ANALYSIS OF LOW REYNOLDS NUMBER BLOOD FLOW IN A RECTANGULAR MICROCHANNEL UTILIZING A TWO-PHASE EULERIAN-EULERIAN MODEL AND INCLUDING A STEADY STATE OXYGEN-HEMOGLOBIN REACTION APPROXIMATION

by

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ABSTRACT

ANALYSIS OF LOW RE BLOOD FLOW IN A RECTANGULAR MICROCHANNEL UTILIZING A TWO-PHASE EULERIAN-EULERIAN MODEL AND INCLUDING A STEADY STATE OXYGEN-HEMOGLOBIN REACTION APPROXIMATION.

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The evolution of oxygenator design has culminated in the current strategy of utilizing micro-porous membranes to separate blood and oxygen phases while utilizing extra-luminal blood flow orientations to promote passive and active secondary mixing of the blood to inhibit the build up of concentration boundary layers near oxygen transfer surfaces that impede efficiency. Advances in fabrication techniques could allow for the manufacturing of oxygenators employing microchannels to decrease the diffusion path between oxygen and the red blood cells, more closely mimicking the strategy employed by the body. Because blood is actually a complex suspension, it is difficult to model. Furthermore, as channel dimensions decrease below about 500 micrometers, the particulate nature of blood becomes increasingly important. The Fahraeus effect and the Fahraeus-Lindquist effect indicate that blood flow in channels comprising dimensions smaller than this exhibit a decrease in hematocrit and apparent viscosity respectively within the microchannel as compared with the feed or discharge hematocrit or viscosity. Additionally, blood is a reactive fluid. Oxygen-hemoglobin binding increases the oxygen carrying capacity of the blood multifold.

The objective of the this work was to develop a CFD model to simulate blood flow in a rectangular microchannel in order to predict the appropriate Reynolds number (Re) or range of Re's to achieve

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optimal O₂ transfer into the blood. It was imperative to include both the particulate nature of blood and the oxygen-hemoglobin binding effects in the model especially within the proposed microchannel dimensions.

Ansys CFX version 11.0 was employed to develop a Eulerian-Eulerian multiphase blood model consisting of a continuous plasma phase and a dispersed red blood cell phase, each possessing independent velocity fields and each phase interacting through friction drag forces. Oxygen diffusion and oxygen-hemoglobin reaction effects were included through the use of volumetric, scalar variables representing oxygen, hemoglobin, and oxyhemoglobin. Hemoglobin and oxyhemoglobin were limited to the dispersed red blood cell phase while oxygen was included as a component of both phases. Oxygen was allowed to transfer between phases as a function of the driving concentration gradient and a membrane resistance value quoted by previous experimenters. The oxygen-hemoglobin binding reaction was modeled using a non-linear source term in the red blood cell phase that adjusted oxygen, hemoglobin, and oxyhemoglobin saturation levels based on unbound oxygen concentrations. Simulations were conducted under 4 different velocity loads spanning Re from 0.2 to 9. A simplified passive Newtonian model was also employed under matching continuous phase velocity loads for comparison.

The multiphase model exhibited attenuated hematocrit and apparent viscosity levels within the microchannel as predicted. In addition, the multiphase model showed an attenuated hydraulic resistance when compared with the Newtonian simulations. The oxygen-hemoglobin binding kinetics of the multiphase model led to increases in Sherwood numbers as a result of the hemoglobin sink maintaining higher driving concentration gradients. Flux to flow rate ratios (N/Q) indicated a peak volumetric gain in oxygen around a Re of 0.2. Furthermore there was up to a 5-fold increase in the volumetric addition of oxygen in the multiphase model as opposed to the Newtonian control.

The model indicates that the microchannel might operate most efficiently under convective loads resulting in Re near 0.1 or 0.2.

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CHAPTER 1

INTRODUCTION

The evolution of oxygenator design has culminated in the current strategy of utilizing hollow fibers surrounded by micro-porous membranes to separate the blood and oxygen phases while utilizing extraluminal blood flow orientations to promote passive and active secondary mixing of the blood to inhibit the build-up of concentration boundary layers near oxygen transfer surfaces that impede efficiency. Advances in fabrication techniques could allow for the manufacturing of oxygenators employing microchannels to decrease the diffusion path between oxygen and the red blood cells, more closely mimicking the strategy employed by the body. It is imperative first to understand lung physiology as well as current oxygenator design.

1.1 Lung Physiology

The lung provides the interface for gas exchange between the blood vessels and air passages of the body. It maintains extremely efficient gas exchange due to the large surface area that is created for gas exchange as well as the low resistances to gas transfer present at the gas exchange interface. These large surface areas for gas exchange are created as a result of systematic branching in both the pulmonary and vascular passages. The pulmonary passages branch sequentially in the following order: trachea, bronchi, bronchioles, alveolar ducts, and alveoli. The vascular system branching begins in the pulmonary arteries which branch into smaller and smaller arterioles until finally culminating in the pulmonary capillaries. Gas exchange occurs between the alveoli and pulmonary capillaries, the two terminal components of pulmonary and vascular pathways. Alveoli are tiny sacs surrounded by a single layer of cells which form a close junction with pulmonary capillaries. The pulmonary branching results in 300 million alveoli in the lung consisting of 60 to 80 m² of surface area that is available for gas exchange [1]. The average thickness at the interface between alveoli and capillaries is 0.5 μ m and there is very little resistance to oxygen diffusion [1]. The pulmonary capillaries surrounding the alveoli are 0.5 to 1 mm in length and about 3 to 7 μ m in diameter [1]. These small diameters ensure very small O₂ diffusion paths

to the red blood cells (rbc's) passing through the capillaries. Because rbc's are larger in diameter than these capillaries, the cells are forced to undergo conformational changes that ensure the cells remain very close to the capillary wall throughout passage. In addition, previous research suggests that the conformational change in an rbc from a biconcave disc to a parachute shape within the pulmonary capillary might in itself contribute to an increase in oxygen transfer into the rbc [16]. In the end the physiology of the lung provides extremely efficient gas exchange that is difficult to match artificially.

1.2 Brief History of Oxygenator Design

One of the primary challenges in oxygenator design is the creation of adequate surface area for gas exchange [1]. Equally important is maintaining biocompatibility. The earliest oxygenators were film oxygenators that used rotating cylinders to constantly renew thin films of blood exposed directly to flowing gas [1], [2]. The surface area created by the film was large but the volume was small compared to the overall volume of blood in the device. Thus these devices had limited gas transfer. In addition the direct blood gas interface led to protein denaturation, blood damage, and blood activation [1]. The next generation of oxygenators was the bubble oxygenator. This design increased the surface area available for gas exchange by introducing bubbles into the blood. Unfortunately, because the efficiency of O_2 and CO_2 exchange varied depending on bubble size, it was difficult to achieve balanced O_2 and CO_2 transfer [1]. Once more, defoaming surfaces were required that increased blood exposure to artificial surfaces decreasing biocompatibility [1], [2], [15]. In addition, the direct contact between phases also increased blood activation [1].

Advances in technology combated blood activation through direct exposure of blood and gas phases by introducing semipermeable membranes that could separate the phases while still allowing gas exchange. The semipermeable membranes did limit blood activation, but also limited CO₂ exchange [1]. Microporous semipermeable membranes were born to increase oxygen and carbon dioxide exchange efficiency while still limiting blood activation by limiting protein denaturation to a thin layer on the membrane surface [1].

Today most oxygenators employ bundles of hollow fibers having diameters of 200 to 250 μ m made up of microporous membranes to allow O₂ gas delivery through the surface [1]. Most incorporate

extraluminal flow orientations that induce passive secondary mixing of the blood to increase oxygenator efficiency by disrupting blood side oxygen concentration boundary layers that develop near the gas transfer surface [1], [15]. Efficiency of these devices remains 2 to 3 times less efficient than the natural lung at rest [1]. The large diameters of these fibers preclude intraluminal blood flow arrangements because of the large diffusion paths required by oxygen. [1]

If small enough channels could be constructed so that diffusion paths could be limited to an order close to that observed physiologically, perhaps the efficiency of these devices could be improved. Unfortunately, any increase in efficiency may also be accompanied by an increase in blood activation. Thus, maximizing biocompatibility would be an integral aspect of any new design.

1.3 Previous Work

There is a good amount of literature on blood properties and on the treatment of blood during simulation for a wide variety of purposes. Some of the experimental literature follows.

Several early experiments and theoretical analyses deal with categorizing the red cell membrane resistance to oxygen transfer. Huxley and Kutchai (1981) used a stopped-flow rapid-reaction apparatus to study the effect of the red blood cell membrane and diffusion boundary layers surrounding the cell on oxygen transfer into a red blood cell. They determined that the resistance from the red cell membrane was negligible while anywhere from 82 to 100 percent of the resistance to O₂ transfer into a cell was due to the diffusion boundary layer developed around the cell [19]. Coin and Olson (1979) using dual wavelength stopped flow techniques also came to the conclusion that oxygen diffusion into the red cell was not membrane limited [22].

Sheth and Hellums (1980) used a discrete cell analysis to conclude that the resistance to oxygen transport in the blood of the microcirculation was larger than previously thought. They also indicated that the accurate simulation of oxygen transfer within the microcirculation should encompass hemoglobin diffusion as well as the oxygen-hemoglobin reaction [18].

Yap and Hellums (1987) incorporated the Adair four-step kinetic model for oxygen-hemoglobin binding along with a previous one-step approximation and a modified one step kinetic model, called the VRC (Variable Rate Coefficient) model, that incorporated a dissociation constant such that at equilibrium

the kinetic expression would reduce to the Hill equation (equilibrium oxygen saturation curve). They found that under conditions of microcirculation, while the original one-step Adair approximation was unreliable, the VRC model was sufficiently accurate to avoid the mathematical complexity of the Adair four-step reaction scheme.

Goerke et al. (2002) developed mass transfer and friction factor correlations for the following three flow arrangements: flow inside hollow fibers, flow outside and across bundles of woven hollow fibers, and flow in thin channels [21]. Mass transfer and friction factor correlations for flow in hollow fibers correlated well with theoretically derived data. They found that flow across bundles could be compared with flow across tube banks in heat exchangers. For flow in thin channels, however, the researchers noticed deviation from the Leveque solution at Graetz numbers less than 10 which the researchers attributed to the presence of screens in flat sheet oxygenators.

In addition, much of the literature deals with simulation of blood for various motives. A small sampling of some of the previous simulation work is provided below.

Bagchi it al (2005) used an immersed boundary method as a front-tracking method for multiple fluids with different properties to develop a 2D CFD simulation of the aggregation of 2 deformable cells in shear flow [25]. The model also took into account cell to cell adhesion kinetics. The results conveyed that the deformability of cells played a significant role in determining the stability and motion of red cell aggregates. Those aggregates made up of more deformable cells were more easily broken apart, whereas the aggregates composed of less deformable cells were not so easily scattered.

Chan et al (2006) examined oxygen exchange in an artificial lung under pulsatile flow conditions using a 2D simulation incorporating a single phase Newtonian blood model [23]. They examined both a staggered and square array of extraluminal blood flow fibers using a 2D simulation incorporating 2 independent unit cell models utilizing symmetry to simplify the problem. Blood was modeled as an incompressible, Newtonian, isothermal fluid governed by the Navier Stokes equation. Two different pulsatile inputs were utilized including a sinusoidal input and a cardiac input that mimicked output from the right ventricle. The experimenters showed that the staggered array had more spacing between fibers and was the more efficient design. They also noted that the cardiac signal increased mixing in the blood

and promoted better O₂ transfer. Once more, the data suggested that increasing the frequency of the pulsatile input could increase oxygen transfer.

Almomani et al (2008) developed a 2D micro-scale model incorporating blood as an incompressible Newtonian fluid containing formed elements representing both platelets and red blood cells, in order to understand the interaction between platelets and red blood cells [24]. Specifically, the group was attempting to understand how red blood cell presence affected platelet margination in the microcirculation. Their data showed that at significant hematocrit levels (greater than 5%) platelet margination or migration to the vessel wall was apparent. This effect was not seen at lower hematocrit levels. Furthermore, data suggested that platelet margination was caused by the size of the red cells. Changing red cell shape had little effect on margination, but changing the size of the cells did effect margination.

Federspiel (1989) studied the effect of cell spacing (hematocrit) on diffusing capacities in the capillary environment using a 2D axis-symmetric model to simulate two-phase blood flow in a capillary [10]. A train of equally spaced cells was assumed to be flowing in a single file line through the capillary. A single unit cell was modeled incorporating oxygen diffusion and oxygen-hemoglobin reaction kinetics but ignoring convection in the plasma layer. The total diffusing capacity was divided into two parts: The erythrocytic diffusing capacity (De_{02}) accounting for oxygen transport and reaction within the erythrocyte and the 'membrane' diffusing capacity (Dm_{02}) accounting for the tissue and plasma regions. They found that red cell spacing affected the total diffusing capacity mostly because of its effect on the membrane diffusing capacity. Thus the membrane diffusing capacity, including the tissue and plasma, was found to be the limiting segment in O_2 conductance as opposed to the erythrocyte diffusing capacity.

1.4 Objective

As mentioned previously, designing a microchannel oxygenator could lead to increased oxygenator efficiency and possibly eventually to an implantable device. Computational fluid dynamics (CFD) provides a numerical approach to study fluid problems without having a physical model. Thus using CFD could help to shed light on how efficiently a microchannel might induce oxygen transfer prior to manufacturing as well as illuminating optimal pressures, flows, and channel lengths that could be utilized

with a particular cross sectional area. Arriving at a tractable simulation involves arriving at a palatable treatment of blood. Because blood is actually a complex suspension it is difficult to model. Furthermore, as channel dimensions decrease below about 500 μm, the particulate nature of blood becomes increasingly important. The Fahraeus and Fahraeus-Lindquist effects indicate that blood flow in channels comprising dimensions smaller than this exhibit a decrease in hematocrit and apparent viscosity respectively within the microchannel as compared with the feed or discharge hematocrit or viscosity. Additionally, blood is a reactive fluid. Oxygen-hemoglobin binding increases the oxygen carrying capacity of the blood multifold. The objective of this work was to develop a CFD model using available resources to simulate blood flow in a rectangular microchannel in order to predict the appropriate Re that should be employed to achieve optimal O₂ transfer into the blood while incorporating both the particulate nature of blood and the effects of steady state oxygen-hemoglobin binding.

CHAPTER 2

METHODS AND MATERIALS

The evolution of oxygenator design has culminated in the current strategy of using hollow fiber microporous membranes to separate the blood and oxygen phases within these devices. The hydrophobicity of the membranes allows more efficient gas transfer to occur through these micropores while retaining separation of the blood and gas phases. Still, the efficiency of most commercial oxygenators is much less efficient than the human lung [1]. Although there are several factors limiting the efficiency of these devices, experiments and observations indicate that the primary resistance to gas transfer occurs in the blood phase boundary layers [1]. Modern oxygenators combat this problem by employing active and passive secondary mixing techniques. One common technique utilized to avoid diminished driving concentration gradients in the boundary layer due to oxygen accumulation there is to employ extraluminal flow orientations. In these orientations the gas phase flows down the interior of the fibers while the blood phase is directed across the fiber exterior. These orientations promote passive mixing, reduce channeling, and limit the driving force needed to induce blood flow.

In addition to the high mass transfer resistances encountered in the blood side boundary layers, the width of the diffusion path in current oxygenators is approximately 25 times larger than the diffusion path encountered in the lung [1]. The diameters of the hollow fibers range from 200 to 250 microns compared with diameters of less than 10 μ m in the pulmonary capillaries where gas exchange occurs in the body [1]. These extended diffusion distances along with plasma skimming, fluid channeling, and boundary layer development lead to regions of higher oxygen concentrations in or near the boundary layers and a complete lack of oxygen penetration into areas removed from the membrane surfaces thus limiting the efficiency of these devices.

Advances in the technology of fabricating microchannels could allow next generation devices to achieve more efficient gas exchange. Fabrication of tiny microchannels similar in size to pulmonary capillaries could yield a breakthrough in oxygenator technology. Channels fabricated with dimensions

approaching 10 μ m could drastically reduce gas diffusive path lengths and significantly shrink the thickness of concentration boundary layers considerably reducing resistance to oxygen transfer in the blood phase. A theoretical microchannel stack that might be achieved through nanofabrication techniques is indicated in figure 2.1. The illustration encompasses a theoretical functional exchange unit in the stack with blood channels and gas channels separated by silicone nitride membranes imprinted with nanopores through which O₂ and CO₂ exchange would take place. The rectangular blood channel is highlighted in red surrounded by the membrane in blue. The gas channel containing flowing O₂ surrounds the membrane and blood channel.



