THE DEVELOPMENT AND APPLICATION OF A 
COMPUTATIONAL METHOD FOR MODELING 
CELLULAR-SCALE BLOOD FLOW IN COMPLEX 
GEOMETRY

by

PETER E. BALOGH

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ABSTRACT OF THE DISSERTATION

The Development and Application of a Computational Method For Modeling Cellular-Scale Blood Flow in Complex Geometry

By Peter E. Balogh

Dissertation Director:
Prosenjit Bagchi

A computational methodology for the direct numerical simulation of 3D cellular-scale blood flow in arbitrary and highly complex geometries is presented. The approach is based on immersed boundary methods, which provide an efficient means of modeling flows in such geometries while simultaneously resolving the large deformation and dynamics of every blood cell with high fidelity. The present methodology seamlessly integrates different modeling components, from stationary rigid boundaries of complex shape, to moving rigid bodies, to highly deformable interfaces governed by nonlinear elasticity. Thus it enables the simulation of ‘whole’ blood suspensions flowing through, for example, physiologically realistic microvascular networks that are characterized by multiple bifurcating and merging vessels, as well as geometrically complex lab-on-chip devices.

The focus of this thesis is twofold: the development of such a versatile numerical tool, and the application of this tool to study blood flow in complex microvascular networks. Towards the first objective, after describing the methodology a series of validation studies are presented against analytical theory, experimental data, and previous numerical results. Then, the capability of the methodology is demonstrated by simulating flows of deformable blood cells and heterogeneous cell suspensions in a variety of highly complex and physiologically relevant geometries. In so doing it is shown that the methodology can predict
several complex microhemodynamic phenomena. Towards the second objective, red blood cells (RBCs) are simulated flowing through realistic in vivo-like microvascular networks over a range of physiological conditions. Details are provided on the design of the networks, and an analysis of some general hemo- and hydro- dynamics is presented revealing several novel and unexpected phenomena. Next, an analysis of RBC partitioning at the network bifurcations is presented. At vascular bifurcations cells typically do not distribute to the daughter branches with the same proportion as the flow, which is important in physiology. Various aspects of such disproportionate partitioning are elucidated as it naturally arises in a complex network of multiple sequential bifurcations. Following this, an analysis of the cell free layer (CFL) in the simulated networks is presented. The CFL is a well known RBC-free plasma layer that forms near vessel walls in the microcirculation, and this provides the first simulation-based analysis of its 3D structure in complex in vivo-like networks, including hydrodynamic origins of the observed behavior. Lastly, a study is presented on the wall shear stress for the simulated vascular networks. The three-dimensional aspects of its highly varying nature are elucidated for the first time in a complex network. Additionally, the cellular influence on the wall shear stress as it arises in such geometries is isolated, quantitatively revealing the specific contribution of the cells.

Overall, this work demonstrates that the present methodology is robust and versatile, and can be used to better understand the cellular-scale microphysics underlying important physiological phenomena. Going forward, it has the potential to scale up to very large microvascular networks at organ levels.
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Chapters 2-4 are mostly based on works that have been published, for which I was the primary author. All simulations and analysis related to these works were performed by myself. These are listed as references [8, 9, 10], and are:


Dedication

To mom and dad, whose unconditional love and support have made it possible for me to follow my dreams.
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Chapter 1

Introduction

1.1 Background and motivation

The circulatory system in humans and other living beings is tasked with the distribution of important nutrients, molecules, hormones, etc. throughout the body via the blood stream. In so doing it constitutes the body’s framework for the dissemination of nourishment, maintaining homeostasis, and fighting disease, among other things. The circulatory system is essentially comprised of networks of vessels, interconnecting all aspects of the body. The size (diameter) of these vessels is different depending on in which part of the body the network is located, and these sizes span orders of magnitude. The largest vessels are on the order of centimeters in diameter, and comprise what is called the macrocirculation. On the other hand, the smallest vessels are on the order of micrometers in diameter, and comprise what is called the microcirculation. Vessels in the microcirculation are collectively referred to as the microvasculature, while networks of such vessels are referred to as microvascular networks. These networks are critical to the healthy functioning of the circulatory system; they are responsible for gas and nutrient exchange, regulation of blood flow in individual organs, and nearly 80% of the pumping power of the heart.

The circulatory system functions such that the macrocirculation feeds the microcirculation, and vice versa. For example, deoxygenated blood leaves the heart via the pulmonary artery, and is pumped to the lungs. This artery is a vessel that is approximately 3 cm in diameter and thus a component of the macrocirculation. The subsequent branching, or bifurcating, of vessels as the blood makes its way to the lungs successively reduces the size of the vessels, eventually culminating in μm-sized capillaries in the lungs. The size of these capillaries is on the order of the size of the individual red blood cells (RBCs) in the blood stream, which squeeze as they flow through the capillaries. The networks formed by these
small vessels are the sites where inhaled oxygen is transferred to the blood stream. These networks are also the locations where carbon dioxide in the blood stream is transferred to the lungs, which we in turn exhale. The oxygenated blood is transferred back to the heart, where it is then pumped to the microcirculation at all other locations in the body, such as the brain, kidneys, liver, eyes, muscles, skin, etc. The deoxygenated blood is then fed back to the heart, and the process continues.

At each location in the body, microvascular networks are the place where such critical exchanges take place. Furthermore, the blood is also responsible for transporting important nutrients, amino acids, hormones, antibodies, etc. The architecture of the microvascular networks varies from organ to organ, and examples of such networks as found in the brain, retina, and muscle are provided in Figure 1.1. In the brain (Figure 1.1(A)), the networks are typically made up of relatively short length vessels branching out in all directions. In the retina (Figure 1.1(B)) there is more of a tree-like structure, while in muscles (Figure 1.1(C)) there is more of a planar structure with parallel capillaries.

