conditions.

6.4.8 Axial diffusion in the extracapillary medium

Over some ranges of the parameters, it is known that the axial transport in the tissue is not negligible for purposes of simulation of the tissue oxygen distribution (100,106). Under this circumstance, the interphase flux is not independent of position; and therefore in principle, the two diffusion problems (inside and outside the capillary) are coupled. They must be solved simultaneously - a considerable complication. A sensitivity study is required at the outset. Specifically, solutions are required over ranges of the parameters to determine the magnitude of the coupling effects. The work so far suggests that the intracapillary Nusselt number is not highly sensitive to changes in flux of the order of the changes with axial position in the capillary. The use of an axial-average Nusselt number may yield an adequate approximation, and tissue axial diffusion could be taken into account without loss of the important property that the two problems uncouple.
6.4.9 Comparison with in vivo measurements

There are considerable difficulties in obtaining measurements in vivo of sufficient accuracy to provide a critical test of a mathematical model. However, rapid progress is being made in this area by use of oxygen electrodes as well as the microspectrophotometric technique (33,95). Several workers are continuing to improve the methodology (32,35,36,37,103). The theoretical model should be tested for consistency with the more reliable in vivo measurements.

6.4.10 Capillary wall resistance

Even though most workers agree that the diffusion in the endothelium can be treated as diffusion through a layer of plasma (50,62,111), there has been some disagreement on this point (99). Rasio et al (99) have evidence from experiments conducted on the isolated Rete Mirabile of the eel, that the resistance to $O_2$ transport in the endothelium is orders of magnitude higher than that of an equally thick layer of plasma. This has to be more carefully studied, since the assumed values of the surface area of the capillaries used in their calculations could affect the results. Also eel endothelial cells in the rete are not typical of mammalian cells in the lungs since they are known to be thicker (119) and perhaps less permeable.
REFERENCES


APPENDIX

A.3.1 Dedimensionalized form of the transport equations for Hb solutions

The transport equations are

\[ 2v_m \left[ 1 - \left( \frac{r}{r_c} \right)^2 \right] \frac{\partial C}{\partial z} = \frac{D_{02}}{r} \frac{\partial}{\partial r} \left[ r \frac{\partial C}{\partial r} \right] - k'C_HC(1-y) + kC_{H^2} \]

\[ 2v_m \left[ 1 - \left( \frac{r}{r_c} \right)^2 \right] \frac{\partial y}{\partial z} = \frac{D_{Hb02}}{r} \frac{\partial}{\partial r} \left[ r \frac{\partial y}{\partial r} \right] + k'C(1-y) - ky \]

Dedimensionalizing

\[
x = \frac{r}{r_c}; \quad t = \frac{z}{L}; \quad u = \frac{C}{C_0}; \quad C_0 = \beta P_0; \quad u_{\text{ext}} = \frac{P_{\text{ext}}}{P_0}; \quad u_{\text{in}} = \frac{P_{\text{in}}}{P_0}
\]

\[
(1-x^2) \frac{\partial u}{\partial t} = \left( \frac{D_{02} L}{2v_m r_c^2} \right) \frac{1}{x} \frac{\partial}{\partial x} \left[ x \frac{\partial u}{\partial x} \right]
\]

\[
- \left( \frac{k' L C_0}{2v_m} \right) \left[ \frac{C_H}{C_0} \right] \left[ u(1-y) - \left( \frac{P_{50}}{P_0} \right) \frac{v^{1/n}}{(1-y)(1-n)/n} \right]
\]

\[
(1-x^2) \frac{\partial y}{\partial t} = \left( \frac{D_{Hb02} L}{2v_m r_c^2} \right) \frac{1}{x} \frac{\partial}{\partial x} \left[ x \frac{\partial y}{\partial x} \right]
\]

\[
+ \left( \frac{k' L C_0}{2v_m} \right) \left[ u(1-y) - \left( \frac{P_{50}}{P_0} \right) \frac{v^{1/n}}{(1-y)(1-n)/n} \right]
\]
At $x=0$

\[ \frac{\partial u}{\partial x} = 0 \]
\[ \frac{\partial v}{\partial x} = 0 \]

At $x=1$

\[ \frac{\partial v}{\partial x} = 0 \]
\[ \frac{\partial u}{\partial x} = \frac{K}{\beta D_{02} \ln \left( \frac{4a}{\pi r_c} \right)} \left( u-u_{\text{ext}} \right) \]

At $t=0$

\[ u = u_{\text{in}} \]
\[ y = \frac{\left[ \frac{u_{\text{in}} P_0}{P_{50}} \right]^n}{1 + \left[ \frac{u_{\text{in}} P_0}{P_{50}} \right]^n} \]

Rewriting the above equations in terms of dimensionless groups,

\[ (1-x^2) \frac{\partial u}{\partial t} = \frac{d_1}{x} \frac{\partial}{\partial x} \left[ x \frac{\partial u}{\partial x} \right] - d_2 d_3 \left[ u(1-y) - d_4 \frac{y^{1/n}}{(1-y)(1-n)/n} \right] \]

\[ (1-x^2) \frac{\partial v}{\partial t} = \frac{d_5}{x} \frac{\partial}{\partial x} \left[ x \frac{\partial v}{\partial x} \right] + d_2 \left[ u(1-y) - d_4 \frac{y^{1/n}}{(1-y)(1-n)/n} \right] \]

At $x=0$

\[ \frac{\partial u}{\partial x} = 0 \]
\[ \frac{\partial v}{\partial x} = 0 \]

At \( x=1 \)

\[ \frac{\partial v}{\partial x} = 0 \]

\[ \frac{\partial u}{\partial x} = d_6 (u - u_{\text{ext}}) \]

At \( t=0 \)

\[ u = u_{\text{in}} \]

\[ y = \left( \frac{u_{\text{in}}}{d_4} \right)^n \]

\[ 1 + \left( \frac{u_{\text{in}}}{d_4} \right)^n \]

where

\[ d_1 = \frac{D_{O_2} L}{2 v_m r_c^2} \]

\[ d_2 = \frac{k' L C_0}{2 v_m} \]

\[ d_3 = \frac{C_H}{C_0} \]

\[ d_4 = \frac{P_{50}}{P_0} \]

\[ d_5 = \frac{D_{HbO_2} d_1}{D_{O_2}} \]

\[ d_6 = \frac{K}{\beta D_{O_2} \ln \left( \frac{4 a}{\pi r_c} \right)} \]
### TABLE A.3.1. Parameters for theoretical calculations with Hb solutions.