Figure 2.1: Functional exchange unit in microchannel stack taken from Uthamaraj et al (2008) [29].

Computational fluid dynamics (CFD) software allows designers and investigators to analyze flow and mass transfer characteristics of various channel geometries and flow characteristics prior to any actual manufacturing. In this case, Ansys CFX 11.0 was utilized to analyze the pressure-flow relationships and mass transfer characteristics for a rectangular blood microchannel under four distinct convective loads employing two unique fluid modeling strategies. Rectangular channels were chosen to be 2000 μ m in length, 10 μ m in height, and 30 μ m in width. Low Reynolds numbers (Re) were selected to characterize the microchannel flow to more closely mimic the low Re's associated with pulmonary capillaries and to reduce shear strain on the blood, thus limiting hemolysis and blood activation. Still a range of Re's was chosen to better characterize the channel.

The modeling of blood flow at low Reynolds numbers provides many unique challenges. In reality, blood is not a simple homogeneous Newtonian fluid, but rather a complex suspension of red blood cells (erythrocytes), white blood cells (leukocytes), platelets, numerous proteins, and various other elements in a plasma solution. Typically red blood cells can account for about 40 to 47 percent of the volume of blood, whereas white blood cells and platelets compose much smaller fractions of the blood volume. The rheological properties of blood have been extensively studied in both larger vessels and microvessels [4], [6], [8]. Modeling the behavior of blood in microchannels becomes more complex the smaller the vessel gets. As the vessel diameters approach sizes on the same order of magnitude as blood's particulate components the fluid ceases to behave as a continuum. Furthermore, blood does not serve as a passive conduit for oxygen transfer, but rather hemoglobin interacts chemically with the oxygen to increase the oxygen carrying capacity of blood. Consequently, blood was simulated using two independent fluid modeling approaches to illuminate the complexity of oxygen loading in microchannels. A multiphase, multicomponent approach was developed to capture the biphasic nature of blood. The blood was modeled as two distinct Eulerian phases that interacted through interphase transfer terms. Thus each phase affected the other. In addition, the effects of steady state oxygen-hemoglobin binding were included in this model to more realistically simulate oxygen loading. Another modeling approach involved treating the blood as a passive Newtonian fluid where viscosity, density, and hematocrit corrections described in the literature were employed to account for modeling differences due to microvessel size. It serves only as a control for comparison with the multiphase approach. The development of each of the models and approaches is described in the remaining sections of chapter 2, and the outline of the modeling process is illustrated in figure 2.2.



Figure 2.2: Outline of modeling procedures.

2.1 CAD and Mesh Development

The first step in the simulation process was the development of the necessary CAD model. In this case the CAD modeling was simple and straightforward. In order to model blood flow in a 10 μ m x 30 μ m x 2000 μ m fluid domain, a solid rectangular channel having a length of 2000 μ m, a width of 15 μ m and a height of 10 μ m was constructed using Solidworks. Because the channels have very long aspect ratios that would require many elements, and because the more complex CFD simulations below can be computationally expensive, the channel was bisected axially and symmetry was used to simplify the simulation.

After the solid model was created, the next step was to import the model into Ansys DesignModeler. The model was then brought into CFX mesh to create the mesh that would later be imported into the CFX 11.0 Pre engine.

Upon importing the model into CFX mesh, the first task to accomplish was to break the model up and assign primitive 2D regions at the surface boundaries of the model so that boundary conditions could be applied during the simulation process. The surfaces of each model were separated into 5 primitive 2D regions. The regions assigned were Inlet (blue), Outlet (red), Diffusion wall (green), Symmetry (transparent), and Default wall (gray) as illustrated in figure 2.3. The Inlet and Outlet regions are the cross sectional areas through which flow will enter and exit the domain. The Diffusion wall region sits atop the model where boundary conditions for oxygen transfer will later be prescribed. The formation of a Symmetry region bisected the model axially and provides the window into the interior of the model as it is transparent in the illustration. The Default region consisted of the remaining passive walls of the channel.





After defining the necessary regions, the next task was to define the meshing parameters to be used to create the mesh. First, the default body spacing was set to 0.5 µm to provide the default mesh sizing in the domain if the area were unaffected by any overriding mesh controls. Next, the Delaunay meshing strategy [9] was chosen to create the surface meshes, and the volume meshing strategy was set to extruded 2D mesh. This allowed mesh on the inlet face to be extruded through the channel body and projected onto the outlet face by designation of the inlet and outlet as a periodic pair. Thus the meshes

on the inlet and outlet faces matched node for node. The channel was then fragmented lengthwise into 300 uniform divisions.

In addition, because of expected large velocity and shear gradients near the walls as well as large concentration gradients near the diffusion wall, regions of mesh refinement were prescribed on all three walls. The inflated mesh region consisted of 10 inflated layers growing by an expansion factor of 1.1 beginning at a first layer thickness of 0.08 μ m at the wall. Upon completion of the boundary layer settings, the surface meshes were generated followed by the volume meshes. Figure 2.4 illustrates the volume mesh obtained for the microchannel. In addition, the locations of the inflated boundary layers at each wall along with the symmetry plane locations are highlighted. The mesh statistics are given in the table 2.1.



Figure 2.4: Microchannel mesh with labeled mesh expansion and symmetry regions

Table 2.1:	Meshing	Statistics for	r CFD	model.
------------	---------	----------------	-------	--------

10x30x2000 μm	
Number of nodes	253,863
Number of elements	322,400
Wedges	162,400
Hexahedra	160,000
Volume	3.00E-13

2.2 Eulerian-Eulerian multicomponent, multiphase model

The main objective of this thesis was to develop a simulation capable of modeling particulate blood flow in a micro-channel environment and include the effects of a steady state oxygen-hemoglobin reaction term. As channel sizes decrease continuum models become less realistic. The assumption of blood as a homogeneous continuum begins to break down as the characteristic size of the channel decreases and the particulate nature of blood becomes increasingly important. As mentioned previously, blood flow in micro-vessels has been examined extensively and the effects of decreasing microchannel size on blood hematocrit and viscosity in the tubes (H_T and μ_T respectively) have been well documented [4, 6, 8]. Construction of a multicomponent, multiphase model incorporating a steady state oxygen-hemoglobin reaction approximation allows for the comparison of experimentally predicted results, particularly hematocrit and viscosity, with simulation results in similarly constructed channels. Once more the addition of source terms to mimic oxygen-hemoglobin binding kinetics should yield results that are more realistic than in passive fluid simulations because up to 95 percent of the oxygen carried in the blood is bound to hemoglobin by chemical reaction [1]. Thus, the construction of a multi-component, multiphase model can give the investigator some insight into possible micro-scale effects as well as more accurately representing oxygen loading in a microchannel.

2.2.1 Eulerian Modeling Strategy Rationale

It was important to carefully select the modeling approach to be utilized in the simulation in order to define the physics of the model to best obtain the desired data. There are several modeling approaches available in CFX to develop multiphase models. Multiphase modeling can be accomplished either through Lagrangian or Eulerian tracking. Both tracking methods assume that the phases are mixed on a microscopic rather than macroscopic scale. Furthermore, each method allows phases to possess different velocity and concentration fields that can be solved independently. Ultimately, phases interact through interfacial forces and mass transfer terms across phase boundaries, which will be discussed in detail shortly [9]. Although, both multiphase implementations allow for phases to be tracked separately there are significant differences in the approaches and both approaches have characteristic strengths and weaknesses. The Lagrangian approach allows the full particulate phase to be modeled by tracking a small sample of individual particles using a set of ordinary differential equations in time for each particle [9]. These equations are integrated through the domain to define the particle behavior. This approach offers the advantage of allowing the calculation of exact particle tracks and better detail on mass and heat transfer per particle. However, the volume assumed by particles is not included in the continuous phase calculation limiting the validity of the model to very low volume fractions of dispersed phase [9]. Once more, particles are modeled as point masses limiting the validity of the approach when particle sizes become large compared to conduit dimensions. In addition particle-particle interactions are ignored [9]. While the Eulerian modeling strategy lacks the detail given by the Lagrangian strategy concerning particle paths and detailed mass transfer within each particle, it is applicable at higher ranges of volume fraction for the dispersed phase as well as providing complete global information for each particle phase because the entire dispersed phase is modeled compared to only a sample of this phase in the Lagrangian strategy [9]. Because the goals of the simulation include illuminating global values of volume fraction and oxygen concentration in the channel, the Eulerian strategy was chosen for analysis. Once more, the dispersed phase in blood is present in volume fractions ranging up to 45 percent, where the Lagrangian strategy is only recommended for very low volume fractions of the dispersed phase. In addition, the Eulerian dispersed phase modeling strategy still allows the particulate nature of the blood to be accounted for through the use of interphase mass and momentum transfer terms. Once the Eulerian strategy was chosen, it was decided that an inhomogeneous model would be utilized in the analysis. This approach employs separate velocity, volume fraction, and concentration fields for each phase while sharing a common pressure field across all phases. Separate fluids interact through interphase momentum and mass transfer terms. Each phase is assumed to be present in each control volume and

is assigned a volume fraction and the sum of these volume fractions for each phase must be equal to one in a converged solution [9]. Once more, the Eulerian modeling strategy allows for the creation of multiple passive scalars that can be used to create additional chemical components in the blood including oxygen, hemoglobin, and oxyhemoglobin. Thus the inhomogeneous Eulerian modeling strategy allows blood to be depicted as a multicomponent, multiphase fluid in which each of the phases are defined independently, but the phases interact with one another via interphase transfer terms.

2.2.2 Multiphase Modeling Assumptions and Fluid Properties

In order to accurately simulate blood flow in a microchannel, it was imperative to make proper assumptions and assign valid fluid properties. Several assumptions were employed during the modeling process. To begin with, it was assumed that the simulation would occur at steady state after any transient effects had disappeared. It was also assumed that the rectangular microchannel possessed smooth walls. Once more, flow was deemed to be laminar and adiabatic. Blood composition was simplified with the less complicated blood model being assumed to contain two discrete phases, a spherical particulate red blood cell phase dispersed in a continuous plasma phase. All other components of blood including leukocytes, platelets, and blood proteins were ignored as red blood cells make up the vast majority of the particulate in blood and as the current investigation was focused on illuminating the effects of micro-sized channels on hematocrit and revealing blood oxygen concentration profiles under various convective loads in microchannels. Deformability and biconcave shape of the red cell phase along with rouleaux forming characteristics of blood were also ignored. Both of the fluid phases were considered incompressible. Table 2.2 lists the properties utilized in the simulation along with the sources from which each value was obtained. The RBC diameter was calculated using a diameter that would yield an RBC volume of 94 μ m³ or the average value for red blood cell volume as measured by Evans and Fung [7].

Fluid Property	·	Value	units	Source
Plasma Density	ρ_{plasma}	1025	kg/m ³	http://hypertextbook.com/facts/2004/MichaelShmukler.shtml
RBC Density	ρ_{rbc}	1125	kg/m ³	http://hypertextbook.com/facts/2004/MichaelShmukler.shtml
Plasma Viscosity	μ_{plasma}	1.2	cP	[6]
RBC Viscosity	μ_{rbc}	6	cP	[6]
RBC Diameter	dp	5.64	um	calculated using [7]
Total Hemoglobin Density (rbc)	HbT	2.03 x 10 ⁻⁵	mol/cm ³	[7]
Diffusion Coefficient (O2)	D _{O2}	9 5 x 10 ⁻⁶	cm ² /s	[7]
Diffusion Coefficient (Hb)	\mathbf{D}_{Hb}	1.4×10^{-7}	cm ² /s	[7]
Solubility (O2)	$\alpha_{\rm O2}$	1.56 x 10 ⁻⁹	mol/mmHg/cm ³	[7]

 Table 2.2:
 Multiphase Fluid Properties.

2.2.3 Oxygen-Hemoglobin Binding Kinetics

As it turns out, oxygen is only moderately soluble in aqueous solutions like blood. Therefore, the passive oxygen carrying capacity of plasma is insufficient to quench the vast needs of various tissues that must be maintained by the circulatory system. To make up for this extensive gap in balance between oxygen carrying capacity of plasma and tissue needs, blood comes equipped with hemoglobin. In fact the binding of oxygen and hemoglobin increases the oxygen delivery by 70 percent [6]. Hemoglobin is a 67 kDa oxygen-binding molecule consisting of four subunits. Each of the 4 subunits contains a nonpolypeptide unit called a heme group equipped with an iron atom bonded to histidine residues. Each heme group is capable of binding one molecule of oxygen. It happens that the binding between oxygen and hemoglobin is cooperative. In other words, the binding of oxygen to one subunit in a hemoglobin molecule facilitates the binding of further oxygen to further subunits. This is reflected in the sigmoidal shape of the oxygen dissociation curve, shown below in figure 2.5, which describes the fractional saturation of oxygen binding sites in hemoglobin in the red blood cell at equilibrium as a function of the blood PO₂. At lower oxygen tensions, oxygen does not bind as efficiently as at higher oxygen concentrations. P_{50} and N_{50} are defined as the oxygen partial pressure and molar concentration at which the hemoglobin subunits are 50 percent saturated by the oxygen present. The values taken from Clark et al. (1985) are respectively 26.4 mmHg and 4.12 x 10⁻⁸ mol/cm³ [7]. The value n is a constant obtained by nonlinear regression and presented in Clark et al. (1985) as 2.65 [7]. The oxygen dissociation curve illustrated in figure 2.5 is described mathematically by the Hill equation given here as equation 2.1.



Figure 2.5: Oxygen dissociation curve.

$$S = \frac{\left(\frac{PO_2}{P_{50}}\right)^n}{1 + \left(\frac{PO_2}{P_{50}}\right)^n} = \frac{\left(\frac{[O_2]}{N_{50}}\right)^n}{1 + \left(\frac{[O_2]}{N_{50}}\right)^n}$$
(2.1)

Note that the sigmoidal shape of the dissociation curve can be shifted either left or right. The curve defined above is determined under standard conditions, including a pH of 7.4, PCO₂ of 40 mmHg, and a temperature of 37 degrees C [30]. There are several factors that can shift this curve including acidity, PCO₂, temperature, 2,3-diphosphoglyerate (DPG), and fetal hemoglobin. The combined actions of CO₂ and pH are termed the Bohr effect. Increases in acidity or PCO₂ cause the dissociation curve to shift to the right. This effect is beneficial in metabolically active tissues where high levels of PCO₂ and H⁺ cause the curve to shift to the right increasing the amount of oxygen released and available to these tissues [6]. An increase in temperature also causes a shift to the right. 2,3 DPG is formed during anaerobic glycolysis and is abundant in rbc's. DPG decreases the affinity of hemoglobin for O₂. Without DPG, hemoglobin would experience difficulty in releasing O₂. Thus, an increase in 2,3-DPG also causes the curve to shift right. In addition, fetal hemoglobin curves are to the left of those for the adult. So the Hill equilibrium curve presented above only provides the oxygen dissociation curve for adults at standard

conditions of pH, temperature, and pCO₂. Thus any clinical changes in the levels of these factors that might accompany disease states have been ignored.

In order to model blood as a reacting mixture it was imperative to develop a source term that could be added to the oxygen, hemoglobin, and oxyhemoglobin transport equations to simulate oxygen-hemoglobin reaction kinetics in the red blood cell. Typically, the complex kinetics involved in the oxygen-hemoglobin reaction had been represented using a four-step Adair reaction scheme. Because of cooperative binding, the Adair reaction scheme utilizes 4 reactions and 5 hemoglobin oxygenation states to describe the sequential binding of oxygen by hemoglobin. The description of each of the 4 sequential reactions is presented below.

$$O_2 + Hb_4 \xrightarrow[k_{-1}]{k_1} Hb_4(O_2)_1$$

(2.2)

$$O_2 + Hb_4(O_2)_1 \xrightarrow{k_2} Hb_4(O_2)_2$$
(2.3)

$$O_2 + Hb_4(O_2)_2 \xrightarrow[k_{-3}]{k_3} Hb_4(O_2)_3$$

(2.4)

$$O_2 + Hb_4(O_2)3 \xrightarrow{k_4} Hb_4(O_2)_4$$

(2.5)

The corresponding rate coefficients, given in Truskey et al (2004), are $k_1 = 17.7 \times 10^4 \text{ M} \cdot 1 \text{s} \cdot 1$, $k_{-1} = 1900 \text{ s} \cdot 1$, $k_2 = 33.2 \times 10^4 \text{ M} \cdot 1 \text{s} \cdot 1$, $k_{-2} = 0.158 \text{ s}$, $k_3 = 4.89 \times 10^4 \text{ M} \cdot 1 \text{s} \cdot 1$, $k_{-3} = 0.539 \text{ s} \cdot 1$, $k_4 = 33.0 \times 10^4 \text{ M} \cdot 1 \text{s} \cdot 1$, and $k_{-4} = 0.5 \text{ s}$ [28]. Although the Adair 4 step scheme provides the most complete description for oxygen-hemoglobin kinetics, the mathematical complexity of this reaction scheme limits its application in the simulation environment.