![Figure 1.1: Microvascular networks in the (A) brain, taken from [119], (B) retina, taken from [113], and (C) muscle, taken from [6].](image)

While this transport of nutrients, etc. is provided by the blood stream, the blood itself is comprised of RBCs, white blood cells (WBCs), and platelets, suspended in plasma. RBCs, WBCs, and platelets are formally referred to as erythrocytes, leukocytes, and thrombocytes, respectively. Plasma, a fluid with properties similar to that of water, is thus the underlying transport medium. RBCs, the primary cellular component that flow with the plasma, are extremely deformable cells, and this property is critical to many physiological functions \[18, 145, 71, 153, 59\]. Their ability to undergo extreme deformation allows them to squeeze through narrow capillaries in the microcirculation without getting damaged. RBC
deformability also causes platelets and WBCs to marginate towards the wall of a blood vessel. The margination of platelets is the first step in the formation of a blood clot, and the margination of WBCs is the first step in the body’s defense against infectious agents. Details on the properties of each of these different cells are provided in the next section. Other examples of cells or other particulate that can be found in the blood stream are cancer cells, circulating tumor cells (CTCs), and drug particles.

When normal physiological functions of the microvasculature are hindered, major pathological conditions may ensue. For example, malfunction in coronary microvessels acts as a precursor to many heart diseases [144]. Hypertension, diabetes, malaria, and sickle cell anemia are each associated with microvascular disorders [85]. Ischemic lesions and alterations to the microvasculature play a major role in the progression of Alzheimer’s disease [3]. Microvascular networks are also the place where metastatic cancer cells enter/exit the blood stream [134]. Furthermore, the architectural complexity of these networks increases significantly in tumor microvasculature, where vascular trifurcations and short-length shunts may be present [160].

Microvascular networks are thus a critical part of the microcirculation. Naturally, then, a detailed understanding of how the various cellular and particulate components of blood individually move, deform, and interact with one another as they traverse these networks is of fundamental importance. The dynamics of such cellular-scale behavior is very intricate, owing to both the properties of the cells as well as the complexity of the geometries through which they flow. Capturing the full 3D, time-dependent nature of such complex behavior is extremely challenging, and consequently the 3D cellular-scale aspects of these flows as they naturally arise in complex in vivo-like networks are largely unknown.

Motivated by these issues, this thesis details an in silico methodology for modeling 3D cellular-scale flows within the highly complex geometries of the microcirculation. The method is then used to study various aspects of such flows within simulated microvascular networks.
1.2 The cellular components of blood, and their properties

Blood at the cellular-scale behaves as a concentrated suspension that is comprised of red blood cells (RBCs), white blood cells (WBCs), and platelets. The underlying fluid conveying these cells is called plasma, a Newtonian fluid with a density and viscosity similar to that of water (1025 kg/m$^3$ and 1.2cP, respectively). The size of these cells is comparable to a typical vessel radius that is encountered in the microcirculation, as well as in microfluidic devices, and each cell has widely different properties [70].

RBCs are the primary cellular component, and are extremely deformable. They are born in the bone marrow, and eventually enter the blood stream via microvascular networks located therein. Their resting shape is that of a biconcave discocyte, with a diameter of approximately 8 $\mu$m and a thickness of 2$\mu$m. RBCs have a deformable outer membrane made up of a lipid bilayer connected to a network of proteins termed the cytoskeleton. This membrane encloses a viscous fluid called hemoglobin, that is neutrally buoyant with respect to the plasma but has a viscosity approximately 5 times greater (6cP) [70]. Both the oxygen and carbon dioxide transported by the blood stream are carried in the hemoglobin of the RBCs. This physical make-up of the RBCs bestows upon them their remarkable ability to undergo extreme deformation without getting damaged.

WBCs are typically larger than RBCs and have a resting shape that is more spherical in nature, with diameters ranging anywhere from 8-20 $\mu$m [70]. These cells are a primary tool of the immune system, and just like RBCs are born in the bone marrow. They circulate throughout the body, protecting against disease and foreign invaders. WBCs are much less deformable than RBCs, and as they flow with the blood stream this property causes them to migrate towards the vessel walls. As mentioned previously, this is the first step in the body’s defense against infections agents, and when needed, they will adhere to the vessel walls and subsequently transmigrate through them.

Platelets flowing in the blood stream are nearly rigid relative to the RBCs, and are much smaller in size. Their shape is disk-like in nature, resembling an oblate spheroid with major and minor diameters roughly 3.6 $\mu$m and 1.1 $\mu$m, respectively [70]. Their primary function is collectively adhering to local sites of injury, forming a blood clot. Much like WBCs, they
also migrate towards the vessel walls primarily due to the disparity in deformability relative to the RBCs, and when needed adhere to the walls.

An image from a scanning electron microscope of each of these cells is provided in Figure 1.2.

![Image of blood cells](image)

Figure 1.2: An image from the National Cancer Institute showing red blood cells (RBCs), white blood cells (RBCs), and platelets as viewed with a scanning electron microscope.

In healthy blood, RBCs typically outnumber the WBCs upwards of 1000:1, and platelets 20:1 [70]. The total volume fraction (i.e. including the plasma) of RBCs in the blood is referred to as hematocrit, and in the microcirculation commonly ranges upwards of 40-45%. In contrast, WBCs comprise around 1% of the volume under healthy conditions, while platelets, due to their relatively small size occupy a negligible volume fraction.