<table>
<thead>
<tr>
<th>Capillary No.</th>
<th>Radius, cm</th>
<th>Length, cm</th>
<th>Silicone slab thickness, cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>$1.425 \times 10^{-3}$</td>
<td>0.5</td>
<td>$1.729 \times 10^{-2}$</td>
</tr>
<tr>
<td>37</td>
<td>$1.355 \times 10^{-3}$</td>
<td>0.5</td>
<td>$1.661 \times 10^{-2}$</td>
</tr>
<tr>
<td>41</td>
<td>$1.365 \times 10^{-3}$</td>
<td>0.5</td>
<td>$1.692 \times 10^{-2}$</td>
</tr>
<tr>
<td>45</td>
<td>$1.375 \times 10^{-3}$</td>
<td>0.5</td>
<td>$1.770 \times 10^{-2}$</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>N. Heme, mM</th>
<th>$D_{O_2}$ cm$^2$/s</th>
<th>$D_{HbO_2}$ cm$^2$/s</th>
<th>$\beta$ M/atm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (25°C)</td>
<td>$2.01 \times 10^{-5}$</td>
<td>$7.4 \times 10^{-7}$</td>
<td>$1.21 \times 10^{-3}$</td>
</tr>
<tr>
<td>2 (25°C)</td>
<td>$1.93 \times 10^{-5}$</td>
<td>$6.5 \times 10^{-7}$</td>
<td>$1.21 \times 10^{-3}$</td>
</tr>
<tr>
<td>2.3 (25°C)</td>
<td>$1.92 \times 10^{-5}$</td>
<td>$6.3 \times 10^{-7}$</td>
<td>$1.21 \times 10^{-3}$</td>
</tr>
<tr>
<td>3 (25°C)</td>
<td>$1.88 \times 10^{-5}$</td>
<td>$5.7 \times 10^{-7}$</td>
<td>$1.22 \times 10^{-3}$</td>
</tr>
<tr>
<td>4 (25°C)</td>
<td>$1.77 \times 10^{-5}$</td>
<td>$5.0 \times 10^{-7}$</td>
<td>$1.23 \times 10^{-3}$</td>
</tr>
<tr>
<td>4.6 (25°C)</td>
<td>$1.75 \times 10^{-5}$</td>
<td>$4.6 \times 10^{-7}$</td>
<td>$1.23 \times 10^{-3}$</td>
</tr>
<tr>
<td>4.9 (25°C)</td>
<td>$1.73 \times 10^{-5}$</td>
<td>$4.5 \times 10^{-7}$</td>
<td>$1.23 \times 10^{-3}$</td>
</tr>
<tr>
<td>4 (37°C)</td>
<td>$2.48 \times 10^{-5}$</td>
<td>$7.0 \times 10^{-7}$</td>
<td>$1.01 \times 10^{-3}$</td>
</tr>
<tr>
<td>4.9 (37°C)</td>
<td>$2.42 \times 10^{-5}$</td>
<td>$6.3 \times 10^{-7}$</td>
<td>$1.01 \times 10^{-3}$</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>pH (°C)</th>
<th>$P_{50}$, mmHg</th>
<th>$n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.4 (25°C)</td>
<td>2.48</td>
<td>7.5</td>
</tr>
<tr>
<td>7.4 + IP$_6$ (25°C)</td>
<td>2.14</td>
<td>27.0</td>
</tr>
<tr>
<td>7.3 (25°C)</td>
<td>2.91</td>
<td>6.3</td>
</tr>
<tr>
<td>7.3 (37°C)</td>
<td>2.2</td>
<td>15.3</td>
</tr>
<tr>
<td>8.2 (25°C)</td>
<td>2.8*</td>
<td>1.8*</td>
</tr>
<tr>
<td>7.4 (25°C)</td>
<td>3.05*</td>
<td>4.7*</td>
</tr>
<tr>
<td>6.6 (25°C)</td>
<td>3.02*</td>
<td>11.7*</td>
</tr>
<tr>
<td>7.4 + IP$_6$ (25°C)</td>
<td>2.7*</td>
<td>41.0*</td>
</tr>
</tbody>
</table>

$O_2$ permeability through silicone: $2.8 \times 10^{-7}$ M $\cdot$ cm$^2$ $\cdot$ atm$^{-1}$ at 25°C; $3.2 \times 10^{-7}$ M $\cdot$ cm$^2$ $\cdot$ s$^{-1}$ $\cdot$ atm$^{-1}$ at 37°C. Association rate constant, $k^{'(117)}$: $3 \times 10^{6}$ M$^{-1}$ $\cdot$ s$^{-1}$, $D_{O_2}$ {$O_2$ diffusion; $D_{HbO_2}$ oxyhemoglobin diffusion constant; $\beta$, $O_2$ solubility constant, $n$, Hill coefficient; $P_{50}$, $O_2$ half saturation pressure of hemoglobin; IP$_6$, inositol hexaphosphate. Asterisk (*) in bottom table indicates data taken from Imai and Yonetani (67, 68).
A.4.1 Simultaneous solution of equations [4.6]-[4.9]

\[
\frac{r_c}{r_c} \quad b = \frac{1}{b^n} 
\]

Equation [4.7] can be rewritten as

\[
QH_F = \int_0^r 2 \pi r D (1-slp) \left[ 1-B \left[ \frac{r}{r_c} \right]^2 \right] h_m \left[ 1-\left[ \frac{r}{r_c} \right]^m \right] dr
\]

\[
= 2 \pi r_c^2 D (1-slp) h_m \int_0^b x(1-Bx^2)(1-Gx^m)dx \quad [x = \frac{r}{r_c}]
\]

\[
\cdot \quad \frac{QH_F}{2 \pi r_c^2 D (1-slp) h_m} = \frac{b^2}{2} - \frac{G b^{m+2}}{m+2} - \frac{B b^4}{4} + \frac{B G b^{m+4}}{m+4}
\]

\[
\cdot \quad \frac{QH_F}{\pi r_c^2 D (1-slp) h_m} = b^2 \left[ 1 - \frac{2}{m+2} \right] - \frac{B b^4}{2} \left[ 1 - \frac{4}{m+4} \right] \quad [A.4.1.1]
\]

Equation [4.8] can be rewritten as

\[
Q(1-H_F) = \int_0^r 2 \pi r D \left[ 1-B \left[ \frac{r}{r_c} \right]^2 \right] \left[ 1-h_m \left[ 1-\left[ \frac{r}{r_c} \right]^m \right] \right] dr
\]

\[
+ \int_{r}^{r_c} 2 \pi r A \left[ 1-\left[ \frac{r}{r_c} \right]^2 \right] dr
\]

\[
\cdot \quad Q(1-H_F) = 2 \pi r_c^2 D \int_0^b x(1-Bx^2)(1-h_m(1-Gx^m))dx
\]

\[
+ 2 \pi r_c^2 A \int_0^1 \frac{1}{b} x(1-x^2)dx
\]

\[
\cdot \quad \frac{Q(1-H_F)}{2 \pi r_c^2 D} = \frac{(1-h_m)b^2}{2} - \frac{B(1-h_m)b^4}{4} + \frac{h_m G b^{m+2}}{m+2} - \frac{h_m G b^{m+4}}{m+4}
\]
\[ + \left[ \frac{1 - Bb^2}{1 - b^2} \right] \left[ \frac{1}{4} + \frac{b^4}{4} \frac{b^2}{2} \right] \]

\[ \frac{Q(1 - H_F)}{\pi r_c^2 D} = \frac{b^4}{2} \left[ 1 - \frac{4}{m+4} \right] - b^2 \left( 1 - \frac{2}{m+2} \right) \]

\[ + \frac{b^2}{2} (2 - Bb^2) \left( 1 - \frac{4}{m+4} \right) \]

\[ [A.4.1.3] \]