Instead of incorporating this complex set of equations into previous blood models, many investigators, including Clark et al (1985) and Federspiel (1989), have chosen to utilize a reaction model similar to the variable rate coefficient (VRC) model developed by Moll in order to approximate the Adair 4

step scheme [7, 10, 11]. The VRC model simplifies the oxygen-hemoglobin reaction kinetics to a 1-step process by using an association constant that is a function of the local oxygen concentration and saturation levels. The logic for the development of the following reaction term was taken from Clark et al (1985) and Federspiel (1989) [7, 10]. The development of this single step approximation is predicated on replacing the hemoglobin molecule with 4 independent heme molecules. It is the reaction of these independent heme groups with oxygen that is described in the simplified single step reaction illustrated in equation 2.6 below.

$$Hb + O_2 \xleftarrow{k_a}{k_d} HbO_2$$
(2.6)

Given that R is the rate expression for the formation of oxygenated hemoglobin, the rates of change in the local chemical concentrations of the reactants and products in the red blood cell as a result of the preceding chemical reaction can be expressed as follows.

$$\frac{d[O_2]}{dt} = -R, \qquad \frac{d[Hb]}{dt} = -R, \qquad \frac{d[HbO_2]}{dt} = R$$
(2.7)

When defining the source term to represent the steady state reaction rate, it was vital that compatibility with the dissociation curve from figure 2.5 was maintained. To elaborate, when R = 0 (steady state), the oxygen dissociation curve must be obtained, or in other words, the oxygen partial pressure in the red blood cell should accurately reflect the oxyhemoglobin concentration within the RBC according to the oxygen dissociation curve. Both Clark et al (1985) and Federspiel (1989) accomplished this as follows. First, they assumed that the overall reaction rate could be written as the difference of an association rate and a dissociation rate as follows

$$\mathbf{R} = \mathbf{R}_{\mathbf{A}} \left([Hb], [O_2] \right) - \mathbf{R}_{\mathbf{D}} \left([HbO_2] \right)$$
(2.8)

They then assumed that the dissociation reaction rate was proportional to the product concentration, with the dissociation constant assumed to be 44 s^{-1} [7].

$$R_{D} = k_{D} [HbO_{2}] = k_{D} * S * HbT$$
(2.9)

After the dissociation rate was obtained, the equilibrium condition (R = 0) was applied and the following relationship was realized.

$$R_{\rm A} = R_{\rm D} \tag{2.10}$$

Since the functional arguments of the association rate differ from those of the dissociation rate as illustrated on the RHS of equation 2.8, the association rate was rewritten in terms of the expected functional components ([Hb], [O₂]). Note that the fractional saturation of hemoglobin can be expressed as either a function of the unbound rbc oxygen content using the Hill equation (equation 2.1) or as the ratio of oxyhemoglobin to total hemoglobin within the RBC as illustrated on the right hand side of equation 2.11. These relationships were utilized to convert the expression for the association rate to the proper functional arguments yielding equation 2.14.

$$S = \frac{C^{n}}{1 + C^{n}} = \frac{[HbO_{2}]}{HbT}$$
(2.11)

$$HbT = [HbO_2] + [Hb]$$
(2.12)

$$C = \frac{[O_2]}{N_{50}}$$
(2.13)

$$R_A = k_D [Hb] C^n = kD * HbT* (1-S) C^n$$
(2.14)

Substituting the expressions obtained for R_A and R_D into equation 2.8 and simplifying yields the following equation for the overall reaction rate.

$$R = k_D * HbT * ((1-S)C^n - S)$$
(2.15)

Although, the reaction rate established by previous investigators does provide an interesting choice for the reaction rate, it is not the only choice for R. In fact there are a myriad of functions for R where R = 0 will yield the equilibrium Hill curve [7]. Although the most accurate R is an experimental

choice, the results in an unloading cell are not very sensitive to the choice of R as long as adherence to the Hill Curve is maintained at equilibrium [7]. Following the same rationale for a loading cell, it is clear that there are a number of choices that could work for R. Once more, the reaction rate expressed in equation 2.15 was difficult to utilize in the simulation environment due to the large changes in component concentrations generated at larger time scales needed to start the simulation initially. A brief calculation using this source term within the expected ranges of component concentrations can help demonstrate one of the potential pitfalls when utilizing equation 2.15 in a simulation. Assuming that an actual oxyhemoglobin concentration of 15.224 [mol/m³], which corresponds to a 75% saturation level, exists within the RBC at some point in time, if equation 2.15 were utilized along with an unbound red cell oxygen concentration of 0.7 [mol/m³], which falls well within the range of expected oxygen concentration levels that might be obtained as a result of the applied BC's, a reaction source term equal to 222.808 [mol/m³s] would be generated and applied to the components. This source term is more than 10 times greater than the heme concentration within the red cell. On the next calculation, the difference between the actual saturation and Hill saturation would be even greater and at this point it is clear that divergence would occur. Although there were difficulties with applying it directly, the source term issued above did provide critical insight into how a reaction source term might be constructed for a steady state simulation.

Remembering that the source term given in equation 2.15 represents the changes in the chemical concentrations (volume conserved quantities) of oxygen, hemoglobin, and oxyhemoglobin over time within the red blood cell due to oxygen-hemoglobin binding, figure 2.6 illustrates how the reaction term works to adjust these variable concentrations until compatibility with the Hill Curve is obtained. Note that figure 2.6 illustrates only a single point in time. At any particular time, the current saturation denoted in the figure suggests the actual ratios of oxygen, hemoglobin, and oxyhemoglobin present in the rbc phase. Once more, the current red cell oxygen concentration along with the equation 2.1 predicts a value of fractional saturation based on empirical evidence. The reaction term adjusts the chemical concentrations of reactants and products over a small time step to move the current saturation level closer to the theoretical saturation level reflected in the Hill Curve at the next iteration. Thus the reaction source term

should become smaller and smaller over progressive iterations while the current saturation level oscillates around the Hill Equilibrium Curve getting closer and closer to the theoretical curve.





Following the same logic that is illustrated in figure 2.6, a new source term was constructed that would force steady state adherence to the Hill curve, allow for varying time step progression, and maintain the intent of the source term throughout the simulation. In order to accomplish this task, it was first necessary to split the definition of saturation into 2 parts. There would need to be a saturation definition based on the current actual ratio of $[HbO_2]$ to the total hemoglobin concentration that would be dubbed the current saturation ($S_{current}$). Another definition of saturation, termed theoretical saturation (S_{theo}), was developed to represent the saturation value predicted by the Hill curve as a function only of the current RBC oxygen concentration. This separation of saturation definitions is exhibited in equations 2.16 and 2.17 below. The goal of the source term would be to mimic oxygen-hemoglobin kinetics by forcing $S_{current}$ to approach and match S_{theo} .

$$S_{current} ([HbO_2]) = \frac{[HbO_2]}{HbT}$$
(2.16)

$$S_{\text{theo}}\left([O_2]\right) = \frac{C^n}{1+C^n}$$
(2.17)

In addition another term, dS, was defined to represent the difference in these two saturation

levels as is expressed in equation 2.18

$$. dS = (S_{theo} - S_{current})$$
(2.18)

Before actually constructing the source term, it was necessary to develop a list of objectives that

should be accomplished by a good source term candidate. These objectives were listed below:

- 1. The source term should mimic O2-Hb reaction at steady state.
- 2. S_{current} should approach and match S_{theo} as the simulation proceeds.
- 3. dS should approach 0 as the simulation proceeds.
- 4. R should approach 0 as dS approaches 0. (The reaction disappears as the theoretical curve is obtained.)
- 5. R should approach some finite, reasonable maximum value as dS approaches 1(maximum saturation differential).

The first step in constructing the reaction source term was to assume that the reaction term would be a function of the saturation differential.

$$R = R(dS)$$

(2.19)

A decaying exponential was chosen to be the vehicle whereby each of the aforementioned objectives would be accomplished. The decaying exponential function is illustrated in figure 2.7. Note that the function approaches 0 as the independent variable approaches 1. It approaches a maximum finite value of P0 as the independent variable approaches 0. In order to accomplish both 4 and 5 in the list of objectives, the independent variable was chosen to be (1 - dS). Thus as dS approaches 0, (1 - dS) approaches 1 and the R will approach 0 thereby accomplishing objective number 4. Furthermore, as dS approaches 1, (1 - dS) approaches 0 and the function approaches a finite maximum value, P0 thereby accomplishing objective number 5. Once again, since dS is minimized by the function objectives 2 and 3 are accomplished by dS approaching 0. Since the current saturation approaches the theoretical Hill saturation at steady state objective number 1 is accomplished. Thus the decaying exponential allows for each of the objectives described above to be met.



Figure 2.7: Illustration of a decaying exponential.

Using the formula for the decaying exponential along with the chosen independent variable (1 – dS), equation 2.20 was developed to represent the reaction source term. R_0 and c were chosen after several trial iterations with CFX to yield the best results. It turns out that starting R_0 at a value of $1^*(k_dHb_T)$ then increasing R_0 as the time-step (τ) decreased up to a final, maximum value of $300^*(k_dHb_T)$ at the smallest time-step worked out very well. The constant c changes the steepness and asymptotic behavior of R and was chosen to be 5. Figure 2.8 illustrates the source term. This new source term allows the oxygen, hemoglobin, and oxyhemoglobin values to constantly adjust towards equilibrium values predicted by the Hill equilibrium curve while avoiding much of the overshooting, undershooting, and divergence that occurred when utilizing the reaction rate used by previous investigators. Even so, the new source term maintains the intent of the earlier version by ensuring compatibility with the oxygen dissociation curve at equilibrium.

$$R = R_0 e^{-c(1-dS)}$$
(2.20)



Figure 2.8: Illustration of reaction source term.

2.3 Multiphase Governing Equations

As stated previously, the Eulerian-Eulerian domain was divided into two distinct phases. To begin with, a continuous phase representing plasma was incorporated into the domain. Fluid properties used to describe the plasma phase were outlined in table 2.2. After defining the material properties of the plasma phase, an RBC phase representing the red blood cell cytoplasm was incorporated into the problem domain as a dispersed phase possessing the red blood cell fluid properties also outlined in table 2.2. The nonhomogeneous Eulerian-Eulerian simulation strategy chosen to model the blood flow allowed for each phase to possess independent field variables with the exception of a shared pressure field. These phases in turn interacted through interphase mass and momentum transfer terms applied within the appropriate governing equations. Figure 2.9 illustrates all phases along with each of the components present in the domain. Note that figure 2.9 shows the presence of a continuous, plasma phase in which a discrete RBC phase is suspended. There were also three components mixed into the domain. The hemoglobin and oxyhemoglobin components shown in the figure were restricted to the RBC phase, while the oxygen component was present in both phases and moved between phases as a function of the concentration gradient and an applied membrane resistance described later. Furthermore, oxygenhemoglobin reaction kinetics were modeled in the RBC phase that will for the most part consume oxygen maintaining higher driving potentials across the RBC membrane into the cytoplasm from the plasma phase.


Figure 2.9: Phases and scalar components.

2.3.1 Continuity Equations

The following equations established the continuity of mass in the control volume. The continuity equations were simplified as a result of the assumption of the incompressibility of both fluid phases. Developing mass continuity for each of the phases yielded two equations for the system.

$$\nabla \bullet \bar{\mathbf{U}}_{pl} = 0 \tag{2.21}$$

$$\nabla \bullet \dot{\mathbf{U}}_{\rm rbc} = 0 \tag{2.22}$$

In the mass continuity equations above \vec{U} represents the velocity vector of the specified phase. Note that the subscript pl was used to indicate the continuous plasma phase while the subscript rbc was used to indicate the dispersed rbc phase.

2.3.2 Navier-Stokes Equations

After establishing the continuity of mass in the system, the next step was to develop the continuity of linear momentum. This was accomplished using the Navier-Stokes (NS) equations depicted for each of the phases in equations 2.23 and 2.24.

$$\varphi_{pl} \left(\rho_{pl} \vec{U}_{pl} \right) \bullet \nabla \vec{U}_{pl} = -\varphi_{pl} \nabla P_{pl} + \varphi_{pl} \mu_{pl} \nabla^2 \vec{U}_{pl} + M_{pl,rbc}$$
(2.23)

$$\varphi_{rbc} \left(\rho_{rbc} \vec{U}_{rbc} \right) \bullet \nabla \vec{U}_{rbc} = -\varphi_{rbc} \nabla P_{rbc} + \varphi_{rbc} \mu_{rbc} \nabla^2 \vec{U}_{rbc} + M_{rbc,pl}$$
(2.24)

In addition to the velocity vector described in the continuity equations there are several new variables. In each equation, ϕ is used to signify the volume fraction of the phase, ρ is used to represent the density of the particular phase, P stands for the pressure, and μ represents the viscosity of the phase. To reiterate, fluid properties including density and viscosity for each phase are given in table 2.2.

Equation 2.23 represents the conservation of linear momentum for the plasma phase and equation 2.24 does the same for the rbc phase. Equations 2.23 and 2.24 are the fluid equivalent of Newton's 2nd law expressed per unit volume. The left hand term in each of the NS equations above describes the convective inertial force or the product of the phase density (mass per unit volume) and the convective acceleration ($\vec{U}_{phase} \nabla \bullet \vec{U}_{phase}$). The right hand side (RHS) of the equation describes the summation of the forces in the domain. The first term on the RHS of each NS equation describes the force due to the pressure gradient. The second term on the RHS in each equation describes the viscous forces, and the final term on the RHS of each equation describes the interfacial forces acting on the current phase as a result of the presence of other phases as described below. Transient inertial forces were left out as the simulation was assumed to be steady state. Body forces were neglected. The interfacial forces added as the final term to the RHS of both equations act to bring the momentum of both phases into equilibrium. The inlet velocities (details in boundary condition section) for each of the phases were prescribed having different values creating an initial slip velocity between the phases to allow the dispersed rbc phase to be carried by interactions with the continuous phase. The interfacial forces were calculated using a prescribed drag coefficient (C_D) that was used to calculate the interfacial drag force terms. The number of rbc's per unit volume were first calculated and shown to be:

$$n_{\rm rbc} = \frac{\rm v f_{\rm rbc}}{\rm V_{\rm rbc}} = \frac{6 \varphi_{\rm rbc}}{\pi d^3}$$

The drag exerted by a single RBC on the plasma phase is implemented in CFX as:

$$D_{rbc} = \frac{1}{2} C_D \rho_{pl} A_{rbc} | U_{rbc} - U_{pl} | (U_{rbc} - U_{pl})$$

Note that A_{rbc} is the area of the particle projected onto the flow field. Multiplying this drag term by the number of rbc's per unit volume gives the total drag per unit volume as:

$$M_{pl,rbc} = \frac{3}{4} \frac{C_D}{d} \rho_{pl} v f_{rbc} \left| U_{rbc} - U_{pl} \right| \left(U_{rbc} - U_{pl} \right)$$
(2.25)

This is the interfacial momentum force on the plasma phase due to the presence of the rbc phase. Notably, the interfacial momentum force exerted on the rbc phase due to the presence of the continuous plasma phase is equal and opposite to this value as indicated by:

$$M_{rbc,pl} = -M_{pl,rbc}$$
(2.26)

If the $U_{rbc} < U_{pl}$, this indicates that the interfacial forces act negatively on the continuous plasma phase causing it to slow and positively on the dispersed RBC phase causing the cells to speed up. Eventually the phases will reach equilibrium with regards to momentum. Note that the drag coefficient was chosen based on correlations for friction factors for low Re flow around a sphere presented in Truskey et al (2008) and indicated here as figure 2.10 [28].





Each of the NS equations above is written in vector form and when expanded actually comprises 3 component momentum equations each. Thus together the momentum equations for both phases represent 6 system equations.