1.3 Computational modeling of cellular-scale blood flow

Computational modeling of cellular-scale blood flow continues to pose new challenges despite significant progress made in recent years [65, 86]. As has been discussed, blood is a very complex fluid, with cellular components that have widely different properties, e.g. size, shape, and deformability. Owing to the ability of RBCs to undergo extreme deformation,
high fidelity computational modeling of such deformation in 3D, and its extension to multiple cells in concentrated suspensions, remains a non-trivial task. Additionally, because the physical properties of RBCs, WBCs, and platelets are so different, ‘whole’ blood behaves as a poly-disperse suspension leading to further difficulty in modeling.

Another major computational challenge in modeling blood flow in the microcirculation arises from the geometric complexity and network-like structure of blood vessels. Blood vessels in the microcirculation are not simply straight tubes; rather, they continually bifurcate and merge with other vessels resulting in complex networks [18, 145, 71, 153]. As mentioned, this network structure is referred to as the microvasculature, and it varies from organ to organ. The influence of the network architecture on the flow of blood cells is expected to be significant, although it is not well understood.

Geometric complexity is also present in microfluidic lab-on-chip devices handling blood. Examples include microchannels with sequential T-bifurcations for cell–plasma separation, channels with repeated expansions and contractions for inertial focusing of cells, and spiraling microchannels for isolating tumor cells [118]. Other examples include artificial vascular networks that are fabricated in an attempt to mimic the real microvasculature [103, 19].

To date, most modeling studies on the flow of deformable blood cells have been limited to flows in simple geometries, such as single, unbranched, straight vessels of uniform circular cross-section, and parallel-plate geometry [65, 86]. Studies of deformable cells in complex geometry are scarce, and are usually limited to a relatively modest complexity, such as a single bifurcation. The motion of an isolated deformable capsule in 2D bifurcating channels was studied using a finite element model [12], boundary integral simulations [198], and Lattice Boltzmann immersed boundary simulations [207], and in 3D using dissipative particle dynamics [112]. Relatively simpler 2D vascular networks having two to three bifurcations were also considered using Lattice Boltzmann methods [180]. A more comprehensive review and discussion of in silico cellular-scale flows through bifurcations is provided in Chapter 4. Axisymmetric motion of a single deformable capsule in a hyperbolic constriction was studied using the boundary integral method [110], while 3D capsule motion in constricted microchannels was studied using spectral boundary integral methods [140, 158]. The boundary integral method was also used to study the deformation of an RBC squeezing through
a narrow passage [64], the motion of a deformable capsule through a square duct with a corner [212], and the interaction of deformable RBCs with platelets flowing in a stenosed capillary vessel [194]. Dissipative particle dynamics has been used to simulate the motion of rigid and deformable particles and cells flowing through cylindrical microchannels, and arrays of posts with different geometrical cross-sections [55, 209]. The Lattice Boltzmann immersed boundary method has been utilized to study the 2D flow of multiple deformable RBCs in stenosed microvessels [188], and the interaction of RBCs and platelets near an intravascular thrombus [175].

Evidently, computational modeling of cellular-scale blood flow in 3D arbitrarily complex geometries, such as physiologically realistic microvascular networks characterized by multiple bifurcations and mergers, or highly complex microfluidic devices, is lacking. To bridge this gap, this thesis presents a 3D direct numerical simulation approach based on the immersed boundary method (IBM) for simulating cellular-scale blood flow in complex geometries. The major strength of immersed boundary methods is they permit the simulation of flows involving arbitrarily complex boundaries without requiring a body-fitted computational mesh [123, 143]. A common means of classifying such methods is to consider continuous-forcing methods and direct-forcing methods. While the continuous-forcing methods are well suited for flows with elastic boundaries, such as highly deformable cell membranes [111, 179, 47, 49], they are not well suited for simulating rigid boundaries. Direct-forcing methods, however, are very well suited for simulating rigid boundaries [123]. In the present approach blood is considered as a suspension of RBCs, WBCs, and platelets. While the RBCs are extremely deformable, WBCs are relatively less deformable, and inactivated platelets are nearly rigid. Thus, from the immersed boundary perspective, the problem involves three types of interfaces: deformable interfaces of the RBCs and WBCs that are governed by nonlinear elasticity, moving rigid boundaries of the platelets, and non-moving but geometrically complex boundaries such as vascular network walls. The numerical methodology for the present work builds on the immersed boundary methodologies of both the continuous- and direct-forcing types, and seamlessly integrates all of these modeling components. Using this approach enables one to simulate geometries that are arbitrarily complex, and not limited to boundaries defined analytically. This permits
the simulation of actual physiological geometry, without requiring any simplifications or assumptions, while simultaneously resolving the motion and large deformation of each individual blood cell with high fidelity.

1.4 Blood flow in microvascular networks

1.4.1 General features and overview of previous studies

Microvascular networks in the human body are made up of the smallest blood vessels, namely, the capillaries, arterioles, and venules. In terms of these, the general direction in which blood flows is from arterioles to capillaries to venules. Arterioles are vessels that continually bifurcate until the smallest vessels – the capillaries – are reached. The venules are vessels downstream of the capillaries that continually merge, forming successively larger vessels. For more than a century, beginning with the celebrated work of Jean L. M. Poiseuille, quantitative studies on blood flow in microvessels have provided invaluable insights into microvascular hemodynamics [181]. Recent advances in experimental techniques, such as intravital microscopy, have made significant progress in this field. In parallel, progress has been made in the theoretical understanding of microvascular blood flow based on mathematical principles of fluid and particulate transport [145].