Equation [4.9] can be written as

\[ H_T = \frac{1}{\pi r_c^2} \int_0^{r_c} 2r \pi r h_m \left[ 1 - \frac{r}{r_c} \right] m \, dr \]

\[ \frac{r_c^2}{\pi r_c^2} \int_0^1 2\pi x h_m (1 - x^m) \, dx \quad (x = \frac{r}{r_c}) \]

\[ = 2b^2 h_m \int_0^1 x(1 - x^m) \, dx \]

\[ = b^2 h_m \left[ 1 - \frac{2}{m+2} \right] \]

\[ . \quad h_m = \frac{H_T}{b^2 \left[ 1 - \frac{2}{m+2} \right]} \quad [A.4.1.3] \]

From A.4.1.1 and A.4.1.2

\[ (1 - H_F)(1 - s lp) \frac{b^2 h_m}{H_F} \left[ \frac{Bb^4}{2} \left[ 1 - \frac{4}{m+4} \right] - b^2 \left[ 1 - \frac{2}{m+2} \right] \right] \]

\[ = h_m \left[ \frac{Bb^4}{2} \left[ 1 - \frac{4}{m+4} \right] - b^2 \left[ 1 - \frac{2}{m+2} \right] \right] + \frac{b^2}{2} (2 - Bb^2) \left( 1 - \frac{4}{m+4} \right) \]

\[ . \quad h_m \left[ b^2 \left[ 1 - \frac{2}{m+2} \right] - \frac{Bb^4}{2} \left[ 1 - \frac{4}{m+4} \right] \right] + \left[ \frac{H_T}{H_F} \right] (1 - s lp) \]
\[
= \frac{b^2}{2}(2-Bb^2) + \frac{1}{2}(1-Bb^2)(1-b^2)
\]

Substituting for \(h_m\) from A.4.1.3

\[
H_T = \frac{[1 - \frac{2}{m+2}] (b^2(2-Bb^2) + (1-Bb^2)(1-b^2))}{2 \left[1 + \left(\frac{1-H_F}{H_f}\right)(1-slp)\right] \left[\left[1 - \frac{2}{m+2}\right] - \frac{Bb^2}{2} \left[1 - \frac{4}{m+4}\right]\right]}
\]

\[
H_T = \frac{[1 - \frac{2}{m+2}] (1+b^2(1-B))}{2 \left[1 + \left(\frac{1-H_F}{H_f}\right)(1-slp)\right] \left[\frac{Bb^2}{2} \left[1 - \frac{4}{m+4}\right]\right]}
\]

[A.4.1.4]

From A.4.1.3 and A.4.1.1

\[
D = \frac{QH_F}{\pi r_c^2(1-slp)H_T} \left[1 - \frac{2}{m+2}\right] \left[\left[1 - \frac{2}{m+2}\right] - \frac{Bb^2}{2} \left[1 - \frac{4}{m+4}\right]\right]
\]

Substituting A.4.1.4

\[
D = \frac{2QH_F}{\pi r_c^2(1-slp)} \left[1 + \left(\frac{1-H_F}{H_f}\right)(1-slp)\right] (1+b^2(1-B))
\]

[A.4.1.5]

Rearranging A.4.1.4 we get

\[
\frac{m+2}{m+4} = \frac{2}{Bb^2} \left[1 - \frac{(1+b^2(1-B))}{2H_T \left[1 + \left(\frac{1-H_F}{H_f}\right)(1-slp)\right]}\right] = \phi
\]

\[
\phi = \frac{m^2+(2-4\phi)m}{(1-\phi)}
\]

or \(m = \frac{2(2\phi-1)}{(1-\phi)}\)

[A.4.1.6]

Equation [4.6] can be rewritten as
\[ A \left[ 1 - \left( \frac{r_e}{r_c} \right)^2 \right] = D \left[ 1 - B \left( \frac{r_e}{r_c} \right)^2 \right] \]

\[ A = \frac{D(1-Bb^2)}{(1-b^2)} \quad \text{[A.4.1.7]} \]

It should be noted that

\( m > 0 \) (for \( h(r) > 0 \))

\[ (2 \phi > 1) \& (\phi < 1) \]

\[ 0.5 < \phi < 1 \quad \text{[A.4.1.8]} \]

This dictates constraints on one of the parameters if all others are fixed. As an illustration if \( b, H_T, H_F, \text{slo} \) are fixed, then the constraints on \( B \) arising from the condition A.4.1.8 are:

\[ B_l < B < B_u \quad \text{[A.4.1.9]} \]

where

\[ B_l = \frac{(b^2 + 1) - 2H_T \left[ 1 + \left( \frac{1-H_F}{H_F} \right) (1-\text{slo}) \right]}{b^2 \left[ 1 - 0.5H_T \left[ 1 + \left( \frac{1-H_F}{H_F} \right) (1-\text{slo}) \right] \right]} \]

and

\[ B_u = \frac{(b^2 + 1) - 2H_T \left[ 1 + \left( \frac{1-H_F}{H_F} \right) (1-\text{slo}) \right]}{b^2 \left[ 1 - H_T \left[ 1 + \left( \frac{1-H_F}{H_F} \right) (1-\text{slo}) \right] \right]} \]

If \( b = 0.86, H_T = 0.25, H_F = 0.3, \text{slo} = 0.1 \)

\( 0.4257 < B < 1.159 \)
But \( B < 1 \)
\[ \cdot \cdot 0.4257 < B < 1 \]

### A.4.2 Dedimensionalized equations for large capillary model

\[
t = \frac{z}{L}; \quad x = \frac{r}{r_c}; \quad u = \frac{C}{C_0}; \quad u' = \frac{C'}{C_0}; \quad u'' = \frac{C''}{C_0}; \quad C_0 = \beta P_0; \quad u_{\text{ext}} = \frac{P_{\text{ext}}}{P_0}
\]

\[
\frac{D}{L}(1-\text{lslp})(1-\text{Bx}^2)\frac{\partial u}{\partial t} = -\frac{k_1 k_2}{k_1 + k_2 \left[ \frac{\beta'}{\beta} \right]} \left[ \frac{S}{V} \right] \left[ \frac{S}{V} \right] \left[ \frac{\beta'}{\beta} \right] u - u' + \frac{C_H}{C_0} f(u, y)
\]

\[
\frac{D}{L}(1-\text{lslp})(1-\text{Bx}^2)\frac{\partial v}{\partial t} = -f(u, y)
\]

where \( f(u, y) = ky - k \left[ \frac{C_0}{C_{50}} \right]^n u^n (1-y) \)

\[
\frac{A}{L}(1-x^2)\frac{\partial u''}{\partial t} = \frac{D'_{02}}{r_c} \left[ \frac{1}{2} \frac{\partial}{\partial x} \left[ \frac{\partial u''}{\partial x} \right] \right] \quad (b \leq x \leq 1)
\]

\[
\frac{D}{L}(1-\text{Bx}^2)\frac{\partial u'}{\partial t} = \frac{1}{(1-h(r))} \frac{D'_{02}}{r_c} \left[ \frac{1}{2} \frac{\partial}{\partial x} \left[ \frac{\partial u'}{\partial x} \right] \right]
\]

\[
+ \frac{k_1 k_2}{k_1 + k_2 \left[ \frac{\beta'}{\beta} \right]} \left[ \frac{S}{V} \right] \left[ \frac{S}{V} \right] \left[ \frac{\beta'}{\beta} \right] \frac{h(r)}{(1-h(r))} \left[ \frac{\beta'}{\beta} \right] u - u'
\]