2.3.3 Additional Variable Transport Equations

The continuity and NS equations presented previously only describe the motion of and interactions between the two phases. In addition to including two phases in the domain, it was necessary to incorporate multiple components of the blood into the simulation using additional variables. Three additional variables were introduced into the domain as scalar conserved quantities per unit volume or as molar concentrations having the units [mol/cm³]. These three additional variables were utilized to model three blood components vital to the reaction of oxygen and hemoglobin, namely oxygen, hemoglobin, and oxyhemoglobin. The variables incorporated to represent the concentration values of oxygen, hemoglobin, and oxyhemoglobin were respectively $[O_2]$, [Hb], and $[HbO_2]$. The additional variable for oxygen was introduced into the domain as a component of both phases. The additional variables representing hemoglobin and oxyhemoglobin, on the other hand, were only introduced as components of the RBC phase in order to mimic the physiological restriction of hemoglobin to the red blood cell interior. The changes in local component concentrations due to convection, diffusion, and chemical reaction were achieved using transport equations. The transport equations dictate the local concentrations of each of these components and are described in detail below. As stated previously oxygen is a component of both phases. Consequently, a separate transport equation was utilized for each phase. The four transport equations to model oxygen, hemoglobin, and oxyhemoglobin concentrations within each of the phases are given in equations 2.27, 2.28, 2.29 and 2.30.

$$\begin{split} \phi_{pl} \vec{U}_{pl} \bullet \nabla [O_2]_{pl} &= \phi_{pl} D_{O2} \nabla^2 [O_2]_{pl} - \pi \\ \{ \textit{convection} \} & \{ \textit{diffusion} \} & \{ \textit{Interphase transfer} \} \end{split}$$

$$\end{split}$$

$$(2.27)$$

$$\varphi_{rbc} \vec{U}_{rbc} \bullet \nabla [O_2]_{rbc} = \varphi_{rbc} D_{O2} \nabla^2 [O_2]_{rbc} - R + \pi$$

$$\{convection\} \qquad \{diffusion\} \qquad \{O2, Hb \text{ kinetics}\}$$

$$(2.28)$$

$$\varphi_{rbc} \vec{U}_{rbc} \bullet \nabla [Hb]_{rbc} = \varphi_{rbc} D_{Hb} \nabla^2 [Hb] - R$$

$$\{convection\} \qquad \{diffusion\} \qquad \{O2, Hb \ kinetics\}$$

$$(2.29)$$

$$\varphi_{rbc}\overline{U}_{rbc} \bullet \nabla [HbO_2]_{rbc} = \varphi_{rbc}D_{Hb}\nabla^2 [HbO_2] + R$$

$$\{convection\} \qquad \{diffusion\} \qquad \{O2, Hb \ kinetics\}$$

$$(2.30)$$

Where the interphase transfer term was defined as follows:

$$\pi = h_{mem} A_{mem} ([O_2]_{pl} - [O_2]_{rbc})$$

Also, the derivation of the oxygen-hemoglobin reaction term described earlier results in the following reaction source term.

$$R = R_0 e^{-c(1-dS)}$$

Several new variables have been introduced in these equations. The presence of D_{O2} in each of the diffusive terms represents the binary diffusion coefficient of oxygen in plasma and has been assigned the value 9.5×10^{-6} [cm²/s] taken from Cokelet et al. (1985) and Federspiel (1989) [7],[10]. D_{Hb} represents the binary diffusion coefficient of hemoglobin within the RBC cytoplasm and is given the value 1.44×10^{-7} [cm²/s] also taken from Cokelet et al. (1985) and Federspiel (1989) [7, 10]. Because Hb is much larger than O2, D_{Hb} can be used to approximate D_{HbO2} fairly accurately [7]. Within the interphase mass transfer term π , h_{mem} symbolizes the mass transfer coefficient for oxygen across the RBC membrane and A_{mem} is used to signify the membrane surface area. The value for h_{mem} was calculated as indicated below using a membrane resistance value equal to 3.18×10^5 [cm² s mmHg / mmol] obtained experimentally by Huxley and Kutchai (1981) who found that the RBC membrane resistance is relatively small compared to the resistance from oxygen transfer due to the diffusion boundary layer developing near the membrane.

$$h_{mem} = \frac{1}{R_{mem}\alpha_{O2}}$$

Note that both equations governing O_2 transport contain a source term for the interphase mass transfer of oxygen across the rbc membrane. Notice also that this source term is subtracted from the transport equation governing the plasma phase but added to the transport equation governing the rbc phase. The source term is positive when the trans-membrane driving potential due to the oxygen concentration gradient forces oxygen into the cell or when the oxygen concentration is higher in the plasma phase than in the rbc phase. Thus the subtraction of the oxygen source in the plasma transport

equation and the addition of the oxygen source term in the rbc phase reflect the physics of the oxygen being transported out of the plasma phase across the rbc membrane and into the rbc phase. If the oxygen concentration becomes higher in the rbc phase than in the plasma phase this situation reverses to mimic the transport of O_2 out of the rbc phase and into the plasma phase. The absence of this interphase mass transfer term in the [Hb], [HbO₂] equations indicates that these components are restricted to the rbc phase.

All three of the transport equations representing components present in the rbc phase also possess volumetric source terms to simulate the oxygen-hemoglobin binding reaction. The reaction term is subtracted from the transport equations for both oxygen and hemoglobin and added into the transport equation for oxyhemoglobin. When the source term is positive, oxyhemoglobin is introduced into the rbc phase and equal stoichiometric quantities of oxygen and hemoglobin are subtracted from the phase. Thus the source term introduces oxyhemoglobin while simultaneously eradicating equal quantities of Hb and O_2 . The derivation and purpose of the source term were discussed previously.

The transport equations for the additional variables introduce 4 new equations into the system of equations. Accordingly, 12 equations have now been introduced into the system (2 continuity equations, 6 momentum equations, and 4 additional variable transport equations). Examination of the previous 12 equations yields 14 unknowns. There are 6 unknowns related to velocity: U_{pl} , V_{pl} , W_{pl} , U_{rbc} , V_{rbc} , and W_{rbc} . There are also 2 unknowns characterizing volume fraction: ϕ_{pl} , and ϕ_{rbc} . In addition there are 2 more unknowns representing the pressure in each phase: P_{pl} , and P_{rbc} . And finally, 4 variables exist describing the concentration of blood components: $[O_2]_{pl}$, $[O_2]_{rbc}$, [Hb], and [HbO2]. Because there are 14 unknowns and only 12 equations in the system, 2 more equations were necessary to close the system. The two additional equations would be derived from a volume conservation equation and a pressure constraint. The first equation is derived from the fact that the volume fractions of all phases must sum to unity. This results in equation 2.31.

$$\varphi_{\rm rbc} + \varphi_{\rm pl} = 1$$

(2.31)

The final equation used to close the system involves describing the pressure constraint. As noted earlier, choosing the inhomogeneous modeling strategy allows each phase to possess independent variable fields with the exception of the pressure field that is shared. Thus the final equation merely describes the fact that all phases share the same pressure field.

$$P_{pl} = P_{rbc}$$
(2.32)

With the addition of equations 2.31 and 2.32, 14 equations have been derived describing 14 unknowns. After completely describing all necessary governing equations, it was next necessary to correctly employ the necessary boundary conditions.

2.4 Multiphase Boundary Conditions

After defining the governing equations, it was next imperative to assign appropriate boundary conditions to the domain. The domain boundaries were separated as in figure 2.11 into 5 primitive 2D regions labelled Inlet, Outlet, Wall, Diffusion Wall, and Symmetry. The boundary conditions were then applied to each of these 2D primitives.



Figure 2.11: 2D primitives assigned to domain.

Boundary conditions describing velocity, volume fraction, oxygen concentration, hemoglobin concentration, and oxyhemoglobin concentration were applied at the 2D primitive labeled Inlet as follows:

$$W_{pl_{in}} = W_{Newtonian} (Re), \quad U_{pl_{in}} = V_{pl_{in}} = 0$$
(2.33)

$$W_{rbc_{in}} = 0.8 * W_{pl_{in}}, \ U_{rbc_{in}} = V_{rbc_{in}} = 0$$
(2.34)

$$\phi_{rbc_{in}} = 0.45, \quad \phi_{pl_{in}} = 1 - \phi_{rbc_{in}}$$
(2.35)

$$PO2_{pl_{in}} = PO2_{rbc_{in}} = 40 \text{ mmHg}$$

(2.36)

$$[HbO_2]_{in} = [Hb]_T S_{inital}, \qquad [Hb]_{in} = [Hb]_T - [HbO_2]_{in}$$
(2.37)

Equation 2.33 indicates that for the plasma phase a normal velocity was applied at the inlet that matched the normal inlet velocity applied in the single-phase Newtonian blood simulations described earlier. The normal RBC phase inlet velocity was assigned a value equal to eighty percent of the normal inlet plasma phase velocity. This condition created a slip velocity between the two phases allowing the momentum of the two phases to interact approaching equilibrium within a short entrance region in the domain. Thus the momentum of the continuous plasma phase would carry the dispersed rbc phase and in turn the drag of the RBC phase would interact with the continuous phase affecting the plasma phase. The blood hematocrit was assigned a value of 45% at the inlet, and the plasma phase was assigned a volume fraction so that the sum of the volume fractions would equal 1. Both phases were assigned oxygen concentrations that correlated with deoxygenated venous oxygen tension levels as indicated in equation 2.36. Note that the PO₂ of 40 mmHg corresponds to venous PO₂ in a healthy individual. In clinical situations, disease states could decrease this inlet PO₂ significantly. Also outlined in equation 2.37, oxyhemoglobin concentration was assigned at the inlet based on the total hemoglobin concentration and the initial saturation calculated using the Hill equation with the inlet oxygen concentration in the rbc phase. In turn, the inlet hemoglobin concentration was assigned as the difference between the total hemoglobin concentration and inlet oxyhemoglobin concentrations.

After designating the inlet boundary conditions, the outlet boundary conditions were specified. A static pressure value of zero was assigned at the outlet. Thus, the driving potential was achieved by designating normal velocity components for each phase on the inlet and by employing a static pressure at the outlet.

After the boundary conditions were specified at the openings, describing the boundary conditions at the walls became the next priority. Velocity, volume fraction and concentration conditions would require proper attention at each wall. Figure 2.11 illustrates that the 3 walls present in the domain were separated into 2 distinct 2D primitives based on discrepancies in boundary conditions describing oxygen conditions at the wall. The primitive labeled Diffusion Wall was allotted boundary conditions as follows:

$$U_{pl, dwall} = V_{pl, dwall} = W_{pl, dwall} = 0$$
(2.38)

$$\tau_{\text{RBC,dwall}} = 0, \quad U_{\text{RBC,n}} = 0$$
(2.39)

$$AF_{rbc,dwall} = 0, AF_{pl,dwall} = 1$$
 (2.40)

$$[O2]_{pl,dwall} = \frac{(713 \text{ mmHg})}{\alpha}$$
(2.41)

Equation 2.38 describes no slip and no penetration boundary conditions employed at all walls. Equation 2.39 describes the no slip, free penetration conditions employed on the RBC phase at the wall. Equation 2.40, in turn, was employed at all walls to describe the physics of plasma skimming described earlier. The area fraction of the dispersed RBC phase at the wall was set to 0 while the area fraction of the continuous phase contacting the wall was set to 1. In CFX, the area fraction of the phase contacting the wall is equal to volume fraction of that phase immediately adjacent to the wall. Thus, this BC implies a thin layer devoid of the RBC phase immediately adjacent to the wall. The Diffusion Wall primitive was also assigned a constant wall oxygen concentration equal to the oxygen tension achieved by pure humidified O₂ gas as indicated in equation 2.41. Also note that no O₂ concentration gradient exists across the transfer membrane in this case.

BC's were then designated at the 2D boundaries titled Default wall as follows:

$$U_{pl, wall} = V_{pl, wall} = W_{pl, wall} = 0$$
(2.42)

$$\tau_{\text{RBC,dwall}} = 0, \quad U_{\text{RBC,n}} = 0$$
 (2.43)

$$AF_{rbc,wall} = 0, \quad AF_{pl,wall} = 1$$
 (2.44)

$$\frac{d[O_2]_{rbc}}{d\hat{n}}\Big|_{wall} = 0$$
(2.45)

Many of the BC's assigned to the Wall primitive were identical to the Diffusion Wall primitive with the exception of the BC describing oxygen concentration. Note that equation 2.42 indicates that the no slip, no penetration BC's were employed at the all wall locations. In addition, once again the area fraction of the dispersed RBC phase was zeroed at the wall. However, instead of the constant wall concentration assigned at the diffusion wall, a zero flux condition was assigned at the 2D areas labeled as wall. Note that \hat{n} in equation 2.45 refers to the unit normal with respect to the wall.

Finally, because symmetry was utilized to simplify the modeling process and reduce the number of elements in the model, symmetry conditions were applied to the 2D region titled Symmetry as follows:

$$\overline{U}_n = 0 \tag{2.46}$$

$$\frac{\partial \varphi_{\text{pl}}}{\partial \hat{n}} = \frac{\partial \varphi_{\text{rbc}}}{\partial \hat{n}} = 0$$
(2.47)

$$\frac{\partial [O_2]_{pl}}{\partial \hat{n}} = \frac{\partial [O_2]_{rbc}}{\partial \hat{n}} = \frac{\partial [Hb]}{\partial \hat{n}} = \frac{\partial [HbO_2]}{\partial \hat{n}} = 0$$
(2.48)

The symmetry condition allows flow to be mirrored across the plane. The velocity components normal to the plane were set to 0 as were the volume fraction gradients normal to the plane. In addition the scalar variable gradients normal to the plane were also set to zero.



Figure 2.12: Illustration of assignment of momentum BC's



Figure 2.13: Illustration of assignment of concentration BC's.

2.5 Multiphase Initial Conditions and Solver Settings

After defining the domain in CFX and assigning appropriate BC's it was imperative to set initial conditions for the domain to achieve accurate results. Two simulations were actually performed to arrive at every solution. The first simulation was performed using a less accurate but more robust solver advection scheme to achieve an initial solution to be utilized in the second simulation. After achieving a solution performing a simulation using an advection scheme of specified blend with a value of 0.75, these results were interpolated onto the mesh of the second simulation and used to set the initial conditions for the second simulation where a more accurate high resolution advection scheme was employed. Convergence for each of the unknown quantities was defined by RMS residuals falling below values of 5e-7 with the exception of the additional variable unknown quantities where convergence was defined by

RMS residuals falling below 5e-6. After all solver BC's and solver settings were allotted, the simulation was sent to the CFX solver and solved.

The results were then observed, analyzed and compared to those results derived from the single phase passive blood simulations described earlier in this chapter

2.6 Newtonian Model Development

The Newtonian model was developed as a control for comparison with the multiphase model. *2.6.1 Assumptions*

Although blood is a complex suspension, the first model assumes a homogeneous passive Newtonian fluid. It is the simplest of the fluid models. The first step in creating this model was to enumerate a list of assumptions that would govern the model. To begin with, the blood was assumed to be Newtonian meaning that shear stress and shear rate were related linearly through the viscosity.. Furthermore, blood was considered incompressible and since the Reynolds numbers to be used were very low, all flow was considered laminar. Heat transfer was ignored and the steady state conditions were assumed. Once more the channel walls were assumed to be smooth. As far as oxygen concentration is concerned, the boundary condition on the diffusion wall was simplified from gas flowing through nano-sized pores to a constant wall BC. Finally, oxygen concentration entering the domain was assumed to be uniform and equal to the partial pressure of oxygen in venous deoxygenated blood prior returning to the heart from systemic circulation. Once again, disease state effects on blood PO₂ levels were ignored.

2.6.2 Newtonian Fluid Properties

The fluid was modeled as a single phase, passive, incompressible, Newtonian fluid with constant properties. Typical blood properties taken at body temperature (37°C) and normal pH are listed in Table 2.3. Typical values for viscosity and hematocrit however do not apply in tubes with diameters under about 500 μ m in diameter. Therefore it was necessary to make corrections based on experimental evidence from the literature. Previous investigators have observed that as tube diameters decrease below about 500 microns, a discrepancy develops between the feed or discharge hematocrit and the tube

hematocrit [6, 8]. As tube diameters decrease below 500 μ m there is an accompanying decrease in the tube hematocrit (H_T) as compared to the feed or discharge hematocrit (H_D) resulting in a decreasing H_T/H_D ratio as tube sizes decrease[8]. This decrease in hematocrit in microchannels has been termed the Fahraeus effect [8]. Speculation indicates that the decrease in tube diameter may result from the plasma skimming effect [6]. Statistically the red blood cells accumulate near the central axis leaving a cell free zone near the wall. Since the velocity is at a maximum near the center of the channel the dispersed red blood cells travel through the tube at a higher average velocity than the plasma phase [6]. This difference in average velocities of the phases would explain the decrease in hematocrit within the tube due to a decrease in the red blood cell residence time while also maintaining the hematocrit balance in the feed and discharge fluid [6]. This decrease in hematocrit is accompanied by a decrease in apparent viscosity known as the Fahraeus-Lindquist effect [6, 8]. The decrease in tube viscosity culminates in a minimum apparent viscosity in tubes with diameters ranging from 4 to 6 microns [8].