High-fidelity in silico modeling of blood flow in microvascular networks, however, remains a major challenge. As mentioned, blood in small vessels behaves as a concentrated suspension comprised of cells such as RBCs which are extremely deformable. Analytical solutions are often limited, and computational modeling is needed that can resolve the dynamics and deformation of individual cells while simultaneously extending to a dense suspension [65, 190].

As discussed in the previous section, most cellular-scale modeling studies to-date have considered blood flow in simple geometries, such as long, straight tubes of uniform circular cross section. This is representative of an in vitro-like setup. In contrast, the architecture of vascular networks is very complex, varies from organ to organ, and is characterized by bifurcating, merging, and winding vessels [71]. Furthermore, in a tumor, blood vessels can even have trifurcations and short-length shunts, adding further complexity to the geometry
In many organs, such as the brain, the average length of a vessel segment between two consecutive bifurcations is as small as a few vessel diameters [167, 119]. Such geometrical differences result in significant deviations in hemodynamics between that achieved in a long straight tube versus a vascular network. For example, the hematocrit and velocity profiles over the cross section of a straight tube is naturally symmetric, but most likely asymmetric in vivo [170]. Another prominent example is the difference in blood viscosity as determined in vitro and in vivo. In vitro viscosity, which is based on measurements in straight glass tubes, is found to be less than in vivo viscosity by several factors [154]. An additional example is the self-sustained spontaneous oscillations in network flows that are absent in straight, unbranched tubes [93, 60, 125, 45, 74]. Evidently, our understanding of blood flow in simple geometry is often inadequate to address the hemodynamics associated with the complex architecture of microvascular networks.

Direct simulation of cellular-scale blood flow in microvascular networks is, however, a daunting task. As such, alternative lower-dimensional approaches exist as a remedy. They generally involve treating each vessel as a 1D straight conduit, and using Poiseuille’s law to specify the pressure-flow relationship [167, 45, 74, 67, 178]. Instead of modeling individual cells, the rheological effects of blood are added using empirical correlations for its viscosity, and measures are taken to account for hematocrit partitioning at vascular bifurcations. Although such approaches are able to consider a large number of vessels and have provided insights into the macro-scale hemodynamics of vascular networks, they lack the ability to resolve the cellular-scale details that are important in many pathophysiological events, such as sequestration and localized adhesion of platelets, leukocytes, and drug particulates. Furthermore, many geometrical features of the networks that are of physiological importance, such as winding and non-circular vessels, are not considered in the lower-dimensional models. Evidently, the next generation of microvascular blood flow modeling must combine the cellular-scale details along with a realistic representation of in vivo network geometry.

Toward that end, this thesis presents the first direct numerical simulation (DNS) and analysis of 3D cellular-scale blood flow in physiologically realistic microvascular networks. This includes the analysis of some general hemo- and hydro-dynamics, which reveal several novel and unusual phenomena with potentially significant consequences.
1.4.2 Cell partitioning at vascular bifurcations

Microvascular networks are basically comprised of microvessels that continually bifurcate into smaller daughter vessels or merge into larger vessels. As blood flows through these vessels, the action of cells being distributed into the daughter vessels as they pass through a bifurcation is typically referred to as cell partitioning. A major consequence of cell partitioning in physiology is the heterogeneous distribution of cells observed across microvascular networks [145]. Such heterogeneity is critical to the healthy functioning of the body as it impacts the transport of oxygen and nutrients to tissues.

Over the past decades, a rich body of work has grown in the literature studying cell partitioning at bifurcations using in vivo, in vitro, and theoretical approaches. Such studies have predominantly shown that RBCs usually do not distribute to the daughter vessels with the same proportion as the blood flow. Owing to the discrepancy in cell and volume flow distributions, the term “disproportionate partitioning” is often used. This phenomenon has also been referred to as the Zweifach-Fung effect [182, 69]. In vivo studies, e.g., by [106, 151, 50], among others, typically consider RBCs flowing within the microvascular networks of live animals, such as that in the cremaster muscle of a hamster [102] or ear of a rabbit [163]. [151] performed a detailed analysis of RBC partitioning at arteriolar bifurcations and developed a quantitative description in terms of an empirical relationship between the RBC flux ratio and the blood flow ratio (see also [151]). Empirical relations have also been developed by [102] and [77] based on in vivo data, among others. In vitro studies usually involve RBCs or representative particles such as polystyrene microspheres, flexible rubber disks, or aluminum disks flowing within microfluidic bifurcations [35, 157, 202, 170, 37, 169]. [57] investigated the effects of hematocrit, diameter, local geometry, and cell properties for RBCs flowing in a bifurcating channel. They also developed an empirical relation between the RBC flux ratio and blood flow ratio, based on their in vitro study. Theoretical studies can be broadly classified into two categories: computational models that seek to predict the transport behavior of individual cells through bifurcations by modeling the cells as discrete objects (e.g. [4, 12]) and analytical models which consider a hematocrit concentration
advected with the fluid streamlines [51]. Computational models usually involve bifurcating tubes [82, 195] or channels [13, 112, 169, 5] and accurately resolve the cellular-scale details.