At \( x = b \)

\[ u' = u'' \]

\[ \frac{\partial u'}{\partial x} = \frac{\partial u''}{\partial x} \]

At \( x = 0 \)

\[ \frac{\partial u'}{\partial x} = 0 \]
At $x=1$

$$-\frac{D^2}{r_c^2} \frac{\partial u}{\partial x} = \frac{K}{\beta' r_c \ln \left( \frac{4a}{r_c} \right)} \left[ u'' - \frac{\beta'}{\beta} \frac{P_{e\text{xt}}}{P_0} \right]$$

At $z=0$

$$u = u_{in}$$
$$u' = \frac{\beta'}{\beta} u_{in}$$
$$u'' = \frac{\beta'}{\beta} u_{in}$$
$$y = f_{eq}(P_{in})$$

Hence the equations may be written as

$$(1-Bx^2) \frac{\partial u}{\partial t} = -a_1(a_9 u - u') + a_2(a_3 y - a_4 u^n(1-y))$$

$$(1-Bx^2) \frac{\partial v}{\partial t} = -a_3 y + a_4 u^n(1-y)$$

$$(1-x^2) \frac{\partial u''}{\partial t} = \frac{a_5}{x} \frac{\partial}{\partial x} \left[ x \frac{\partial u''}{\partial x} \right] \quad b \leq x \leq 1$$

$$(1-Bx^2) \frac{\partial u'}{\partial t} = \frac{a_6}{(1-h(x))} \frac{1}{x} \frac{\partial}{\partial x} \left[ x \frac{\partial u'}{\partial x} \right] + a_7 \frac{h(x)}{(1-h(x))} (a_9 u - u')$$

where $h(x) = h_m \left[ 1 - \left( \frac{x}{b} \right)^m \right]$

At $x=b$

$$u' = u''$$
$$\frac{\partial u'}{\partial x} = \frac{\partial u''}{\partial x}$$

At $x=0$
\[ \frac{\partial u'}{\partial x} = 0 \]

At \( x=1 \)

\[ -\frac{\partial u''}{\partial x} = a_8 (u'' - a_9 u_{\text{ext}}) \]

At \( z=0 \)

\[ u = u_{\text{in}} \]
\[ u' = a_9 u_{\text{in}} \]
\[ u'' = a_9 u_{\text{in}} \]
\[ y = \frac{a_{10} u^n}{1 + a_{10} u^n} \]

where

\[ a_1 = \left[ \frac{\frac{k_1 k_2}{k_1 + k_2 \beta'}}{\beta'} \right] \left[ \frac{L}{D(1 - s_l p)} \right] \left[ \frac{S}{V} \right]_{\text{rbc}} \]

\[ a_2 = \frac{C_H}{C_0} \]

\[ a_3 = \frac{k_L}{D} \]

\[ a_4 = \left[ \frac{k_L}{D} \right] \left[ \frac{C_0}{C_{50}} \right]^n = a_3 a_{10} \]

\[ a_5 = \frac{D_0 L}{A c_{\text{2}}} \]

\[ a_6 = \frac{D'_{02} L}{D c_{\text{2}}} \]

\[ a_7 = a_1 (1 - s_l p) \]
\[ a_8 = \frac{K}{D_0^2 \beta' \ln \left( \frac{4a}{\pi r_c} \right)} \]

\[ a_9 = \frac{\beta'}{\beta} \]

\[ a_{10} = \left[ \frac{P_0}{P_{50}} \right]^n \]

A.4.3 Space average fraction saturation

Equation [4.35] can be rewritten as

\[ \langle y \rangle_{sa} = \frac{1}{\pi r_c^2 H_T} \int_0^r 2\pi rh_m \left[ 1 - \left( \frac{r}{r_r} \right)^m \right] y \, dr \]

Let \( x = \frac{r}{r_r} \)

\[ \therefore \langle y \rangle_{sa} = \frac{2(m+2)}{m} \int_0^1 x(1-x^m) \, dx \]

A.4.4 Mixed mean oxygen concentration in the rbc

Equation [4.37] can be rewritten as

\[ \langle C \rangle_{mmrbc} = \frac{2\pi h_m D(1-sl_p)}{\pi r_c^2 H_T \langle v \rangle_{rbc}} \int_0^r r_c \left[ 1 - \left( \frac{r}{r_r} \right)^m \right] \left[ 1 - B \left( \frac{r}{r_c} \right)^2 \right] C \, dr \]

\[ \begin{align*}
u &= \frac{C}{C_0} ; \quad x = \frac{r}{r_c} ; \quad b = \frac{r}{r_c} \\
\end{align*} \]

\[ \langle u \rangle_{mmrbc} = \frac{r_r^2}{\Phi H_T} \int_0^1 2\pi h_m (1-x^m) D(1-sl_p)(1-b^2 x^2) \, dx \]
\[ = \frac{2\pi r^2 D(1-slp)h}{QH_F} \int_0^1 x(1-x^m)(1-b^2x^2)u\,dx \]

\[ = \frac{2\pi r^2 D(1-slp)H_T(m+2)}{QH_F mb^2} \int_0^1 x(1-x^m)(1-b^2x^2)u\,dx \]

\[ = \frac{2\pi r^2 D(1-slp)H_T(m+2)}{QH_F m} \int_0^1 x(1-x^m)(1-b^2x^2)u\,dx \]

\[ = \frac{4H_T}{H_F m+2} \frac{m+2}{m} \frac{[1+\left(\frac{1-H_T}{H_F}\right)(1-slp)]}{(1+b^2(1-B))} \int_0^1 x(1-x^m)(1-b^2x^2)u\,dx \]

where \( \langle u \rangle_{mrmrbc} \) is the dedimensionalized mixed mean oxygen concentration in the rbc.

A.4.5 Mixed mean oxygen concentration in the capillary

Equation [4.43] can be rewritten as

\[ \langle C^- \rangle_{mm} \pi r_c^2 \langle v \rangle = \left[ \int_0^r 2\pi rh_m \left[1-\frac{r-x}{r_c}\right]^m D(1-slp) \left[1-B \left[\frac{r-x}{r_c}\right]^2\right]C\,dr \right. \]

\[ + \int_0^r 2\pi r h_m \left[1-\frac{r-x}{r_c}\right]^m D \left[1-B \left[\frac{r-x}{r_c}\right]^2\right]C\,dr \]

\[ + \left. \int_0^r c_2 \pi r A \left[1-\left[\frac{r-x}{r_c}\right]^2\right]C\,dr \right] \]

\[ u^- = \frac{C^-}{C_0}; \quad x = \frac{r-x}{r_r}; \quad y = \frac{r-x}{r_c}; \quad b = r_x/r_c \]

\[ \therefore \langle u^- \rangle_{mm} \langle v \rangle = 2b^2 h_m D(1-slp) \int_0^1 x(1-x^m)(1-Bb^2x^2)u\,dx \]

\[ + 2b^2 D \int_0^1 x(1-h_m(1-x^m))(1-Bb^2x^2)u\,dx \]
\[ + 2A \int_{b}^{1} y(1-y^2)u''(y)dy \]

\[ P_{mm} = \frac{P_0}{\beta'} \langle u^- \rangle_{mm} \]

where \( P_{mm} \) is the mixed mean oxygen tension
\( \langle u^- \rangle \) is the dedimensionalized mixed mean oxygen concentration