In order to more realistically portray blood properties in the microchannel it was important to make adjustments to fluid properties such as hematocrit, viscosity, and density based on the microscale tube dimensions. As was mentioned earlier, many researchers have investigated the effect of decreasing channel size on apparent viscosity and hematocrit in blood. Before publishing their findings supporting the existence of an endothelial surface layer in vivo as an explanation for the discrepancies between in vivo and in vitro data regarding blood viscosity and hematocrit in vessels characterized by microscale diameters, Pries and Secomb (2005) outlined a mathematical expression obtained based on results from a meta-analysis performed by Pries et al. (1992) that described the apparent viscosity of blood in glass micro-tubes as a function of the tube diameter [12, 13]. The equation describing the apparent viscosity based on tube diameter, given below in equation 2.49, was utilized to predict the altered apparent blood viscosity in the microchannel. The hydraulic diameter or 4 times the cross sectional area of the tube divided by the wetted perimeter was used with equation 2.49 to predict the apparent viscosity that would be used in the simulation. Note that equation 2.49 can only be used if the discharge hematocrit is 45% as is the case in the current simulation.

$$\mu_{0.45} = 220e^{-1.3D} + 3.2 - 2.44e^{-0.06D^{0.645}}$$
(2.49)

In addition to predicting the apparent viscosity of blood in microtubes, equations have also been developed to predict the hematocrit ratio H_T/H_D that can in turn be used to predict the expected tube hematocrit in microchannels. Equation 2.2 was taken from Sugihara-Seki and Fu (2005) and from Pries et al (1992) to describe the ratio H_T/H_D as function of tube diameter [4, 13]. Once again the hydraulic diameter of the rectangular channel was used as the characteristic length in equation 2.50.

$$\frac{H_{T}}{H_{D}} = H_{D} + (1 - H_{D}) (1 + 1.7e^{-0.415D} - 0.6e^{-0.011D})$$
(2.50)

After calculating the apparent viscosity of the blood and the hematocrit of the fluid within the microchannel, it was then decided to adjust the density of the blood based on the hematocrit and the typical density properties of both the RBC cytoplasm and the plasma. Equation 2.51 was utilized to calculate the blood density value used in the simulation.

$$\rho = \varphi_{rbc}(\rho_{rbc}) + (1 - \varphi_{rbc})(\rho_{pl})$$
(2.51)

In addition the temperature of the blood was assumed to be normal body temperature or 37 degrees C. Table 2.3 lists all material properties used for the Newtonian simulation.

Table 2.3:	Fluid Properties and Model Dimensions.	

Fluid Properties:			Source (if any)
Blood density	ρ	1060 kg/m ³	[5]
Plasma density	$ ho_{pl}$	1025 kg/m ³	[14]
RBC cytoplasm density	ρ_{rbc}	1125 kg/m ³	[14]
Blood density (adjusted)		1057 kg/m ³	calculated
Typical blood viscosity	μ	3 cP	[6]
Adjusted blood viscosity	μ	1.47 cP	equation 2.1
Feed Hematocrit	H _F	0.45	Typical value
Tube Hematocrit	HT	0.32	equation 2.2
Oxygen Diffusion Coefficient	D _{O2}	9.8E-10 m ² /s	[6]
Oxygen solubility coefficient in blood	α	0.00156 mol/mmHg/m ³	[6]
Microchannel Geometry:			
Channel height	h	10 µm	
Channel width	W	30 µm	
Channel length	L	2000 µm	
Hydraulic diameter	D _H	15μm	

2.6.3 Newtonian Governing Equations

In order to completely describe the Newtonian simulation using a system of equations, the number of unknowns in the system must first be established so that the proper number of governing equations can be employed. The Newtonian simulation will be described using 5 degrees of freedom or 5 unknown including the 3 cartesian components of the velocity vector, the pressure, and the oxygen concentration(U, V, W, P, [O₂]). Thus 5 equations will be needed to completely describe the system. The first equation that would be employed was the continuity equation or the equation describing the conservation of mass.

$$\nabla \bullet \vec{U} = 0 \tag{2.52}$$

The \vec{U} in equation 2.52 represents the velocity vector, and the equation describes mass conservation for an incompressible fluid.

In addition the Navier-Stokes equation (equation 2.53) was applied to enforce the conservation of linear momentum. In this equation ρ represents blood density, p stands for pressure, and μ stands for the kinematic viscosity. The first term on the left hand side is the mass term in unit volume format multiplied by the convective acceleration. The terms on the right hand side of the equation represent the surface forces exerted by pressure and viscous stresses. Gravitational forces have been neglected in the model. The vector form of the Navier stokes (NS) equation is given below, and actually represents three component equations.

$$\rho \vec{U} \bullet \nabla \vec{U} = -\nabla p + \mu \nabla^2 \vec{U}$$
(2.53)

Since the NS equation above represents 3 scalar equations, the number of system equations stands at 4 with one more needed. The final system equation employed describes the concentration per unit volume. The left hand side of equation 2.54 represents the convective acceleration of oxygen through the domain, whereas the right hand side of equation 2.54 describes oxygen diffusion in the domain.

$$\vec{U} \bullet \nabla ([O_2]) = D_{O_2} \nabla^2 [O_2]$$
(2.54)

The 5 governing equations described above are the system of equations needed to solve the problem at hand. The simulation, however, has not been completely defined at this point. In addition to the governing equations, boundary conditions and initial conditions are needed to completely describe the problem.

2.6.4 Newtonian Boundary Conditions and Initial Conditions

Beside the governing equations, boundary conditions were needed to completely define the problem. In this case, the boundary conditions were prescribed on each of the 2D primitives that were created during the meshing process all of which are illustrated in figure 2.3. Boundary conditions were implemented at each 2D primitive to describe both velocity and oxygen concentration.

Two BC's were applied at the inlet as follows. The momentum was described at the inlet using a velocity BC. An average velocity was applied at the inlet that was calculated according to equation 2.55 as a function of the Re desired at that location. Velocities were calculated ahead of time attempting to achieve 4 independent convective loads characterized by 4 different laminar Re's. The Re's included in the initial calculations were 0.01, 0.1, 1, and 5.

$$Uavg(Re) = \frac{Re \,\mu}{\rho \, D_h}$$
(2.55)

In addition to the momentum BC, a concentration BC was also employed at the inlet. The oxygen concentration was specified at the inlet so that the PO_2 at the inlet matched PO_2 from deoxygenated veins in systemic circulation as described in equation 2.56. As in the multiphase case, effects of disease state that could reduce inlet PO_2 were neglected.

$$PO_{2inlet} = PO_{2deox} = 40 \text{ mmHg}$$
(2.56)
After describing the inlet, an average static pressure of 0 Pa was applied at the outlet. This was

the only BC applied at the outlet.

The walls of the channel were split into two 2D primitives, the Diffusion wall and the Default wall. At the Diffusion wall, no slip, no penetration BC's were applied as illustrated in equation 2.57. In addition a constant wall BC was applied equal to the PO_2 of pure oxygen as depicted in equation 2.58 below.

$$U_{wall} = V_{wall} = W_{wall} = 0$$

$$PO2_{wall} = 713 \text{ mmHg}$$

$$(2.58)$$

At the primitive titled Default wall, no slip no penetration BC's were also applied. But, since no oxygen mass transfer would occur across the Default wall, no flux boundary conditions were utilized as described in equation 2.59. The symbol was utilized to \hat{n} represent the unit normal to the Default wall.

$$\frac{d[O_2]}{d\hat{n}}\Big|_{\text{Default wall}} = 0$$
2.59

Finally, a symmetry condition was placed on the 2D primitive titled Symmetry that implied the following BC's. Once again \hat{n} represents the unit normal, but this time refers to the symmetry plane.

$$\hat{\mathbf{n}} \bullet \vec{\mathbf{v}} = 0$$

$$\frac{d[O_2]}{d\hat{\mathbf{n}}} = 0$$
(2.60)
(2.61)

Each of the boundary conditions described above are illustrated in figure 2.14.

Even after defining the governing equations and application of relevant boundary conditions, the problem still required the setting of appropriate initial conditions. The channel velocity was initialized using a velocity profile taken from chapter 3.4.1 of Truskey et al (2004) that describes the velocity field for pressure driven flow in a rectangular channel [28]. The velocity profile is given in equation 2.62.

$$V(t=0) = M\left(1 - \frac{4y^2}{h^2}\right) - M\sum_{n=0}^{\infty} \frac{32(-1)^n \cosh\left(\frac{\pi x(2n+1)}{h}\right) \cos\left(\frac{\pi y(2n+1)}{h}\right)}{(2n+1)^3 \pi^3 \cosh\left(\frac{\pi W(2n+1)}{h}\right)}$$
(2.62)

where,

$$M = \frac{\Delta p h^2}{8 \mu L}$$

In equation 2.63, x and y are the coordinates at the cross sectional plane, and w and h are the width and height of the channel respectively. Also, the infinite sum was approximated using the first three terms in the series. V(t=0) was chosen to yield an average velocity in the channel that would characterize a Reynolds number close to the initial specified value.



Figure 2.14: Illustration of Newtonian BC's applied at 2D primitives.

After applying all BC's and initial conditions, the CFX solver engine was utilized to solve the problem at steady state. The solver was set to high resolution and residuals were forced to decrease below 5E-7. The results are illustrated and explained in chapter 3.

CHAPTER 3

RESULTS

In order to assess the performance of a theoretical microchannel oxygenator, the preceding simulations were developed to model blood flow over a selected range of convective loads incorporating both the multiphase nature of blood as well as the steady state approximation of oxygen-hemoglobin binding kinetics within the red blood cell phase. In addition, simulations incorporating passive, Newtonian single-phase representations of blood were implemented for comparison. The Newtonian and multiphase results along with a description of the dimensionless parameters used to describe the results are presented in this chapter.

3.1 Dimensionless Quantities

Many of the results presented in this chapter are presented in terms of dimensionless parameters and the definitions of these parameters are included in this section.

To begin with, there were two variables that were simply normalized to yield non-dimensional descriptors. First, the velocity was normalized using the average velocity in the channel. For the multiphase simulation the velocity of each phase was divided by the average velocity of the continuous plasma phase in the hydrodynamically developed portion of the channel. Equations 3.1 and 3.2 below describe the normalization of the velocity components.

$$\mathbf{U}^* = \frac{\mathbf{U}}{\overline{\mathbf{U}}}$$

(3.1)

(3.2)

$$U_{\alpha}^* = \frac{U_{\alpha}}{\overline{U}_{pl}}$$

Where * signifies the dimensionless quantity and bar over the variable (\overline{U}) signifies the average value. In addition, for the multiphase case, α represents the specified phase, either plasma or rbc. The oxygen concentration was normalized using the constant wall concentration. Equations 3.3 and 3.4 represent the normalized oxygen concentrations in the plasma and rbc phases respectively in the multiphase simulations. Equation 3.4 describes the normalized oxygen concentration within the single-phase control.

$$[O_{2}]_{pl}^{*} = \frac{[O_{2}]_{pl}}{C_{w}},$$

$$[O_{2}]_{rbc}^{*} = \frac{[O_{2}]_{rbc}}{C_{w}}$$
(3.3)

$$[O_2]^* = \frac{[O_2]}{C_w},$$
(3.4)

(3.5)

In addition to the normalized values above, several other critical dimensionless descriptions were utilized to analyze the results. The Reynolds number (Re) was employed to classify the flow in terms of the ratio of convective inertial forces to viscous forces. In each of the simulations, low Re's were chosen to signify the dominance of viscous forces in the laminar flow regime expected. The Re's were calculated from the flow rates.

$$Re = \frac{\rho Q d_{h}}{\mu A_{c}}$$
(3.6)

$$Re = \frac{\rho' Qd_{h}}{\mu' A_{c}}$$
(3.7)

Where ' and ' are the fluid averaged density and the calculated apparent viscosity and are defined as follows:

$$\rho' = \varphi_{rbc} \rho_{rbc} + \varphi_{pl} \rho_{pl},$$
$$\mu' = \frac{\pi r_h^4 \Delta P}{8LQ}$$

Note that the hydraulic diameter (d_h) and hydraulic radius were used in the preceding definitions to describe the characteristic length of the rectangular micro-conduit. The hydraulic diameter was defined as 4 times the cross sectional area of the channel divided by its wetted perimeter. In addition, the fluid

averaged density was calculated by summing up the products of the individual phase densities and phase volume fractions then averaging these over the domain volume. The particle Re was also calculated for the dispersed phase and is given below in equation 3.8.

$$\operatorname{Re}_{\operatorname{rbc}} = \frac{\rho_{\operatorname{pl}} \left| U_{\operatorname{pl}} - U_{\operatorname{rbc}} \right| d_{\operatorname{h}}}{\mu_{\operatorname{pl}}}$$
(3.8)

In addition to the Re, the Scmidt number (Sc) was utilized to characterize the ratio of momentum and mass diffusivities, the Peclet number (Pe) was used to demonstrate the ratio of advection of flow to the rate of mass diffusivity, and the Graetz number (Gz) was used to characterize laminar flow in conduits as well as being important in describing mass transport analogies for Newtonian flow in conduits. The mathematical description of each of these dimensionless variables is given below in equations 3.9 – 311.

$$Sc = \frac{\mu}{\rho D_{O2}} = \frac{Momentum diffusivity}{Mass diffusivity}$$
(3.9)

$$Pe = \frac{U_{avg} d_{h}}{D_{O2}} = \frac{Rate \text{ of advection of flow}}{Rate \text{ of mass diffusivity}}$$
(3.10)

$$Gz = \left(\frac{d_h}{L}\right) * ReSc$$
(3.11)

The Sherwood number (Sh) was critical too. Sh represents the dimensionless mass transfer at the surface of gas exchange, in this case the diffusion wall. The relationships between the flux per unit area (N"), the mass transfer coefficient (k), and the dimensionless Sh are emphasized in equations 3.12 and 3.13.

$$N'' = k(\Delta[O_2]) = D_{O2} \frac{d[O2]}{d\hat{n}} \Big|_{dwall}$$
(3.12)

$$Sh = \frac{kd_h}{D_{O2}}$$
 = Dimensionless mass transfer at surface (3.13)

Note that the mass transfer coefficient can be defined as the product of the oxygen diffusion coefficient at the wall and the oxygen gradient normal to the diffusion wall divided by the driving oxygen concentration gradient.

3.2 Multiphase Results

To reiterate, the Newtonian model was employed as a control whereby the results of the Eulerian-Eulerian, multiphase simulation could be compared later. Both Newtonian and multiphase results were separated into two sub-categories: hydrodynamic results and oxygen mass transfer results. As indicated previously, the multiphase simulation was employed to illuminate the effects of the particulate nature of blood in micro-channels as well as to approximate the effects of the oxygen-hemoglobin reaction on oxygen transfer in the micro-channel environment.

3.2.1 Hydrodynamic Results

For each model, multiphase and Newtonian, 4 simulations were employed with 4 distinct convective loads. Each of these simulations yielded data.

Figures 3.1 and 3.2 illustrate the normalized plasma phase velocities and normalized rbc phase velocities respectively. Cross sectional planes were utilized every 250 μ m to illustrate the 3D velocity profiles throughout the channel. The images were oriented so that the channel inlet appears in the lower left hand corner. The channel's axis stretches diagonally across the image from the lower left hand corner to the upper right corner culminating in the outlet. The diffusion wall resides on top of the channel and the symmetry wall to the right. In each case, the left hand of the channel is presented up to the symmetry plane. The right half of the channel, which has been neglected, is a mirror image of the left hand side. Results were divided into 4 images corresponding to the 4 different Re's achieved using different convective loadings. Corresponding variables at each of the 4 Re's have been presented together for comparison. Because the velocities for each of the phases have been normalized by the average velocity of the continuous phase, the average velocity for the given phase has been labeled on each simulation for comparison.

The continuous phase velocity profiles in figure 3.1 indicate that the flow is fully developed before even reaching the first cross sectional plane in all of the cases. This is obvious due to the constant

velocity profiles after the first cross sectional plane placed at 250 μ m. Average velocities increase with the Re as is expected. The plasma phase velocity profiles indicate a maximum velocity in the center of the tube that decreases to zero velocity at the wall. This condition of zero velocity at the wall exists because of the no slip boundary conditions placed on the plasma phase at the wall. This area of zero flow adjacent to the walls is exaggerated at the corners where two no slip walls meet.