Various studies have shown that the disproportionate partitioning, in general, arises in two ways: a daughter branch receiving a higher flow fraction either receives an even higher RBC fraction or a lower RBC fraction (e.g. [163, 151, 170, 169, 37]). The former is termed as classical partitioning and the latter as reverse partitioning. [169] observed the reverse partitioning in a single bifurcation to occur as the result of a two-file-type cell pattern in the feeding vessel with a depleted core and outer layer. This led to the low flow branch receiving less plasma than the high flow branch, which explained the observed reverse partitioning. [163, 151] observed such reverse behavior as the result of disturbances caused by nearby upstream bifurcations, as was also observed in [170]. In addition to identifying such novel phenomena and quantifying the cell partitioning in terms of controlling parameters, studies have elucidated the underlying hydrodynamic mechanisms. [12, 48] considered the mechanisms associated with the passage of one cell through a bifurcation. Opposing tendencies were identified that caused individual cell trajectories to deviate from the fluid streamlines. The most notable of which was an attraction tendency toward the low-flow branch of the bifurcation. [13] considered the passage of two cells through a bifurcation. They specifically identified two general types of interaction dynamics, resulting in a tendency to create either a balance or imbalance in the hematocrit distribution to the daughter vessels. These and other computational studies generally tend to suggest that the individual cell trajectory through a bifurcation is affected by cell deformability, cell-to-vessel size ratio, initial cell location in the feeding vessel, as well as the geometrical features of the bifurcation [195, 82, 207].

Disproportionate cell partitioning has also been referred to in the literature as phase separation, and the two classic components which comprise such behavior have been termed plasma skimming and cell screening (e.g. [200, 51]). Plasma skimming is based on the advection of a concentration (i.e. hematocrit) profile through a bifurcation by the fluid velocity field and how the profile is partitioned to the daughter vessels. Thus, an inherent assumption underlying this component is that the cells are volume-less point particles, which allows an analytical treatment of the phenomenon as considered, e.g., by [201, 142].
Additionally, experimental studies have utilized a plasma skimming analysis to aid in the interpretation of the results (e.g. [57, 151]). Cell screening, on the other hand, refers to the effects of the finite size of the cells with respect to the vessel diameter. Because of the finite-size effects, cell deformation and cell-cell interactions come into consideration, which have been investigated in the aforementioned studies.

The aforementioned computational models on cell partitioning in single bifurcations have offered highly valuable insights. The next step is to consider cell partitioning in successive bifurcations as observed \textit{in vivo} [38]. It has been shown that upstream bifurcations necessarily have an impact on the partitioning behavior. [163, 151] each demonstrated this \textit{in vivo}, where in the latter the proximity of an upstream bifurcation was shown to result in a notable asymmetry in partitioning. This was also demonstrated \textit{in vitro} by such studies as [26, 157, 170]. It appears, however, that computational studies investigating cell partitioning with RBC suspensions flowing through multiple sequential bifurcations have not been performed, to our knowledge.

Using the aforementioned 3D simulations of RBCs flowing through \textit{in vivo}-like microvascular networks comprised of many sequential bifurcations, this thesis presents the first study and analysis of RBC partitioning based on such large-scale modeling.

1.4.3 The cell free layer

A well-known characteristic of blood flow in the microcirculation is the formation of a plasma layer adjacent to the vascular walls that is devoid of RBCs. As mentioned, RBCs are the primary cellular component of blood, and they tend to flow in the central core region of the microvessels. This plasma layer, often referred to as the cell-free layer (CFL), separates the RBC core from the vessel walls [98]. The existence of the CFL has important hemorheological and physiological consequences under both healthy and diseased conditions. Since plasma viscosity is less than hemoglobin viscosity, the CFL provides a means of reducing the apparent viscosity of blood in small vessels. The variation of the CFL thickness with respect to the vessel diameter is related to the decrease in the apparent blood viscosity (Fahraeus-Linquvist effect) and hematocrit (Fahraeus effect) with decreasing vessel diameter [153]. As the RBCs occupy the central core region, inactivated platelets and leukocytes
marginate towards the vessel walls. The near-wall accumulation of platelets and leukocytes is important in maintaining the body’s hemostasis and immune response, respectively. The characteristics of the CFL play a large role in such processes (e.g. [63, 42, 210, 53]). Being situated between the RBC core and the vessel wall, the CFL also affects the wall shear stress which is sensed by the endothelial cells to trigger diverse pathophysiological functions (e.g. [176, 44, 11]). In addition, the CFL provides a barrier that inhibits the consumption of nitric oxide (NO), a vasodilator, produced in the vascular endothelium (e.g. [114, 155]). Furthermore, the thickness of the CFL is directly related to the plasma skimming phenomenon which contributes to a heterogeneous distribution of hematocrit to the daughter branches at a vascular bifurcation [51]. In terms of theoretical applications, several low-dimensional models of microvascular blood flow utilize the CFL thickness as an input parameter (e.g. [142, 200, 168, 193, 166]).

Because of its fundamental importance, the CFL has been studied extensively in vivo (e.g. [39, 177, 129]), in vitro (e.g. [22, 57, 156]), and in silico (e.g. [54, 207]). A significant amount of information exists in the literature on the dependence of the CFL thickness on vessel diameter, hematocrit, flow rate, and shear rate, among other pertinent quantities. Such works have generally shown that the thickness increases with decreasing hematocrit, increasing flow rate, and increasing vessel diameter [98]. In long, straight vessels, a number of competing hydrodynamic mechanisms can be identified to play roles in the formation of the CFL [165]. Under normal conditions, healthy RBCs are extremely deformable. This deformability results in a migration of the RBCs away from vessel walls, and from regions of higher to lower velocity gradient [24, 1, 173]. The center-ward migration is countered by the cell-cell interactions (shear-induced diffusion) which tend to disperse the cells over the vessel cross-section [107, 108]. For a fully developed and otherwise steady flow in long, straight vessels of circular cross-section, the balance of these competing mechanisms results in the time-averaged CFL being axisymmetric and of constant thickness along the vessel length. Studies on the CFL in such vessels have elucidated its characteristics under a diverse range of conditions, including non-axisymmetric entrance profiles (e.g. [54, 135, 90]).
As has been discussed, in the microcirculation blood vessels form complex networks, and as such, are typically not straight in length, and frequently either bifurcate into smaller vessels or merge to form larger vessels. Owing to these complexities, the CFL as it arises under such circumstances is not expected to be axisymmetric. Rather, the vascular bifurcations, mergers, and vessel tortuosity are expected to result in a fully three-dimensional and highly varying CFL along the length of a vessel in a microvascular network. In the microvasculature of many organs, such as the brain, the blood vessels are of short length so that the flow cannot fully develop. To date, however, these complex aspects of the CFL have been studied either by considering single, isolated vessels, or by considering single bifurcations or mergers. For example, [20] performed a comprehensive in vivo study of cells flowing in microvascular networks in various organs of different vertebrates. The CFL thickness was observed to be different between the two sides of the vessel, providing evidence suggestive of the 3D, asymmetric nature of the CFL in vivo. Similar discrepancies in the CFL thickness on either side of individual vessels were noted by [97] in long, unbranched vessels in the rat microvasculature. Studies such as these suggest that CFL asymmetries can arise far away from any disturbances caused by upstream bifurcations or mergers. The hydrodynamics underlying such behavior, however, remains an open question [97].