A.4.6 Parameters used in the calculations for Large capillaries

The control values of all the parameters used in the simulations are given below. If the values used are different from the control values they are shown on the figures where the results are plotted.

\[ \beta' = \text{Bunsen solubility coefficient in the plasma} \]
\[ = 1.33 \times 10^{-6} \frac{\text{M}}{\text{mmHg}} \quad (22,84) \]

\[ \beta = \text{Bunsen solubility coefficient in the rbc} \]
\[ = 1.47 \times 10^{-6} \frac{\text{M}}{\text{mmHg}} \quad (22,84) \]

\[ D_{O2} = \text{Diffusivity of O}_2 \text{ in the rbc} \]
\[ = 1.48 \times 10^{-5} \frac{\text{cm}^2}{\text{sec}} \quad (60,76,113) \]

\[ D_{O2}' = \text{Diffusivity of O}_2 \text{ in the plasma} \]
\[ = 2.75 \times 10^{-5} \frac{\text{cm}^2}{\text{sec}} \quad (76) \]

\[ D_{HbO2} = \text{Diffusivity of HbO}_2 \text{ in the rbc} \]
\[
\frac{S}{V}_{rbc} = 1.467 \times 10^{-7} \text{ cm}^2 \text{ sec}^{-1} \quad (72, 76, 113)
\]

\[
\frac{S}{V}_{rbc} \quad \text{Surface to volume ratio of the rbc}
\]

\[
C_H = 1.87 \text{ mm}^{-1} \quad (112, 119)
\]

\[
C_H \quad \text{Internal heme concentration of the erythrocyte}
\]

\[
(t_{rbc})_{max} = 5.35 \text{ mM} \quad (119)
\]

\[
(t_{rbc})_{max} \quad \text{maximum thickness of the rbc disk}
\]

\[
r_{rbc} = 1.3 \text{ mm} \quad (112, 119)
\]

\[
r_{rbc} \quad \text{radius of the rbc disk}
\]

\[
s_{lp} = 4 \text{ mm} \quad (112, 119)
\]

\[
s_{lp} \quad \text{slip coefficient}
\]

\[
B = 0.1 \quad (110)
\]

\[
B \quad \text{Blunting factor}
\]

\[
a = 0.9 \quad (96)
\]

\[
a \quad \text{Half sheet thickness of Si rubber film}
\]

\[
r_c = 81.5 \mu m
\]

\[
r_c \quad \text{radius of the Silicone rubber capillary}
\]

\[
K = 27.5 \mu m
\]

\[
K \quad \text{Permeability of the Silicone rubber at 37°C}
\]

\[
K = 0.4167 \times 10^{-9} \text{ M-cm}^2 \text{ sec-mmHg} \quad (Ch 2)
\]

\[
K \quad \text{Permeability of the Silicone rubber at 37°C}
\]
A.5.1 Nusselt numbers in the plasma film

\[ \frac{D_{O_2}}{r} \frac{d}{dr} \left[ r \frac{dC}{dr} \right] = 0 \]

At \( r = r_c \)

\[-D_{O_2} \frac{dC}{dr} = k_s C \]

At \( r = r_w \)

\[ C = C_w \]

\[ \frac{dC}{dr} = \frac{C_1}{r} \]

\[ C = C_1 \ln r + C_2 \]

\[ C_1 = -\frac{C_w}{\frac{D_{O_2}}{k_s r_c} + 1 \ln \left( \frac{r_c}{r_w} \right)} \]

\[ C = C_w + C_1 \ln \left( \frac{r}{r_w} \right) \]

\[ C^* = \frac{1}{\pi (r_c^2 - r_w^2)} \int_{r_w}^{r_c} r c_2 \pi r C dr \]

\[ = \frac{1}{\pi (r_c^2 - r_w^2)} \int_{r_w}^{r_c} r c_2 \pi r (C_w + C_1 \ln \left( \frac{r_c}{r_w} \right)) dr \]

\[ = C_w - \frac{C_1}{2} + \frac{C_1 r_c^2}{(r_c^2 - r_w^2)} \ln \left( \frac{r_c}{r_w} \right) \]
\[ C_c = C_w + C_1 \ln \left( \frac{r_c}{r_w} \right) \]

\[ C_{c^*} = -\frac{C_1}{2} + C_1 \ln \left( \frac{r_c}{r_w} \right) \frac{r_w^2}{(r_c^2 - r_w^2)} \]

\[ C_{c^*} = \frac{C_1}{2} \left[ \frac{2r_w^2}{(r_c^2 - r_w^2)} \ln \left( \frac{r_c}{r_w} \right) - 1 \right] \]

\[ \frac{-2r_w}{dr} \left. \frac{dC}{dr} \right|_{r=r_w} = \frac{-2C_1}{(C_w - C_{c^*})} \]

\[ = \frac{-2C_1}{C_1 \left[ \frac{1}{2} - \frac{r_c^2}{(r_c^2 - r_w^2)} \ln \left( \frac{r_c}{r_w} \right) \right]} \]

\[ = \frac{4}{\left[ \frac{2\gamma_{cw}^2 \ln \gamma_{cw}}{(\gamma_{cw}^2 - 1)} - 1 \right]} \]

where \( \gamma_{cw} = \frac{r_c}{r_w} \)

\[ \frac{-2r_c}{dr} \left. \frac{dC}{dr} \right|_{r=r_c} = \frac{-2C_1}{(C_{c^*} - C_c)} \]

\[ = \frac{-2C_1}{C_1 \left[ \frac{2r_w^2}{(r_c^2 - r_w^2)} \ln \left( \frac{r_c}{r_w} \right) - 1 \right]} \]
\[
\frac{4}{21 n \gamma_{cw}} \left[ 1 - \frac{\gamma_{cw}^2}{(\gamma_{cw}^2 - 1)} \right]
\]

The results are the same even if the boundary condition is -

\[ D_0 \frac{dC}{dr} = q. \]

A.5.2 Nusselt numbers in the plasma gap

\[
\frac{1}{r} \frac{\partial}{\partial r} \left[ r \frac{\partial C}{\partial r} \right] + \frac{\partial^2 C}{\partial z^2} = 0 \quad \text{[A.5.2.1]}
\]

At \( r = r_c \)

\[-D_0 \frac{\partial C}{\partial r} = k_e (C - C_{ext}) \text{ in case of uptake}\]

\[ = q \text{ in case of release} \]

At \( z = 0 \)

\[ C = C_r \]

At \( z = L \)

\[ C = C_r \]

Dedimensionalizing

\[
x = \frac{r}{r_c}; \quad y = \frac{z}{L_p}; \quad \frac{C - C_r}{C_r}
\]

\[
\frac{a}{x} \frac{\partial}{\partial x} \left[ x \frac{\partial u}{\partial x} \right] + \frac{\partial^2 u}{\partial y^2} = 0 \quad \text{[A.5.2.2]}
\]

\[ u'(0, y) = 0 \]

\[ u'(1, y) + N_u u_{ext}(1, y) = N_u u_{ext} \]

\[ u(x, 0) = 0 \]
where \( a = \left( \frac{L_D}{R_c} \right)^2 \)

\[
\text{Nu}_{\text{ext}} = \frac{k_{\text{ext}} R_c}{D_{02}}
\]

\[
u_{\text{ext}} = \frac{C_{\text{ext}} - C_r}{C_r}
\]