The dispersed rbc phase velocity profiles exhibit a similar pattern as far as the maximum velocity appearing in the center of the microchannel. Also, the rbc phase velocity appears fully developed very quickly, similar to the continuous phase. Near the walls, however, the rbc phase velocity does not go to zero. This is due to the fact that there is a free slip condition imparted on the rbc phase at the wall and because due to plasma skimming there is no contact of the dispersed phase at the wall. Furthermore, the rbc phase average velocity is higher than the continuous phase average velocity.

Figure 3.3 illustrates the hematocrit profiles achieved at steady state in each simulation. It is obvious from the figure that the hematocrit profiles are almost identical in each of the cases. The value of the volume-averaged hematocrit in each case was 0.29. The similar hematocrit profiles, along with the identical values of average hematocrit in all of the simulations corroborate previous investigators findings that the tube hematocrit in these micro-conduits is a function of the feed hematocrit and characteristic channel dimension. Furthermore, the decrease in hematocrit within the tube as compared to the feed hematocrit employed at the inlet exhibits the behavior described by the Fahraeus effect [6].

The apparent viscosity was calculated using the following formula with the hydraulic radius

$$\mu' = \frac{\pi r_h^4 \Delta P}{8LQ}$$

(3.14)

The value calculated for the apparent viscosity in each case was around 0.8 cP. This is lower than the value predicted by the equation used to calculate the apparent viscosity in the Newtonian section.



Figure 3.1: Plasma phase normalized velocity profiles at a) Re = 0.02, b) Re = 0.2, c) Re = 2, and d) Re = 9



Figure 3.2: Red blood cell phase normalized velocity profiles at a) Re = 0.02, b) Re = 0.2, c) Re = 2, and d) Re = 9



Figure 3.3: Hematocrit profiles at a) Re = 0.02, b) Re = 0.2, c) Re = 2, and d) Re = 9.

Re	Р	Q(total)
0.02	3 cm H ₂ O	2.53E-07cm ³ /s
0.2	31 cm H ₂ O	2.53E-06cm ³ /s
2	310 cm H ₂ O	2.53E-05cm ³ /s
9	1459 cm H ₂ O	1.27E-04cm ³ /s

Table 3.1 lists the pressures utilized to achieve the given Re's along with total flow rate that is achieved in the channel. This total volumetric flow rate is the flow rate for the combined phases. The pressures and flow rates are illustrated in figures 3.4 and 3.5 below.



Figure 3.4: Pressures required to achieve Re.



Figure 3.5: Volumetric flow rates achieved at each Re.

The pressure versus Re plot in figure 3.4 was plotted on a log-log scale to better illuminate differences at lower Re's. The pressure change is linear with the change in convective load and the volumetric flow rate is linearly proportional to the Re as illustrated in figure 3.5.

Table 3.2 summarizes the nondimensional values obtained for each simulation. Note that the Schmidt number remains almost constant since the ratio of momentum to mass diffusivity remains nearly constant because the value of kinematic viscosity within the tube changes very little between simulations. This makes sense as the Fahraeus-Lindquist effect predicts that the ratio of apparent viscosity to feed or discharge viscosities should be dependent on the tube's characteristic dimension which is constant in all

cases [6, 12]. The Peclet number increases as the rate of advection increases while the mass diffusivity remains constant. Thus as the Re and Pe numbers increase, the axial advection of O_2 dominates increasingly over the radial diffusion of O_2 . This means that more O_2 is carried axially by the fluid before this O_2 can diffuse into the center and bottom of the channel. The Graetz number reflects a combination of the Re, the Sc, and the ratio of the channel's characteristic length scale divided by its overall length.

Re	Pe	Sc	Gz
0.02	13	744	0.1
0.2	133	744	1.0
2	1332	745	10.0
9	6658	744	49.9

 Table 3.2:
 Dimensionless
 Characteristics

3.2.2 Oxygen transfer results

The multiphase model has been utilized to assess oxygen transfer from a constant concentration diffusion wall through a continuous plasma phase across a membrane, characterized by minimal resistance to O₂ transfer, and into an rbc phase where it will ultimately interact with hemoglobin to form oxyhemoglobin. A reaction source term was employed within the rbc phase to approximate the oxygen-hemoglobin reaction at steady state in order to more realistically predict the oxygen transfer into the microchannel during steady state conditions.



Figure 3.6: Normalized oxygen values for a) Re = 0.02 in plasma, b) Re = 0.02 in rbc, c) Re = 0.2 in plasma, d) Re = 0.2 in rbc, e) Re = 2 in plasma, f) Re = 2 in rbc, g) Re = 9 in plasma, h) Re = 9 in rbc.

Figure 3.6 illustrates the steady state dimensionless oxygen concentration, [O₂]*, in each of the two phases at increasing Re. The concentration profiles in the left hand column illustrate the free [O₂]* in the plasma phase and profiles in the right column illustrate the free unbound [O2]* in the rbc phase. Each of the rows contains results from the same simulation (same Re). Consequently, the free oxygen in the plasma phase and in the rbc phase have been placed side by side for easy comparison. It can be noted that for each simulation the free oxygen concentration in the plasma matches that found in the rbc phase very closely. This would affirm that the membrane resistance to oxygen transfer is very small. In addition, as the Re increases and the convective load becomes larger, there is a subsequent increase in the Pe and oxygen is increasingly advected axially through the domain more quickly than it can diffuse radially. Finally in the case of highest Re of 9, the oxygen moves so quickly axially that is maintained in a thin concentration boundary layer near the diffusion wall surface. Thus at higher Reynolds numbers there is less oxygen in the center and bottom portions of the channel.

To reiterate, the source terms represent the approximation of the oxygen-hemoglobin reaction at steady state. This source term was added to the rbc phase in order to act as a sink or source to adjust the values of oxygen, hemoglobin, and oxyhemoglobin to match the oxygen dissociation curve thereby mimicking the effect of hemoglobin. The end result should be the adjustment of hemoglobin saturation levels to match the values of hemoglobin saturation predicted by the Hill equation. Figure 3.7 illustrates both the actual saturation values achieved in each simulation along with those saturation levels predicted by the Hill equation based on the unbound oxygen concentration. Each image on the left hand side represents the fractional saturation of total oxygen binding sites in the hemoglobin. The images on the right hand side demonstrate the Hill predicted saturation levels based only on the unbound oxygen concentration within the blood. As in prior figures, different Re's are represented in different rows. It is apparent that the actual hemoglobin saturation levels match the Hill predicted saturation levels.

The reaction of oxygen with hemoglobin results in increased oxygen carrying capacity in the blood. Figure 3.8 illustrates the oxyhemoglobin profiles in each simulation. The oxyhemoglobin concentrations were adjusted to indicate concentration levels per unit volume of blood, not per unit volume of phase, as this also reflects the volume fraction of the phase at each location. Also listed in

each diagram are the average hematocrit at the outlet, and the exit oxygen concentration. Once more, this concentration is extrapolated to the discharge reservoir where the hematocrit will rise significantly back to 45 percent. These images indicate that as the rate of convection increases the amount of oxygen combining with hemoglobin in the center of tube decreases. There is a dramatic decrease in oxygen-hemoglobin combination in the case employing the largest convective load. Furthermore, within the tested Re numbers, there is a maximum oxyhemoglobin concentration at the outlet obtained at any Re below 0.2.

Figure 3.9 illustrates the specific gradient achieved at the oxygen diffusion boundary for each Re number. The specific oxygen gradient at the wall is indicative of the oxygen flux at the wall. These images illustrate that the majority of the oxygen flux occurs in the developing region near the beginning of the channel where the oxygen concentration boundary layer still exists. After the oxygen concentration entrance region has been passed and the fully developed region of oxygen transfer has been reached, the images (a and b) in figure 3.9 indicate that the specific gradient becomes constant at the wall. In the final 2 cases, Re of 2 and 9, this condition is never met. These images also indicate that as the average velocity in the channel increases, the driving oxygen gradient at the surface of the channel also increases. This makes sense as the oxygen that diffuses into the channel is quickly convected axially leaving an oxygen void in the lower portions of the channel and increasing the local driving oxygen gradient. Thus as the average velocity within the channel increases so does the oxygen specific gradient at the surface and the entry length before a fully developed oxygen concentration boundary layer develops. The saturation levels in figure 3.7 and the normalized oxygen profiles in figure 3.6 indicate this same behavior. The oxygen concentration becomes fully developed before reaching the first cross sectional indicator at Re of 0.02, and the Re of 0.2 case reaches fully developed concentration approximately half-way down the channel. The two higher Re never achieve fully developed oxygen concentrations as can be noted by the presence of gradients in figure 3.7 (e and g) as well as in figure 3.6 (c and d).



Figure 3.7: Saturation profiles for a) $S_{current}$ at Re = 0.02, b) S_{theo} at Re = 0.02, c) $S_{current}$ at Re = 0.2, d) S_{theo} at Re = 0.2, e) $S_{current}$ at Re = 2, f) S_{theo} at Re = 2, g) $S_{current}$ at Re = 9, and h) S_{theo} at Re = 9.



Figure 3.8: Oxyhemoglobin concentration profiles in the blood for a) Re = 0.02, b) Re = 0.2, c) Re = 2, and d) Re = 9. Concentration is given per unit volume of blood (as opposed to per unit volume of the phase).



Figure 3.9: Vector plot indicating specific oxygen gradient at diffusion wall at a) Re = 0.02, b) Re = 0.2, c) Re = 2, d) Re = 9. Sherwood numbers obtained in each case are given for reference.

As mentioned previously, the specific gradient at the wall is indicative of the oxygen flux at the wall as well as the mass transfer coefficient (k) and Sh. The relationship between flux, Sh, and k is given in equations 3.15 and 3.16.

$$N'' = k(\Delta[O_2]) = D_{O2} \frac{d[O_2]}{dy}\Big|_{dwall}$$
(3.15)

$$Sh = \frac{kd_h}{D_{O2}}$$
 = Dimensionless mass transfer at surface

(3.16)

Table 3.3 gives the values for the surface averaged flux (N"), overall flux (N), and Sh for each of the cases.

Re	N"		N		k		Sh
0.02	2.14E-03	µmol/cm²s	1.28637E-06	μmol/s	1.29E-04	cm/s	0.3
0.2	2.31E-02	µmol/cm²s	1.38423E-05	μ mol/s	1.38E-03	cm/s	3.5
2	6.25E-02	µmol/cm²s	3.74837E-05	μ mol/s	3.75E-03	cm/s	9.4
9	7.24E-02	µmol/cm²s	4.34281E-05	μmol/s	4.34E-03	cm/s	10.9

 Table 3.3:
 Oxygen Transfer at Surface.

In addition to the flux at the surface it is important to characterize the oxygen transfer per unit volume. The increase in Sh can be deceiving. Although the oxygen flux across the diffusion surface increases as the Re number increases (see table 3.3), figure 3.7 clearly indicates that at higher Re oxygen is convected away axially before it can diffuse into the center of the channel. Consequently, the flux at the surface increases dramatically but the radial migration of oxygen from the diffusion surface to the rbc phase is hindered resulting in decreased oxygen-hemoglobin interaction and a thin O₂ concentration boundary layer near the diffusion surface. The ratio of flux (mol/s) to flow rate (cm³/s) yields a volumetric result corresponding to the volumetric gain in oxygen concentration (mol/cm³). For this reason, the N/Q ratio described above was utilized to characterize the volumetric effect of oxygen transfer at each Re. The N/Q ratios calculated for each Re are provided in table 3.4. The values clearly indicate that the maximum N/Q ratio occurs around a Re of 0.2.

Table 3.4:	Oxygen	Flux to	Flow	Rate	Ratios
Table 3.4:	Oxygen	Flux to	Flow	Rate	Ratios

Re	N/Q	
0.02	5.1	μmol/cm³
0.2	5.5	μmol/cm³
2	1.5	µmol/cm³
9	0.3	μmol/cm ³
3.3 Newtonian Results

The Newtonian simulation was integrated as a control to which the results for the multiphase simulation could be compared and contrasted. Thus results from the Newtonian simulations were processed using the CFX 11.0 post-processor and utilized to characterize the results obtained in the multiphase simulation.

3.3.1 Hydrodynamic Results

Unlike the multiphase simulations, the results obtained for the Newtonian simulations were fewer and more straightforward. The hematocrit was deduced to be around 0.32 as described in chapter 2. The viscosity was calculated to be 1.4 cP based on the channel's hydraulic diameter.

Although the velocities of the continuous phases were matched between multiphase and Newtonian simulations, the Re numbers in each case varied slightly because of differences in the kinematic viscosity and because of the effect of the dispersed phase in the multiphase simulation. Still, the Re numbers remained close, especially at the lower end of the convective loading scale. The normalized velocity profiles for the blood approximation are illustrated in figure 3.10. The same general profile is shown as in continuous phase of the multiphase solution. The maximum velocity is achieved in the center of the channel with zero velocity achieved immediately adjacent to the wall. Once again, the average velocities achieved are slightly higher in the Newtonian solutions as compared with the continuous phase of the multiphase case, the flow becomes fully developed before the first cross sectional plane and the average channel velocity increases with the Re as expected.



Figure 3.10: Newtonian velocity profiles along with the average velocities at a) Re = 0.01, b) Re = 0.1, c) Re = 1, and d) Re = 5.

Table 3.5 provides the dimensionless data obtained for the Newtonian case. Notice that the Sc remains constant in the Newtonian cases again because the kinematic viscosity remains constant. The Sc number here is higher than in the multiphase case as the apparent viscosity achieve in the multiphase cases is lower than that calculated for the Newtonian cases. The Peclet number increases dramatically as the convective load increases indicating that in the higher Re cases the advection axially will greatly

outweigh the diffusion radially. The Gz number increases with the Re as it is a product of Re, Sc, and a proportionality constant based on the geometry.

Re	Sc	Pe	Gz
0.01	1464	15	0.1
0.1	1464	147	1.1
1	1464	1468	11.0
5	1464	7320	54.9

Table 3.5: Newtonian Dimensionless Quantities.

Figures 3.11 and 3.12 illustrate the pressure and flow rate relationships respectively to the Re number for each case. As expected for pressure and flow in a Newtonian fluid, both are linearly proportional to the Re. Figure 3.11 is illustrated as a log-log plot in order to better illuminate differences in lower Re range.



Figure 3.11: Pressure-Re relationship for Newtonian model.



Figure 3.12: Flow rate-Re relationship for Newtonian model.

3.3.2 Oxygen mass transfer results

Figure 3.13 below illustrates the normalized oxygen concentration at steady state in each case. Both of the lower Re cases of 0.01 and 0.1 have channels that reach saturation and whose oxygen concentration becomes fully developed within the length of the channel. The Re = 0.01 case saturates with oxygen almost immediately whereas the Re = 0.1 case saturates a little more than halfway down the channel. Neither of the higher 2 Re's of 1 or 5 achieve full oxygen saturation in the channel. It is apparent that the higher unbound oxygen concentrations are achieved closer to the inlet in the Newtonian case than in the multiphase case as is illustrated in the differences between figures 3.13 and 3.6.

Figure 3.14 illustrates the oxygen specific gradient at the diffusion wall at steady state for the Newtonian case. Just as in the multiphase case, the oxygen specific gradient is an indicator of the oxygen flux and mass transfer coefficient at the surface. Again, the specific gradient increases and thus Sh increases with the convective load. In the Newtonian cases, however, the specific gradients are smaller resulting in lower Sh numbers. Once more, it appears that the first 3 models have achieved constant mass transfer at the surface by the end of the channel. In any case, this indicates that there is an increase in mass transfer at the surface in the multiphase cases as opposed to the Newtonian cases.



Figure 3.13: Normalized oxygen concentration profiles for a) Re = 0.01, b) Re = 0.1, c) Re = 1, and d) Re = 5.



Figure 3.14: O_2 specific gradient at the diffusion wall for Newtonian simulations at a) Re = 0.01, b) Re = 0.1, c) Re = 1, and d) Re = 5.

Table 3.6 below gives the values for the parameters describing the mass transfer of oxygen into the channel at the surface including the flux per unit area of diffusion surface (N"), total flux(N), mass transfer coefficient(k), and Sherwood number(Sh). Each of these indicates that oxygen transfer at the surface increases as the Re number increases.