Near bifurcations and mergers, the CFL has been shown to be asymmetric immediately downstream due to the disturbances caused by these structures. The in vivo work of [131] studied variations in the CFL near bifurcations, as did the 2D in silico works of [207, 205]. These studies reported a thinner CFL on the side of the daughter vessel that was closest to the bifurcation. The in vivo work of [129] studied the change in the CFL caused by two merging vessels, and observed the downstream CFL to be asymmetric. They further noted that the asymmetry increased with increasing discrepancy in the flow contributions from each feeding vessel, which apparently alludes to a hydrodynamic mechanism for the CFL development within such geometries.

The existing knowledge of the CFL in vivo, however, has been based on characterizing it as a 2D projection onto the image plane. As such, the reported asymmetry in the CFL in the aforementioned studies is based on the thickness values on either side of a vessel as observed in the 2D projection. As noted before, because of the presence of frequent
bifurcations, mergers, and vessel tortuosity, the asymmetry of the CFL is expected to be fully 3D in nature and to evolve within the network in a more complex manner than what can be captured by the 2D projection. The full 3D nature of the CFL asymmetry, and the underlying hydrodynamic mechanisms by which it arises are not well understood, and are thus another focus of this thesis.

1.4.4 Wall shear stress

As blood flows through vessels in the microcirculation, it exerts a shear stress on the vessel walls by fluid friction. This stress plays an important role in many physiological functions; it has been shown that the endothelial cells lining the vessels walls can sense the wall shear stress and trigger diverse events. The wall shear stress stimulates the release of nitric oxide (NO) from the endothelium [33], which is a known vasodilator central to the regulation of blood pressure [155]. It drives the realignment of endothelial cells as well as induces growth factors leading to vascular remodeling [172, 34]. It also encourages the absorption of oxygen carried in the blood by intended targets in the endothelium [23]. In addition to these, the wall shear stress modulates leukocyte adhesion and rolling [34], which is a fundamental component to the body’s defense against disease. It affects platelet adhesion as well, which results in the formation of blood clots following injury. However, when platelet aggregates grow on the vessel walls and obstruct blood vessels (i.e. thrombosis), this can be detrimental. The wall shear stress can counter this by stimulating the production of molecules and proteins in the endothelium that inhibit such aggregation [23, 62].

The wall shear stress is clearly a central component to maintaining vascular homeostasis, as well as the healthy functioning of the circulatory system in general. As such, various aspects of its nature have been extensively studied in the literature using both experimental and theoretical approaches. [115] determined the wall shear stress in vivo in microvascular networks in the mesentery of a cat, and considered single, unbranched vessels on both the arterial and venous sides of the networks. The wall shear stress in microvascular networks in the human retina was investigated by [127], and in other locations within human eyes in [105, 104]. Such works have generally shown that the wall shear stress is higher in vessels on the arterial side of the networks than on the venous side. Other works have focused
on more specific aspects of the wall shear stress. [61] looked at the variation in wall shear stress in vivo between different branched vessels on the arterial side, and the connections between endothelial response and the variations in stress. [130] also studied variations in the wall shear stress in arterial vessels, but related to characteristics of cellular-scale flow. [95] looked at wall shear stress patterns in vivo in vessels on the venous side, specifically near merging vessels. More general effects on structural adaptation of the vasculature were investigated in [7] using both in vivo and in vitro approaches.

A number of in silico works have also studied the wall shear stress by looking at cells flowing in single, straight vessels, or vessels with a bifurcation. [66] performed 3D cellular-scale simulations of RBCs in a straight tube using a boundary integral-based approach. They looked at both the time-averaged and time-dependent wall shear stress, and the differences between them as a result of the cellular influence. 2D Lattice Boltzmann simulations were performed by [199], and also by [206], who each looked at different dependencies of the wall shear stress on cell and flow characteristics. Wall shear stress patterns near a single bifurcation were studied in [205], also using 2D Lattice Boltzmann simulations. [193] studied stress patterns in a curved tube with a theoretical model of blood as a two-phase fluid, and showed that the wall shear stress was higher on the side of the vessel with the smaller radius of curvature.