We expand the solution in terms of \( x \)

\[
u(x,y) = \sum_i \langle u(x), u_i(x) \rangle u_i(x)
\]

Where \( u_i(x) \) are the eigenfunctions of the eigenvalue problem for \( x \). The corresponding eigenvalue problem for \( x \) is.

\[
- \frac{1}{x} \frac{d}{dx} \left[ x \frac{du_i}{dx} \right] = \lambda_i u_i
\]

\[
u_i'(1) + \text{Nu}_{\text{ext}} \; u_i(1) = 0
\]

\[
u_i'(0) = 0
\]

Define \( \langle u(x), v(x) \rangle = \int_0^1 xu v dx \)

\[
L = - \frac{1}{x} \frac{d}{dx} \left[ x \frac{d}{dx} \right]
\]

\[
D_c = \{ u/u'(0) = 0 \; \text{and} \; u'(1) + \text{Nu}_{\text{ext}} u(1) = 0 \}
\]

\[
\langle Lu, v \rangle = \int_0^1 \frac{d}{dx} \left[ x \frac{d}{dx} \right] v dx
\]

\[
= -v x \frac{du_i}{dx} \bigg|_0^1 + \int_0^1 v' x \frac{du_i}{dx} dx
\]

\[
= -v(1)u'_i(1) + uv' \big|_0^1 - \int_0^1 u(xv')' dx
\]

\[
= -v(1)u'_i(1) + v'(1)u_i(1) + \langle Lv, u \rangle
\]

\[
= v(1) \text{Nu}_{\text{ext}} u_i(1) - \text{Nu}_{\text{ext}} v(1)u_i(1) + \langle Lv, u \rangle
\]

\[
\therefore \langle Lu, v \rangle = \langle u, Lv \rangle
\]
L is symmetric w.r.t. the boundary conditions
and L is formally self adjoint

\[ <Lu,v> = \int_0^1 -u_x u_x dx + \int_0^1 u' v dx \]

\[ = -u(1)u'(1) + \int_0^1 x(u')^2 dx \]

\[ = a7 u(1)^2 + <u,u> > 0 \]

L is positive definite and \( \lambda_i \)'s are real and positive

Solving the eigenvalue problem

\[ x^2 \frac{d^2 u_i}{dx^2} + x \frac{du_i}{dx} + \lambda_i u_i x^2 = 0 \]

Let \( \eta^2 = \lambda_i x^2 \)

\[ \eta^2 \frac{d^2 u_i}{d\eta^2} + \eta \frac{du_i}{d\eta} + \eta^2 u_i = 0 \]

\[ u_i(\eta) = C_1 J_0(\eta) + C_2 Y_0(\eta) \]

\[ C_2 = 0 \text{ (Since finite at } \eta=0) \]

\[ u_i(x) = C_1 J_0(\sqrt{\lambda_i} x) \]

At \( x=1 \)

\[ C_1 J'_0(\sqrt{\lambda_i}) \sqrt{\lambda_i} + N u_{\text{ext}} C_1 J_0(\sqrt{\lambda_i}) = 0 \]

\[ C_1 \neq 0 \]
\[ J_0(\sqrt{\lambda_i}) \sqrt{\lambda_i} = \text{Nu}_{\text{ext}} J_0(\sqrt{\lambda_i}) = 0 \]

\[ J_0(\sqrt{\lambda_i}) = \frac{\sqrt{\lambda_i}}{\text{Nu}_{\text{ext}}} J_1(\sqrt{\lambda_i}) \]

Normalizing \( \langle u_i, u_i \rangle = 1 \)

\[ \int_0^1 x C_i^2 J_0^2(\sqrt{\lambda_i} x) = 1 \]

\[ C_i^2 = \frac{\lambda_i}{\int_0^{0.5} \sqrt{\lambda_i} \eta J_0^2(\eta) d\eta} \]

\[ C_i = \left[ \frac{\lambda_i}{\int_0^{0.5} \sqrt{\lambda_i} \eta J_0^2(\eta) d\eta} \right] = d \]

Taking the inner product of [A.5.2.23] with \( u_i(x) \)

\[ a\int_0^1 \frac{\partial}{\partial x} \left[ x \frac{\partial u_i}{\partial x} \right] dx + \int_0^1 x \frac{\partial^2 u_i}{\partial y^2} dx = 0 \]

\[ a(u_i(x)xu'(x,y))_0^1 - \int_0^1 u_i'(x)xu'(x,y) dx + \frac{d^2}{dy^2} \langle u, u_i \rangle = 0 \]

\[ au_i(1)u'(1,y) - aux_i u'_i + \int_0^1 u(xu'_i)' dx + \frac{d^2}{dy^2} \langle u, u_i \rangle = 0 \]

\[ au_i(1)u'(1,y) - au(1,y)u'_i - a\int_0^1 u_i u_i dx + \frac{d^2}{dy^2} \langle u, u_i \rangle = 0 \]

\[ au_i(1)u'(1,y) - au(1,y)u'_i(1) - a\lambda_i \langle u, u_i \rangle + \frac{d^2}{dy^2} \langle u, u_i \rangle = 0 \]
\[ a_{u_i}(l)u'(1,y) + au(1,y)N_{u_{ext}}u_i(l) - a\lambda_i \langle u, u_i \rangle + \frac{d^2}{dy^2} \langle u, u_i \rangle = 0 \]

\[ a_{u_i}(l)N_{u_{ext}}u_i\text{ext} - a\lambda_i \langle u, u_i \rangle + \frac{d^2}{dy^2} \langle u, u_i \rangle = 0 \]

\[ \frac{d^2}{dy^2} \langle u, u_i \rangle - a\lambda_i \langle u, u_i \rangle = -au_i(l)N_{u_{ext}}u_i\text{ext} \]

At \( y=1 \)

\[ \langle u, u_i \rangle = 0 \]

At \( y=0 \)

\[ \langle u, u_i \rangle = 0 \]

Let \( \phi = \langle u, u_i \rangle \)

\[ \frac{d^2}{dy^2} \phi - a\lambda_i \phi = -au_i(l)N_{u_{ext}}u_i\text{ext} \]

\[ \frac{d^2}{dy^2} \phi - q^2 \phi = -c \]

At \( y=0 \)

\[ \phi = 0 \]

At \( y=1 \)

\[ \phi = 0 \]

\[ \phi = C_1 e^{qy} + C_2 e^{-qy} + \frac{c}{q^2} \]

where \( q^2 = a\lambda_i \)

\[ c = au_i(l)N_{u_{ext}}u_i\text{ext} \]

\[ \phi = \frac{c}{q^2} \frac{(e^{q-1})}{(e^{-q} - e^{-q})} (e^{-qy} - e^{qy}) + \frac{c}{q^2} (1 - e^{qy}) \]
\[ u(x,y) = \sum_{c} \left[ \frac{c}{g^2} \left( \frac{e^{-gY}}{e^{-gY} - e^{gy}} \right) + \frac{c}{g^2} (1-e^{gy}) \right] dJ_0(\sqrt{\lambda_i} x) \]

where \[ d = \left[ \frac{\lambda_i}{\int_0^{\sqrt{\lambda_i}} \eta J_0^2(\eta) d\eta} \right] \]

\[ c = adJ_0(\sqrt{\lambda_i}) Nu_{\text{ext}} u_{\text{ext}} \]

\[ g^2 = a \lambda_i \]

and \( \lambda_i \) is the solution of

\[ J_0(\sqrt{\lambda_i}) = \frac{\sqrt{\lambda_i}}{Nu_{\text{ext}}} J_1(\sqrt{\lambda_i}) \]