Re	N"	Ν	k	Sh
0.01	$4.44E-04 \mu mol/cm^2s$	2.66E-07 μmol/s	4.24E-04 cm/s	0.07
0.1	4.67E-03 μmol/cm ² s	2.79E-06 µmol/s	4.45E-03 cm/s	0.70
1	2.14E-02 µmol/cm ² s	1.28E-05 μmol/s	2.04E-02 cm/s	3.22
5	3.87E-02 µmol/cm ² s	2.32E-05 μmol/s	3.70E-02 cm/s	5.84

Table 3.6: Variables Describing Oxygen Flux at Diffusion Wall in Newtonian Models.

Just as in the multiphase cases, the flux to flow rate ratio (N/Q) was used to quantify the amount of oxygen gained per unit of fluid processed. Table 3.7 gives the data of N/Q ratio over the interval of Re numbers used. Much like the multiphase cases, the Newtonian cases indicated a peak gain in oxygen per unit flow of fluid at around a Re of 0.1. This is very close to the multiphase model prediction of 0.2.

Table 3.7: Volumetric Oxygen Accumulation in Microchannel.

Re	N/Q
0.01	$0.95\mu mol/cm^3$
0.1	$1.00\mu mol/cm^3$
1	$0.46\mu mol/cm^3$
5	0.17 μmol/cm ³

CHAPTER 4

DISCUSSION

The hydrodynamic and oxygen mass transfer results were presented in the previous chapter for the multiphase model along with the Newtonian model for comparison. Further analysis of the results is provided in the following sections.

4.1 Hydrodynamic Discussion

4.1.1 Effects of Microenvironment on Hematocrit and Apparent Viscosity

A major impetus behind the multiphase simulation was the fact that as dimensions decrease in blood carrying conduits below about 500 µm, the particulate nature of blood becomes more and more important [4, 6, 12, 13]. Two major consequences of shrinking the scale of blood carrying conduits into the microenvironment are the Fahraeus effect and the Fahraeus-Lindquist effect [6]. The Fahraeus effect describes the decrease in tube hematocrit of blood as compared to the feed or discharge hematocrit accompanying decreasing vessel scales into the microenvironment. The Fahraeus-Lindquist effect, on the other hand, describes the decreasing apparent viscosity in the tube under the same circumstances. For convenience in comparison, figures taken from Fournier (1999) [6] are included as figure 4.1(a) and (b) below. The value for hematocrit within the tube obtained during multiphase simulation for each of the Re numbers was 0.29. The value predicted by equation 2.49 was 0.32. The value obtained using the multiphase analysis clearly indicates that there is a drop in hematocrit within the tube. Furthermore, the fact that the hematocrit is consistent across all Re numbers supports the idea that the hematocrit is based on tube diameter since the geometries in each simulation do not change. The decrease in the tube hematocrit was even more pronounced than that predicted by equation 2.49. The data in figure 4.1(a) below, however, indicates that the ratio of tube hematocrit to discharge hematocrit at a hydraulic diameter of 15 μ m could be as low as 0.5 leading to a hematocrit as low as 22.5% within the tube. Either way, the decrease in hematocrit within the tube is consistent with previous data given that any discrepancies can

be explained by the difference in geometry when employing a rectangular conduit as opposed to a circular one. Once more there could be a slight change in the drag experienced by each cell if parachute red cell shapes were employed as opposed to spherical cells and if deformability were included in the simulation.

The multiphase simulation also shows a marked decrease in the apparent viscosity of the fluid within the tube. The value of about 0.8 cP obtained in each simulation is significantly lower than the 1.47 cP apparent viscosity calculated using equation 2.1. However, when looking at figure 4.1(b) below, there are experimental data on the lower curve that support a viscosity ratio as low as about 0.3 within the range of hydraulic diameter used. This ratio would result in a tube viscosity of 0.9 cP, assuming a typical blood viscosity of 3 cP at the inlet, which would be fairly close to the 0.8 cP predicted by the multiphase model. Once again, the previous data has also been collected from circular conduits as opposed to the rectangular micro-channel being employed in these simulations. The difference in cross sections could account for the small discrepancies seen. Again, a small change in the drag coefficient calculation due to the assumption of perfectly spherical cells could also account for some discrepancy along with the neglected cell deformability. Still, the calculation used to obtain the apparent viscosity is around 1.2 cP by itself.

One reason frequently attributed to both the Fahraeus and Fahraeus-Lindquist effects in microchannels is plasma skimming [6]. Typically the dispersed phase is forced closer to the center of the conduit where velocities are higher, and consequently the dispersed phase moves through the channel much more quickly than the continuous phase which travels closer to the wall where velocities are much smaller. Because the volume fraction of the dispersed phase, which has the higher viscosity, decreases in the channel, the apparent viscosity within the channel also decreases. In addition the higher viscosity dispersed phase travels in the center of the tube where resistance is at a minimum, while the lower viscosity continuous phase occupies the periphery of the tube where resistance is much higher. Once more, In this way plasma skimming can account for the reduction in viscosity.



Figure 4.1: a) Fahraeus effect taken from Fournier(1999), p. 75, and b) Fahraeus-Lindquist effect taken from Fournier(1999), p. 77.

To reiterate, the average hematocrit value obtained for each of the multiphase simulations was 29%. But how does this translate to the number of rbc's in a given volume? Let's begin by constructing a volume of fluid obtained by extruding the channel cross section $(10 \times 30 \ \mu m^2)$ axially by a distance that will be proportional to a unit length of the conduit or 1 μ m. The volume of fluid represented by this arrangement is 10 μ m x 30 μ m x 1 μ m or 300 μ m³. If 29% of this volume were assumed to be attributable to the rbc phase this would yield a volume of 87 μ m³ occupied by the rbc phase. Note that the volume of 1 rbc, given as 94 μ m³, is slightly higher than this value. Thus there is slightly less than 1 rbc per unit length of channel. Remember that the width of the channel is 30 μ m. Figure 4.2 was taken from Sugihar-Seki and Fu (2005) and illustrates different rbc flow configurations at varying tube diameters and hematocrits [4]. The left side of the figure was taken at low values of hematocrit and right side of the

figure was proposed at higher hematocrit levels. This figure would indicate that there is probably some zippering along the width of the channel (30 μ m dimension). Thus the degree of zippering would be dependent on the tube diameter as well as the hematocrit in the tube. Simulation results indicate that there is slightly less than 1 rbc per unit length of channel. This implies that over the axial distance assumed by one spherical rbc diameter, 4 whole rbc's would exist. This would indicate a zippering pattern along the 30 μ m width dimension much like that seen in the 11 μ m high hematocrit case below. Since 30 μ m is much larger than 11 μ m there would be more room between rbc's and a larger cell-free layer near the wall as on the left hand side of the image. Thus 4 or so rbc's would stretch laterally across the long dimension of the channel over an axial distance of about 5 μ m. Meanwhile, these cells would most likely migrate single file along the height of the channel.



Figure 4.2: Red cell configurations for low hematocrit (left) and high hematocrit (right) situations taken from Sugihara-Seki and Fu (2005) [4].

4.1.2 Velocity, Resistance, and Pressure-Flow Rate Comparisons

The cross-sectional normalized velocity profiles for the plasma and rbc phases were illustrated in figures 3.1 and 3.2 along with the average velocity for each phase in the channel. Tables 4.1 and figure 4.3 further compare the results obtained for the average velocity of each phase at each Re. Table 4.1 lists the data to indicate the exact values especially at low Re where the data are difficult to ascertain on the graph. Figure 4.3 illustrates the relationship of the velocities of each phase. The average velocity of

the dispersed rbc phase is clearly higher than the average velocity of the continuous plasma phase at each Re. Given the information above, this makes perfect sense. Since plasma skimming should be occurring, the rbc phase should move statistically closer to the center of the channel, where the velocity is higher, resulting in a higher average velocity than the continuous plasma phase which exhibits higher volume fractions closer to the wall where velocities are smaller and resistance is higher. In addition it appears that the change in average velocity with respect to the change in Re is higher for the rbc phase than the plasma phase. Notice that the slope of the line is greater for the rbc phase velocity. As the Re increases the maximum velocity in the center of the tube increases accordingly. The velocity of the continuous phase immediately adjacent to the wall however is still zero and is unaffected by the change in Re. So the increase in Re affects the center of the conduit more. Consequently, it could be expected for the velocity of the dispersed rbc phase to increase more dramatically than that of the continuous plasma phase.

Table 4.1: Average Phase Velocities in Multiphase Simulations.

Re	Uavg (plasma)	Uavg (rbc)
0.02	0.1cm/s	0.1cm/s
0.2	0.8cm/s	1.1cm/s
2	8.2cm/s	10.9cm/s
9	40.1cm/s	57.1cm/s



Figure 4.3: Average phase velocities in multiphase models.

Figure 4.4 describes the relationship between the pressure and volumetric flow rate for the multiphase and Newtonian simulations. It is clear that in each case the pressure and flow rate are linearly proportional to one another. The proportionality constant in this case represents the resistance to flow in the channel. Figure 4.4 indicates that the multiphase model exhibits a lower resistance to flow than the Newtonian model with adjusted viscosity. One explanation to justify this would once again be plasma skimming. Plasma skimming suggests that the dispersed phase with higher density and viscosity flows in the center of the channel where flow resistance is at a minimum. Once more, the continuous plasma phase with its lower density and smaller viscosity flows on the channel periphery where resistance to flow would be higher. Consequently, by limiting the viscosity and density of the fluid in high resistance areas of the microchannel, the overall resistance in the multiphase domain decreases.



Figure 4.4: Pressure-flow relationships in both simulations

4.2 Oxygen transfer

To review, the multiphase model has been utilized to assess oxygen transfer from a constant concentration diffusion wall through a continuous plasma phase across a membrane, characterized by minimal resistance to O2 transfer, and into an rbc phase where it will ultimately interact with hemoglobin to form oxyhemoglobin. A reaction source term was employed within the rbc phase to approximate the oxygen-hemoglobin reaction at steady state in order to more realistically predict the oxygen transfer into

the microchannel during steady state conditions. But is there any evidence that the source term was working correctly?

The reaction source term was added to the rbc phase in order to adjust the rbc phase [O₂], [Hb], and [HbO₂] in accordance with the Hill equilibrium curve. In other words, at each iteration during the solution process the current concentrations of rbc components were compared to the values predicted by the Hill curve based upon the unbound oxygen concentration within the rbc phase. This comparison was accomplished through contrast of theoretical saturation levels based on the Hill equation and actual saturation levels based on the ratio of oxyhemoglobin to total hemoglobin. Thus the source term forces the actual saturation level to approach the theoretical saturation level as the simulation proceeds. If the source term were working properly, then at steady state these two saturations should have been identical.

Figure 3.8 illustrates 3D profiles for the actual and theoretical saturation levels for each simulation side by side. Figure 4.5 below is a closer look at the case of Re = 0.2. A close look at each cross section reveals that the actual saturation matches the Hill saturation. At each cross sectional plane the saturation profiles seem to be exactly the same. To further illustrate this point, figure 4.6 below demonstrates the actual and theoretical saturations along a line taken from the 500 μ m plane that runs vertically along the center of the channel. When the two actual saturation and theoretical saturation are plotted together, the plots follow one another point for point proving that the saturations match. This plot makes it clear that the actual and theoretical saturations match across the channel and thus the source term employed to approximate the oxygen-hemoglobin reaction at steady state is working properly. Examining each of the cases in figure 3.8 reveals that the saturation and theoretical saturation profiles match at every Re.



Figure 4.5: (a) Actual saturation levels for Re of 0.2. (b) Theoretical saturation levels for Re of 0.2.



Figure 4.6: Comparison of actual and theoretical (Hill) saturation along a vertical center-line.

Once it had been established that the source term was working properly, it was important to examine the surface mass transfer characteristics. The Sh number is the dimensionless equivalent of the mass transfer coefficient at the diffusion surface. Figure 4.7 below indicates that the multiphase models achieve greater mass transfer at the surface than the corresponding Newtonian cases. This makes sense because the multiphase model contains an oxygen sink in the oxygen-hemoglobin reaction source term that helps to maintain a higher unbound oxygen differential between the diffusion surface and the fluid. This higher driving potential yields greater oxygen transfer at the surface.



Figure 4.7: Comparison of dimensionless mass transfer at surface of multiphase and Newtonian simulations.

If oxygen transfer at the surface were the most important design consideration then higher Re numbers would prove to be better design criteria as the increased oxygen advection in the axial direction creates a larger oxygen driving potential into the channel. The increased fluid velocity increases the concentration entry length region where fully developed oxygen concentrations within the channel have yet to be realized. In these entry length regions, local Sh numbers are larger and there is greater flux into the surface. Looking at figure 3.10 illustrates that the greatest flux of oxygen into the channel occurs near the channel entrance. As Re numbers increase so does the region of greater oxygen flux (the entrance region). Once fully developed conditions have been met, a lower constant Sh number is achieved. Unfortunately, increasing the velocity at the inlet also increases the volumetric flow rate of the fluid, and as described in chapter 3 relegates any oxygen transferred into the channel into thinner and thinner concentration boundary layers near the wall and out of the reach of the dispersed rbc phase traveling in the center of the conduit. Consequently, higher oxygen transfer at the surface does not necessarily translate to greater oxygen gain by the blood.

One way to characterize the oxygen transfer into the multiphase blood simulation would be to examine the blood oxygen concentration at the outlet. Figure 4.8 illustrates the outlet O_2 concentration at each Re for the multiphase simulations. This figure illustrates that the highest oxygen transfers into the system are associated with the lower Re numbers. Furthermore, maximum oxygen transfers can be obtained using Re as high as 0.2. This figure indicates that decreasing the blood velocity to obtain a Re

lower than 0.2 is not productive. Figure 4.9 indicates the same trend, but the outlet hematocrit has been extrapolated to 45 percent. Remember that the feed and discharge hematocrit are about 45 percent while the tube hematocrit falls to hematocrit levels of around 29 percent. As a result, when the blood reaches the discharge reservoir it will approach a hematocrit of 45 percent increasing the oxygen concentration per unit of blood. This again is a result of plasma skimming. Since rbc's are traveling through the tube faster, they have a shorter residence time and the hematocrit lowers within the tube. At any rate, both figures seem to indicate that Re numbers around 0.2 seem to be the best choice to achieve efficient oxygen transfer while maintaining as much flow rate as possible.

Table 4.2 provides a look into the values obtained using the multiphase model. The upper left hand side of the table contains values taken from Fournier (1999) [6]. The upper right hand side of the table lists values predicted by the current model. The values are slightly higher in the model because of variation in some of the parameters used in the calculation of concentration like oxygen solubility and the molecular weight of hemoglobin. These discrepancies are noted in the bottom of the table. The simulation incorporated the values used by Clark et al (1985). In addition, some sources listed arterial blood PO_2 at 95 mmHg while other listed this value at 104 mmHg. After taking these variations into account, the oxygen values rendered by the multiphase simulations seem very reasonable.



Figure 4.8: Area averaged oxygen concentration at outlet.



Figure 4.9: Oxygen concentration when outlet hematocrit is extrapolated to 45.

	Fournier (Table 41)		Predicted from model		
Oxygen Description:	Arterial	Venous	Arterial	Venous	
Partial pressure, PO ₂ Dissolved O ₂ As Oxyhemoglobin Total Effective	95 mmHg 130 μM 8500 μM 8630 μM	40 mmHg 54 μM 5820 μM 5874 μM	104 mmHg 162 μΜ 8901 μΜ 9063 μΜ	40 mmHg 62 μM 6854 μM 6916 μM	
Blood Properties:	Fournier		Clark et al.		
Heme Group (Density in rbc phase)	Not given		20299 μ M		
Assumed arterial Hematocrit	Not given		0.45		
Hb Molecular Weight	68000 g/mol		67000 g/mol		
[O ₂] at full saturation	8800 µM		9134 μM		

Table 4.2: (Comparison	of [O ₂]	obtained	with	Literature
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Another way to characterize the effects of oxygen flux on the channel volume was to look at the ratio of oxygen flux across the surface to blood flow through the channel. Thus the oxygen transfer per unit time is normalized by the volume of fluid pumped through the channel per unit time. This ratio naturally gives the amount of oxygen gained per unit volume of fluid (see equation 4.1). The N/Q ratio for all Re numbers for both multiphase and Newtonian simulations is presented in figure 4.10. It is evident from figure 4.6 that the multiphase simulations provide a larger N/Q ratio than the Newtonian simulations. This makes sense because the multiphase simulations have a built in oxygen sink where excess oxygen can be stored. Hemoglobin increases the oxygen carrying capacity of the blood many times. But figure 4.10 also demonstrates that there is a clear region where the N/Q ratio is highest. This is also the region

of largest difference in N/Q ratio between multiphase and Newtonian simulations. This region occurs around a Re of 0.2. This is the point of largest O_2 volumetric gain in the multiphase simulation. It its also the point of almost a 5 fold discrepancy in O_2 volumetric gain between multiphase and Newtonian simulations. This would appear to be the region where the most efficient transfer of O_2 into the blood volume occurs. Figure 4.10 also reinforces that although the Sh and oxygen surface flux increase with corresponding increases in Re, the amount of oxygen gained per unit volume decreases substantially as the Re increases.