Collectively, all of these works have generally shown that the wall shear stress is dependent on both the geometry through which blood flows, as well as the cellular character of blood. To-date, the understanding of the spatial variations as they arise in complex networks and other in vivo-like geometries, however, is at most two-dimensional. Determination of the full 3D spatial variations in wall shear stress require a knowledge of the 3D velocity field, or some other 3D field, which presents significant challenges. As such, these aspects of the wall shear stress in complex geometries have not been studied, to our knowledge. The final chapter of the thesis thus focuses on the three-dimensional spatial variations in the wall shear stress, including the cellular influence, as it naturally arises in the in vivo-like microvascular network simulations.
1.5 Scope of thesis

The scientific objective of this thesis is to both develop and apply a novel numerical technique for simulating the flow of deformable cells and rigid bodies in arbitrarily complex geometries as encountered in physiology and microfluidics. To achieve this, the scope of this thesis covers the following topics, broken into the chapters in which they are addressed.

After introducing the relevant content and motivating the present work in Chapter 1:

- Chapter 2 presents the details behind the development of the numerical methodology. It includes a rigorous validation, the demonstration of a wide variety features and potential applications, and a discussion on some considerations in developing such a tool.

- Chapter 3 details the application of this numerical technique to simulate in 3D red blood cells flowing through physiologically realistic microvascular networks. An overview of the simulations is provided, in addition to an analysis of some general hemo- and hydro-dynamics.

- Chapter 4 presents a detailed analysis of the partitioning of the RBCs at bifurcations in the simulated networks. This includes the identification of underlying cellular-scale mechanisms that give rise to different distribution behaviors, time-dependency of the cell partitioning, and a revisiting of two well-known components that cause disproportionate cell distributions to occur.

- Chapter 5 presents a study on the cell free layer as it arises in the simulated networks. The focus is on the three-dimensionality of the layer, including the mechanisms and hydrodynamic origins underlying variations in its structure.

- Chapter 6 presents an analysis of the three-dimensional nature of the spatial variations in the wall shear stress as it arises in the simulated networks. The contribution of the RBCs to such variations is also isolated, and regions are identified where this cellular influence is most enhanced.
• Chapter 7 provides a summary of the main conclusions presented in this thesis, and the overall contributions to this field of science.
Chapter 2
Numerical Method

2.1 Overview

The generic problem of cellular-scale blood flow in complex geometry is schematically shown in Figure 2.1. Blood is considered as a suspension of RBCs, WBCs, and platelets, with the suspending fluid being the plasma. As illustrated in Figure 2.1, the problem involves three types of boundaries: (i) deforming cellular membranes, (ii) rigid but moving boundaries, and (iii) non-moving but geometrically complex boundaries such as vascular walls. The deforming interface is primarily the membranes of the red blood cells, which are extremely deformable. Activated white blood cells, and other circulating elements, such as vesicles, are also deformable. The membrane deformation of these cells is governed by complex nonlinear (visco)-elasticity. Inactivated platelets, in contrast, behave like rigid particles. The vascular walls are considered to be rigid for the present work. The continuous-forcing and direct-forcing immersed boundary methods are used to integrate these diverse types of interfaces. Structurally, the RBCs are viscous liquid drops surrounded by hyperelastic membranes. The liquid interior of the cell is the hemoglobin which has a different viscosity than the outside fluid, plasma. Viscosity of the cytoplasmic fluids of the WBCs and other circulating cells also differs from that of the plasma. Thus the problem involves multiple fluids of different viscosity.

The different types of interfaces present in the problem require different numerical treatments. A finite element method (FEM) is used to obtain the stresses generated in the deforming cell membranes. The membrane stresses are then coupled to the bulk fluid by the continuous-forcing IBM. A sharp-interface ghost-node immersed boundary method (GNIBM) is used to treat the non-moving vascular walls and the moving rigid objects.
Figure 2.1: Schematic describing the generic problem of cellular-scale blood flow in complex geometry. The problem involves deformable interfaces (membranes of red blood cells and other deformable cells), moving rigid bodies (e.g., inactivated platelets), and non-moving vascular walls. The problem also involves multiple fluids of different viscosities. Boundaries are immersed in a fixed (Eulerian) rectangular Cartesian mesh that is used to discretize the entire computational domain.

The flow solver is based on a coupled finite-volume/spectral method. In the following sections, each of these modeling components is described. Section 2.2 first discusses the new developments made in implementing these modeling components, in addition to specific considerations with regard to the fundamental approach. The methodology associated with deformable cells has been developed previously [47, 203, 204, 40], and is discussed in Section 2.3. Section 2.4 details a methodology for extending this approach into a computational framework that can also model complex rigid interfaces, both stationary and moving. The method is then validated in Section 2.5, and its versatility is demonstrated in Section 2.6. Lastly, Section 2.7 discusses fluid leakage considerations, and details a novel technique for ensuring it remains negligible with highly complex geometries.

### 2.2 Developments and considerations

General numerical developments and considerations are now discussed with regard to implementing each of the modeling components.
For complex rigid interfaces, the general idea is adapted from that developed in [124], whereby a constraint is enforced at certain Eulerian grid points such that desired boundary conditions are achieved at the interfaces. In adapting this methodology, an explicit method of enforcing the constraints associated with the rigid interfaces has been developed. This does not require modifying the linear system on account of the rigid boundaries and thus permits use of efficient inversion techniques for solving the system. With regard to moving rigid objects, a novel methodology is considered to couple the rigid body dynamics using the Euler parameters with the fluid flow. This incurs minimal additional computational overhead and can in principle be applied to rigid bodies of any shape, not just the ones considered here. The types of complex stationary geometries considered here represent the first of their kind to be modeled with this type of method, namely complex microvascular networks. The procedure detailed later provides an efficient approach to incorporate these physiological structures into a simulation.