The required Nusselt numbers are

\[ Nu_{cg} = \frac{k_{cg} d_c}{D_0 Z} = \frac{-2\left. \frac{\partial u}{\partial x} \right|_{x=1} y}{\langle u \rangle_{x=1} x - \langle u \rangle_{x=1} y} \]

\[ Nu_{kg} = \frac{k_{kg} \tilde{L}_p}{D_0 Z} = \frac{-\left. \frac{\partial u}{\partial y} \right|_{y=0} x}{\langle u \rangle_{y=0} x - \langle u \rangle_{x, y}} \]

where \( \langle \cdot \rangle = \int_0^1 \cdot dy \)

\( \langle \cdot \rangle_x = \int_0^1 \cdot dx \)

\( \langle \cdot \rangle_{x,y} = \int_0^1 \int_0^1 \cdot dxdy \)
\[ \frac{\partial u}{\partial x} \bigg|_{x=1} \bigg|_{y} = \sum_{i} \lambda_{i} \left( \sum_{i} \lambda_{i} \right) A \frac{q}{g} \left( B(e^{q}+e^{-q}) - (g+1-e^{q}) \right) \]

\[ \langle u(1,y) \rangle_{y} = \sum_{i} \lambda_{i} \left( \sum_{i} \lambda_{i} \right) A \frac{q}{g} \left( (g+1-e^{q}) - B(e^{q}+e^{-q}) - (g+1-e^{q}) \right) \]

\[ \langle u(x,y) \rangle_{x,y} = \sum_{i} \lambda_{i} \left( \sum_{i} \lambda_{i} \right) A \frac{q}{g} \left( ((g+1-e^{q}) - B(e^{q}+e^{-q}) - (g+1-e^{q}) \right) \]

\[ \langle \frac{\partial u}{\partial y} \rangle_{y=0} \bigg|_{x} = \sum_{i} \lambda_{i} \left( \sum_{i} \lambda_{i} \right) A \frac{q}{g} \left( B(2B+1) \right) \]

\[ \langle u \rangle_{y=0} = 0 \]

where
\[ A = \frac{c}{g^{2}} \]
\[ B = \frac{e^{q}+1}{e^{-q}} \]

\[ \therefore \quad Nu_{cg} = \frac{N_{1}}{D_{1}-D_{2}} \]

\[ Nu_{zg} = \frac{N_{2}}{D_{1}} \]

where
\[ N_{1} = -2 \sum_{i} \lambda_{i} \left( \sum_{i} \lambda_{i} \right) A \frac{q}{g} \left( B(e^{q}+e^{-q}) - (g+1-e^{q}) \right) \]
\[ D_1 = \gamma \left[ \frac{A}{g} ((g+1-e^g) - B(e^g + e^{-g} - 2)) \right] \frac{d}{\lambda_i} \int_0^{\lambda_i} j_0(\eta) d\eta \]

\[ D_2 = \gamma \frac{d}{\eta} j_0(\sqrt{\lambda_i}) \frac{A}{g} ((g+1-e^g) - B(e^g + e^{-g} - 2)) \]

\[ N_2 = \frac{i A g (2B+1)}{\lambda_i} \frac{d}{\lambda_i} \int_0^{\lambda_i} j_0(\eta) d\eta \]

In case the boundary condition at the capillary wall is

\[ -D\frac{\partial C}{\partial r} = q \]

then by a similar analysis the results are found to be the same except that

\[ c = -adj_0(\sqrt{\lambda_i}) \frac{qr_c}{D_{Oz}} \]

and \( \lambda_i \) is a solution of \( J_1(\sqrt{\lambda_i}) = 0 \)

A.5.3 Nusselt numbers in the plasma film at the lateral ends

\[ \frac{\partial^2 C}{\partial z^2} = 0 \]

At \( z=0 \) (center of the cell)

\[ C = C_r \]

At \( z = \frac{L_r}{2} \)

\[ -D\frac{\partial C}{\partial z} = q \]

\[ C = C_1 z + C_2 \]

\[ C_2 = C_r \]
\[ -D_{O2}C_1 = q \]
\[ \therefore C_1 = -\frac{q}{D_{O2}} \]

\[ \therefore C^* = \frac{2}{L_x} \int_0^{L_x/2} (C_1 z + C_2) dz = \frac{C_1 L_x}{4} + C_2 \]

\[ -D_{O2} \frac{dC}{dz} \bigg|_{z=L_x/2} = k_{zr} (C^* - C_1 L_x/2) \]

\[ \therefore -D_{O2} C_1 = k_{zr} \left[ \frac{C_1 L_x}{4} + C_2 - \frac{C_1 L_x}{2} - C_2 \right] \]

\[ \therefore \frac{k_{zr} L_x}{D_{O2}} = 4 \]

A.5.4 Nusselt numbers in the endothelium and the extravascular space

\[ \frac{D_{O2} dr}{r} \frac{dC}{dr} \bigg|_{r = r_0} = 0 \]

At \( r = r_0 \)

\[ -D_{O2} \frac{dC}{dr} = q \]

At \( r = r_{in} \)

\[ C = C_{in} \]

\[ C = C_1 \ln r + C_2 \]

\[ \frac{dC}{dr} = \frac{C_1}{r} \]
\[ \frac{D_{O2} C_1}{r_o} = q \]

\[ C_1 = -\frac{qr_o}{D_{O2}} \]

\[ C_{in} = C_1 \ln r_{in} + C_2 \]

\[ C_2 = C_{in} - C_1 \ln r_{in} \]

\[ C = C_{in} + C_1 \ln \left( \frac{r}{r_{in}} \right) \]

\[ C|_{r=r_o} = C_{in} + C_1 \ln \left( \frac{r_o}{r_{in}} \right) \]

\[ Nu = \frac{qd_o}{(C|_{r=r_{in}} - C|_{r=r_o}) D_{O2}} \]

\[ = -\frac{qd_{in}}{C_1 \ln \left( \frac{r_o}{r_{in}} \right) \ln \left( \frac{r_o}{r_{in}} \right)} \]

For the endothelium \( r_o = r_{en}, \ r_{in} = r_c \)

For the extravascular space \( r_o = r_{ex}, \ r_{in} = r_{en} \)