Figure 4.10: N/Q ratio for multiphase and Newtonian runs.



Figure 4.11: Re = 0.2 channel indicating that arterial saturation levels are accomplished axially at about 1300 μ m.

Although the channel velocity corresponding to a Re of about 0.2 has been indicated as the best choice to achieve efficient oxygen transfer, it is important to remember that saturating beyond typical arterial saturation may be counter-productive. Remember that increased exposure to the artificial surface increases the risk of blood activation. Typically arterial blood saturates at a PO₂ of around 104 mmHg, which in turn is equal to about 97.4 percent saturation. Figure 4.11 above illustrates where the current channel achieve this saturation level of 97.4% at a Re of 0.2. This is important to note because after achieving this saturation the rest of the channel is wasted space. In figure 4.11, the volume in blue represents the blood that has not yet reached full saturation. Anything in color other than blue represents blood that has achieved full arterial saturation. This simulation indicates that at a Re of 2, the current channel would achieve arterial saturation around an axial distance or 1250 to 1300 μ m. This would mean that a channel of the same cross-sectional area as the channel above could operate under the same wall boundary condition and pressure gradient at a length of 1300 μ m to achieve arterial saturation levels.

4.3 Shear Strain Rate, Shear Stress, and Biocompatibility.

In addition to the oxygen transfer data established in the channel, it was important to examine the shear rates and shear stresses established in the channel. Figure 4.12 below depicts the shear strain rate profiles for the plasma phase for the lowest three Re numbers on the left hand side of the figure.

These profiles were then multiplied by the viscosity of the plasma phase to yield the shear stress profiles for each of the cases that are illustrated on the right hand side of the figure.

Figure 4.13 [27] below taken from Chandran et al (2006) illustrates the effect of shear stress over a given exposure time on red blood cells and platelets. The solid line indicates the exposure time at a given shear stress rate at which hemolysis will occur. The darker dashed line indicates when platelet destruction will occur at a specific shear stress over a given duration, and the lighter colored dashes line indicates how long it takes for platelet activation to begin at a specified shear stress. Table 4.3 indicates that calculated time of exposure for the red cells in each simulation based on the quotient of the channel length and the average cell speed in the channel or the average rbc residence time in the channel.

Note that figure 4.12 (f) at a Re of 2 encompasses the highest shear stress but also retains the shortest exposure time. At a shear stress of 711 dynes/cm² (the highest stress for a Re of 2) for an exposure time of 0.018 s, figure 4.13 indicates that the result is still below the threshold of hemolysis, platelet destruction, or platelet activation. Likewise, figure 4.12 (d) encompasses a shear rate of 71 dynes/cm² at an exposure time of 0.184 s, which in turn proves to be below the threshold for hemolysis, platelet destruction, or platelet activation. The values established for a Re of 0.02 also prove to be well below the threshold for hemolysis, platelet destruction, or platelet activation. The values established in any of the simulations of Re of 2 or lower should result in hemolysis, platelet destruction, or platelet activation.

However, exposure to artificial surfaces can increase the likelihood of hemolysis or platelet activation. Wegner (1997) indicates that shear rates in oxygenators range from 480 to 2100 s⁻¹ [1]. Figure 4.12 indicates that only the simulation characterized by the Re of 0.02 falls within this range. Highest shear rates in the other cases are well out of this range. Shear rates in the optimal oxygen transfer case of Re of 0.2 are slightly more than double this range. Thus the combination of information from figure 4.11 and Wegner (1997) cloud the waters a little bit on the biocompatibility of such a channel at various Re numbers. However, it is possible that the increase in effective saturation that might be afforded by this channel might be accompanied by a decrease in biocompatibility. Further testing would be needed to clarify concerns, and better surface treatment options should be pursued simultaneously.



Figure 4.12: Shear strain rate for a) Re = 0.02, c) Re = 0.2, and e) Re = 2. Shear stress for b) Re = 0.02, c) Re = 0.2, and d) Re = 2.





Figure 4.13: Effects exposure to given shear stresses for an rbc and platelet. (Taken from Chandran et al (2006) p. 151.)

Re	Exposure time
0.02	1.838s
0.2	0.184s
2	0.018s
9	0.004s

Table 4.3: Red Cell Channel Residence Time.

CHAPTER 5

CONCLUSION

5.1 Summary

The difficulties in modeling blood flow in the microscale environment are numerous. As mentioned previously, blood is a complex suspension of red blood cells, white blood cells, platelets and plasma proteins. As the domain scale decreases and the ratio of cell length scales to domain length scales increases, these particulate effects become increasingly vital to the fluid description. The continuum models of blood as a single-phase fluid cease to provide an adequate fluid description. Consequently, this 3D, multiphase, multicomponent blood model was developed to perform a CFD simulation on a rectangular microchannel having a cross sectional area of 10 µm x 30 µm to ascertain the Re of optimal O₂ transfer. Blood was modeled as two independent phases containing 3 independent volumetric scalars representing oxygen, hemoglobin, and oxyhemoglobin. The inhomogeneous particle model was utilized in Ansys CFX 11.0 to develop a fluid domain consisting of a particulate spherical rbc phase dispersed in a continuous plasma phase each possessing independent variable fields with the exception of a shared pressure field. All other formed elements were ignored. Each of the phases interacted through mass and momentum interphase transfer terms. Hemoglobin and oxyhemoglobin were limited to the rbc phase, while oxygen was allowed to pass between phases utilizing an interphase transfer term governed by a resistance value experimentally obtained by Huxley and Kutchai [19]. A source term was developed and implemented within the rbc phase to approximate the steady state oxygen-hemoglobin reaction. Blood flow was simulated using 4 different inlet velocity loads constituting 4 different Re numbers.

The multiphase results clearly indicate a drop in both hematocrit and viscosity within the tube. These drops are consistent qualitatively with the experimental data derived by previous investigators. Quantitatively, the hematocrit within the tube matches very closely to predictions based on the Fahraeus effect. Any discrepancies could be explained by the differences in geometries of tubes with circular cross

sections and rectangular conduits. The apparent viscosity values were a little low, but if one were to assume that the characteristic dimension were actually the height of the channel as opposed to the hydraulic diameter, the results would more closely match the previous experimental results describing the Fahraeus-Lindquist effect. In addition, it is readily apparent that in each simulation the average velocity of the dispersed red cell phase exceeds the average value of the plasma phase. This would seem to support the notion that velocity differences between continuous and dispersed phases are at least partly responsible for the changes in hematocrit and apparent viscosity within microchannels.

In addition, oxygen profiles between the rbc and plasma phases matched very closely indicating that membrane resistance was negligible. This supports data obtained by previous investigators like Frank et al (1997) and Federspiel (1989) who found that the resistance to O_2 transfer in the cell membrane and erythrocyte portion of the domain was minor compared to the resistance in the tissue and plasma portion of the model [10, 16]. Results indicated that as the Re increased so did the Sh and O_2 mass transfer at the surface of the conduit. This increased surface transfer was attributed to an increased ratio of axial convection to radial diffusion which carried the O₂ axially more quickly creating a greater driving potential at the surface. Results indicated also that there was an optimal range for O2 transfer into the domain. Unlike O_2 mass transfer at the surface, the volumetric oxygen gain did not increase with Re. Rather, the oxygen concentration increased at the outlet as the Re dropped. Furthermore, the ratio of oxygen flux to blood flow rate indicated that the most efficient Re at which to oxygenate the blood was in the realm of 0.2. Furthermore, it was concluded from data that a channel length of about 1300 μ m would be required to saturate the blood to arterial levels. Although figure 4.10 indicates that the shear stresses developed within the channel are within an acceptable range for exposure time, Wegner (1997) indicates that typical shear rates employed in oxygenators range up to 2100 s⁻¹ [1]. The values for shear strain rate illustrated in figure 4.11 demonstrate that the maximum shear rates generated in the case of Re = 0.2 are more than twice this value. Thus the increase in oxygen efficiency may be accompanied by a decrease in biocompatibility. It may be imperative to develop better surface treatments to prevent hemolysis and blood activation to accompany such a undertaking.

5.2 Model Critique.

Because of the complexity of the physical situation, many simplifications and assumptions were employed to create an executable CFD simulation. Unfortunately, these simplifications and assumptions can lead to results that either over or underestimate the physical reality. Because blood is such a complex suspension, assumptions regarding its character were unavoidable. The blood model employed in the multiphase simulation involved tracking both phases as Eulerian phases that communicated with one another through interphase transfer source terms added into the governing equations. The Eulerian model works by assuming that each phase is present in a fluid element. The amount of each phase present is controlled by volume fractions and the phases are governed by separate equations with respect to unknowns. Thus each of the phases acts somewhat as a continuum, but their interaction is governed by source terms based on particle theory. This Eulerian-Eulerian fluid modeling strategy is somewhat of a compromise between mixture theory and a Eulerian-Lagrangian model in which cells would be discrete particles in the domain whose movement would be governed by a set of ordinary differential equations. The result is a forfeiture of information about individual particle tracking and about specific mass transfer in individual cells. Thus the current model lacks the ability to track the paths of specific particles and oxygen movement into individual cells. Consequently, the current simulation is unable to shed any light on rouleaux formation or dispersion within the channel. What is gained is global information about volume fraction tracking and mass transfer within each of the phases as a whole.

In reality blood is a complex suspension of red blood cells, white blood cells, platelets, and plasma proteins. The multiphase simulation, however, removed all formed elements with the exception of red blood cells and neglected the effects of plasma proteins on rbc interactions. In reality plasma proteins and other formed elements can affect the flow properties of blood significantly. In effect some of the complexity of the hydrodynamic behavior of blood is lost. Red blood cells make up about 95% of the formed elements in blood [6]. White blood cells have been neglected since they compose only about 0.1% of the formed elements in blood. Still, since their size is on the order 7 to 20 μ m, one white blood cell could significantly impede channel flow and drastically effect hydrodynamic effects within the channel. Platelets compose about 4.9% of the formed elements and have been neglected because of their small

numbers as well. Although platelets may have some minor effect on the hydrodynamics within the channel, Almomani et al (2008) indicated that in the microcirculation platelets will tend to move to the exterior of channel in the presence of hematocrit levels indicated for the experiment [24]. Their effect upon rbc dynamics would be minimal, with any effect on oxygen transfer being minimized by their small numbers. Plasma proteins on the other hand could cause rbc's to stick together and effect the hydrodynamics within the channel although this effect would be mitigated by the smaller hematocrits within the microchannel. In the end, the lack of other formed elements and plasma proteins in the simulation may lead to a hydrodynamic flow is developed very quickly and maintained throughout the length of channel. The reality may be more complex with fully developed hydrodynamic flow being developed then disturbances in the flow field leading to another developing region. Thus there may be long stretches of fully developed flow interrupted by small areas of hydrodynamically redeveloping flow due to disturbances from leukocyte rolling or rbc's attaching to one another.

In addition to the simplification of composition, blood has been simplified by assuming that rbc's are spherical particles. The spherical assumption is important in the development of the drag coefficient between the rbc and plasma phases. One important variable in the calculation of the drag coefficient is the area of the particle projected in the flow direction. This would vary if the shape were to change. This change could slightly affect the drag coefficient. In addition there is a possibility that a change in shape might play a role in changing the oxygen diffusivity into the rbc. Since, the resistance to oxygen transfer provided by the erythrocyte is a very small percentage of the overall resistance, this change in shape of the cell should not affect oxygen transport into the rbc too drastically.

The membrane resistance of the rbc was taken from the experimental observations of Huxley and Kutchai (1981). However the experimental data exhibited a large standard deviation and the resistance to oxygen transfer provided by the red cell membrane, taken to be minimal, could be anywhere from 0 to 18%. Thus, the resistance to oxygen flow into the rbc could be underestimated. Other experimenters, however, have also found the rbc component of resistance to oxygen transfer to be minimal [18], [16], [10]. The current simulations also support this idea that the resistance to O_2 transfer across the rbc

membrane is minimal compared to the resistance encountered in the plasma phase. Thus any discrepancies in the rbc portion of resistance should be minimal compared to the resistances experienced in the plasma phase.

Once more, the oxygen-reaction kinetics were approximated using a decaying exponential that worked by bringing the actual fractional hemoglobin saturation by O₂ closer to the theoretical Hill curve with each iteration. The kinetics are not included in the traditional sense. Instead compatibility is forced with the oxygen dissociation curve at each iteration. Clark et al (1985) noted that there are an infinite number of reaction terms that can lead to the Hill equilibrium curve at equilibrium [7]. They also noted that oxygen distribution in an unloading cell is not very sensitive to the reaction rate as long as compliance with the Hill curve is maintained [7]. Since compatibility with the Hill Curve is clearly maintained, any inaccuracies developed from employing the approximation should be negligible. Also, since this simulation is performed at steady state and the transient changes in components are ignored, the difference should have little impact on the outcome.

In addition, the use of the Hill curve to approximate the oxygen dissociation curve belies the clinical situation encountered when employing the device. As mentioned previously, the curve can be shifted by numerous factors including pH, temperature, and PCO₂. The Hill curve implies treatment in a healthy individual. In clinically relevant situations it is likely that increased PCO₂ and decreased pH would lead to a curve that was shifted to the right causing a change in P_{50} in the Hill equation and leading to lower saturation levels at identical PO₂'s. Thus, the use of the Hill curve underestimates the PO₂ necessary to achieve a given saturation state, thereby causing the model to overestimate the saturation at any given point and thus the total amount of oxygen transferred into the blood.

In addition to the simplifications to the fluid properties of blood, there were some important simplifications in the boundary conditions that could lead to errors in the results. To begin with an assumption of 45% hematocrit was assumed for blood at the inlet. This boundary condition insinuates that there is a reservoir at the inlet containing blood at normal hematocrit from which blood is directed immediately into the proposed microchannel. This belies the physical reality that would exist in an oxygenator. In reality, blood would be pumped from a reservoir through a series smaller and smaller

conduits decreasing in size until entering the proposed microchannel. Thus the hematocrit will have sequentially decreased in these pipes until finally arriving at the microchannel. Consequently, the inlet hematocrit and by extension the tube hematocrit in a true situation would be decreased. This could also decrease the mass transfer at the surface by decreasing the driving oxygen concentration due to a smaller hemoglobin source. This could also slightly decrease the N/Q ratio for the channel. The effect, on the overall oxygen concentration in the discharge reservoir would be minimal, since the rbc's should still reach the same approximate saturation by the outlet and upon returning to the reservoir channel would once again exhibit a 45% hematocrit. This error could be reduced by performing an analysis beginning with a reservoir containing blood at 45% hematocrit and using the Fahraeus data provided earlier at each sequentially smaller conduit until the inlet was reached, then substituting the hematocrit value obtained as the inlet hematocrit.

Once more, the assumption that the inlet PO_2 matches venous PO_2 observed in healthy individuals overestimates the PO_2 that would be seen at the inlet. The clinically relevant population might exhibit venous PO_2 's anywhere from 20 to 40 mmHg [31]. Consequently, the results almost certainly underestimate the length of channel needed to achieve arterial saturation as the beginning oxygen tension could be significantly lower.

Another boundary layer simplification was the assignment of a diffusion wall at constant oxygen concentration. The physical oxygenator would bestow a microporous membrane to separate the blood and gas phases. Thus the current constant concentration wall boundary condition overestimates the oxygen flux that would occur into the channel. This issue might be fixed by adding a porous domain or by including a factor to account for porosity in the future.

5.3 Significance

The current model does provide a multiphase, multicomponent simulation of blood flow that does address the particulate nature of blood flow in the microenvironment along with a steady state approximation of oxygen-hemoglobin kinetics. It also yields insight into the nature of blood flow in micro-ducts by confirming the Fahraeus and Fahraeus-Lindquist effects and the role of differential phase velocities in establishing these effects. Once more, the results indicated that the oxygen-hemoglobin

reaction approximation was an important consideration in blood simulation, and that its effect varied over different Re numbers. The model indicated that there was an optimal Re range for oxygen transfer in microchannel flow and established this Re for the current configuration to be about 0.2.

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BIOGRAPHICAL INFORMATION

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