**A.5.5 Dedimensionalized small capillary model equations**

\[ u = \frac{C}{C_0}; \quad x = \frac{r}{r_w}; \quad u' = \frac{C'}{C_0}; \quad u'' = \frac{C''}{C_0}; \quad C_0 = \beta P_0; \quad \lambda = \frac{r_w}{r_c} \]

\[ \frac{\partial u}{\partial t} = \left[ \frac{D_{O2}}{r_w^2} \right] \frac{1}{x} \frac{\partial}{\partial x} \left[ \frac{x \partial u}{\partial x} \right] + \left[ \frac{C}{C_0} \right] f(u, y) - \frac{2k q r}{L_r} (u_{\beta} - u) \]
\[ \frac{\partial y}{\partial t} = \left[ \frac{D_{\text{HbO}_2}}{r_w^2} \frac{1}{x} \frac{\partial}{\partial x} \left[ x \frac{\partial y}{\partial x} \right] \right] - f(u, y) \]

\[ \frac{du'}{dt} = \left[ \frac{(u''-v') + 2k_{fg}}{L_r} \right] (u''-u') + \frac{k_{ef}}{V_p} (u_{\beta'}-u') - \frac{F_c}{C_0} \frac{2\pi r_c L_r}{V_p} \]

\[ \frac{du''}{dt} = \left[ \frac{(u''-v') + 2k_{fg}}{L_r} \right] (u''-u'') + \frac{k_{rg}}{r_c} \left[ \frac{r_w}{r_c} \right]^2 \frac{2}{L_p} (u_{\beta'}-u'') - \frac{2}{r_c} \frac{F_c}{C_0} \]

where \( f(u, y) = -k \left[ \frac{C_0}{C_{50}} \right] u^n (1-y) + ky \)

At \( x=1 \)

\[ -\frac{\partial u}{\partial x} = \left[ \frac{k_{ef} r_w}{D_{\text{O}_2}} \right] (u_{\beta'}-u') \]

\[ \frac{\partial y}{\partial x} = 0 \]

At \( x=0 \)

\[ \frac{\partial u}{\partial x} \]

\[ \frac{\partial y}{\partial x} = 0 \]

At \( t=0 \)

\[ u_{\text{in}} = 0 \]

\[ u_{\text{in}} = u_{\text{in}} \]
\[ \dot{u}' = \frac{\beta'}{\beta} u'_{in} \]

\[ \ddot{u}' = \frac{\beta'}{\beta} u'_{in} \]

Hence

\[ \frac{\partial u}{\partial t} = \frac{b1}{x} \frac{\partial}{\partial x} \left[ x \frac{\partial u}{\partial x} \right] + b2(b3y-b4u^n(1-y))-b5(ub9-u'') \]

\[ \frac{\partial v}{\partial t} = \frac{b6}{x} \frac{\partial}{\partial x} \left[ x \frac{\partial v}{\partial x} \right] - (b3y-b4u^n(1-y)) \]

\[ \frac{\partial u'}{\partial t} = b7(u''-u') + b8(ub9-u')-b10 \]

\[ \frac{\partial u''}{\partial t} = b7b11(u''-u') + b5\lambda^2 b11(b9u-u'')-b12 \]

At \( x=1 \)

\[ -\frac{\partial u}{\partial x} = b13(b9u-u') \]

\[ \frac{\partial v}{\partial x} = 0 \]

At \( x=0 \)

\[ \frac{\partial u}{\partial x} = 0; \quad \frac{\partial v}{\partial x} = 0 \]

At \( t=0 \)

\[ u = u_{in} \]

\[ u' = b9u_{in} \]

\[ u'' = b9u_{in} \]

where \( b1 = \frac{D_{02}}{r_w^2} \)

\[ b2 = \frac{C_H}{C_0} \]
\[ b_3 = k \]
\[ b_4 = k \left[ \frac{C_0}{C_{50}} \right]^n \]
\[ b_5 = \frac{2kqrst}{L_r} \]
\[ b_6 = \frac{D_{Hb02}}{r_w^2} \]
\[ b_7 = \left( (v''-v') + 2k_{fg} \right) \left( \frac{1-\lambda^2}{L_r} \right) \]
\[ b_8 = \frac{k_{rf}S_r}{V_p'} \]
\[ b_9 = \frac{g'}{\beta} \]
\[ b_{10} = \frac{F_C 2\pi r_c L_r}{C_0 V_p'} \]
\[ b_{11} = \frac{L_r}{L_p} \]
\[ b_{12} = \frac{2}{r_c} \frac{F_C}{C_0} \]
\[ b_{13} = \frac{k_{rf}r_w}{D_{O2}} \]

For in vivo release \( F_C \) is the value of the flux calculated from the oxygen consumption in the tissue. For in vivo uptake or in vitro oxygen transport \( F_C = k_{cg}(C''-C_{cw}) \).
The dedimensionalized equations are the same as above except:

$b_{10}$ is replaced by $b_{10}'(u'-u_{cw}')$

$b_{12}$ is replaced by $b_{12}'(u''-u_{cw}'')$

where

$$u_{cw}' = b_{14} \frac{(u'+u'')}{2} + (1-b_{14}) b_{9} u_{ext}$$

$$u_{cw}'' = b_{15} \frac{(u'+u'')}{2} + (1-b_{15}) b_{9} u_{ext}$$

$$b_{10}' = \frac{k_{cf} 2 \pi r_c L_r}{r_c p}$$

$$b_{12}' = \frac{2 k_{cg}}{r_c}$$

$$b_{14} = \frac{k_{cf}}{k_s + k_{cf}}$$

$$b_{15} = \frac{k_{cg}}{k_{cg} + k_s}$$

A.5.6 Values of parameters used in the simulation for the small capillary model.

The values of the parameters used in the simulations are given below. Values of parameters not given below are indicated in the figures. Also if the values of parameters used are different from the control values below, it is indicated on the figures showing the results of the simulations.
$\gamma_{cw}$ = ratio of the capillary to rbc radius
= 1.1 (112,119)

$d_c$ = diameter of the capillary
= 5 $\mu$m (112,119)

$D'_{O_2}$ = Diffusivity of oxygen in the plasma
= $2.75 \times 10^{-5}$ cm$^2$/sec (76)

$L_p$ = Length of the plasma gap
= 8-10 $\mu$m (38)

$L_r$ = Length of the rbc
= 8-10 $\mu$m (5,46)

$D_{O_2}$ = Diffusivity of oxygen in the rbc
= $1.48 \times 10^{-5}$ cm$^2$/sec (60,76,113)

ten = Thickness of the endothelium
= 1 $\mu$m (119)

tex = Thickness of the extravascular space
= 2 $\mu$m (119)

$D_{O_2en}$ = Diffusivity in the endothelium
= $2.75 \times 10^{-5}$ cm$^2$/sec (111)

$D_{O_2ex}$ = Diffusivity in the extravascular space
= $2.75 \times 10^{-5}$ cm$^2$/sec (50)

$R_o$ = Oxygen consumption in the tissue
= $3.75 \times 10^{-8}$ mols/cc/sec (119)

$[S]_{rbc}$ = Surface to volume ratio of the rbc
= 147-175 $\mu$m (112,119)

$C_H$ = Internal heme concentration of the rbc
= 5.35 mM (112, 119)

\[ \beta' = \text{Bunsen solubility coefficient in the plasma} \]
\[ = 1.335 \times 10^{-6} \frac{M}{\text{mmHg}} \quad (22, 83) \]

\[ \beta = \text{Bunsen solubility coefficient in the rbc} \]
\[ = 1.484 \times 10^{-6} \frac{M}{\text{mmHg}} \quad (22, 83) \]

\[ r_t = \text{Radius of the tissue cylinder} \]
\[ = 30 \, \mu m \quad (\text{in release tissue}) \quad (119) \]

\[ t_t = \text{Thickness of the tissue} \]
\[ = 0.62 \, \mu m \quad (\text{in uptake tissue}) \quad (119) \]