The implementation of the deformable cell methodology has been done in prior works [47, 203, 204, 40] in which a co-located arrangement of the velocity and pressure are used for the Eulerian grid on which the governing equations are solved. When using a co-located arrangement of variables one runs the risk of encountering the classic oscillations in the pressure field [58] on account of the discrete form of the Laplacian required to satisfy the continuity equation to machine epsilon. This issue is not encountered if only deformable interfaces are present due to the diffuse nature of continuous-forcing type methods. With the introduction of complex rigid interfaces to the problem, however, oscillations in the pressure field were found to result when tested. A pressure-velocity coupling algorithm was implemented to mitigate this, which resulted in a smooth pressure field for all simulations tested. However, the de-coupling between the pressure and velocity fields resulted in the rigid interface constraints being only weakly enforced using the explicit technique developed with increasing geometric complexity. This is primarily due to the fact that the discrete velocity field that is solenoidal is different from the velocity field associated with the momentum forcing, where the rigid interface constraints are enforced.
It was found that use of a staggered-grid arrangement of variables provides a highly robust means of simulating the complex rigid interfaces using the explicit technique developed for enforcing the rigid interface constraints. A well known benefit of a staggered arrangement is that it obviates the need for any special pressure-velocity coupling on account of the discrete form of the Laplacian being naturally compact. As such, there is an inherently strong coupling between the velocity and pressure fields. With increasingly complex geometries, this significantly improved the degree to which the explicit rigid interface constraints were enforced, compared with the co-located arrangement. However, as discussed later, with geometric complexity such as that of the microvascular networks, additional measures were needed to ensure fluid leakage remains negligible. This inherently strong pressure-velocity coupling is also highly desirable with regard to the methodology for moving rigid particles where the pressure is directly used to compute the motion of the particle, as discussed later.

2.3 Modeling deformable cells

2.3.1 Principles of approach

Deformable blood cells are modeled as capsules, i.e., viscous drops enclosed by zero-thickness hyperelastic membranes. In this model, the ultra-fine structure of the cell membrane, namely the lipid bilayers and the spectrin network, are indistinguishable. Below the discussion is limited to the modeling of an RBC; a similar approach is taken for modeling other deformable cells. The resting shape of the RBC is taken as the experimentally observed biconcave discocyte with an end-to-end distance of 7.8 µm, surface area $134.1 \mu m^2$, and volume $94.1 \mu m^3$ (Figure 2.2a) [71]. The fluids both interior (hemoglobin) and exterior (plasma) to the cells are assumed to be incompressible and Newtonian. The RBC membrane is assumed to resist shear deformation, area dilatation, and bending. The resistance against shear deformation and area dilatation can be modeled using a suitable constitutive relation for the strain energy function $W_s$ of the membrane material. A common form of $W_s$ that is often used is based on the work of Skalak et al. [174] as

$$W_s = \frac{G_s}{4} \left[ (I_1^2 + 2I_1 - 2I_2) + C I_2^2 \right].$$ (2.1)
Here $G_s \sim 2-5 \times 10^{-6}$ N/m is the membrane shear elastic modulus, $I_1 = \epsilon_1^2 + \epsilon_2^2 - 2$ and $I_2 = \epsilon_1^2 \epsilon_2^2 - 1$ are the strain invariants of the Green strain tensor, and $\epsilon_1$ and $\epsilon_2$ are the principal stretch ratios. The Green strain tension is defined as $E = (F^T \cdot F - I)$, where $F = \partial \mathbf{x} / \partial \mathbf{X}$ is the deformation gradient of the current configuration $\mathbf{x}$ relative to the original configuration $\mathbf{X}$ of the membrane (Figure 2.2). The RBC membrane can undergo large shear deformation but almost negligible surface area dilation. In Eq. 2.1, the parameter $C$ is used to control the amount of surface area dilation, and a large value of $C$ results in a small area dilation. Other forms of $W_s$ have also been tested for the RBC membrane, and can be used within the framework of the present methodology. For example, a higher-order neo-Hookean model can be expressed as

$$W_s = \frac{G_s}{2} \left( \epsilon_1^2 + \epsilon_2^2 + \frac{1}{\epsilon_1 \epsilon_2} - 3 \right) + C_3 \left( \epsilon_1^2 + \epsilon_2^2 + \frac{1}{\epsilon_1 \epsilon_2} - 3 \right)^3$$

(2.2)

where $C_3$ is a constant that was experimentally determined as $\sim G_s/30$ [122]. The experimental study in [122] has shown that at extreme deformation, the generalized neo-Hookean model works well for RBC deformation. In the present work, this law has been used for the micropipette aspiration simulations (Section 2.5.3), since the RBC exhibits extreme deformation for such experiments. It was also found that for this specific case, the generalized neo-Hookean law predicts the experimental results better than Skalak et al’s law. Indeed this observation merits further detailed study on the role of different constitutive models, but that is not within the scope of the current study.

![Figure 2.2](image.png)

Figure 2.2: (a) Undeformed shape and Lagrangian mesh on the surface of a red blood cell. (b) An arbitrary deformed cell. (c) Deformed and undeformed Delauney triangles.

Once an appropriate form of $W_s$ is chosen, the principal elastic tensions (or stresses) in the cell membrane can be obtained as [146]

$$\tau_1 = \frac{1}{\epsilon_2} \frac{\partial W_s}{\partial \epsilon_1}, \quad \tau_2 = \frac{1}{\epsilon_1} \frac{\partial W_s}{\partial \epsilon_2}$$

(2.3)
A finite element method (FEM) is used to obtain the membrane tensions resulting from
the shear deformation and area dilatation [47, 49, 171]. In this approach, the surface of
each cell is first discretized using Delauney triangles, as shown in Figure 2.2, with each
vertex (or node) shared by five or six triangles. The nodes also serve as the Lagrangian
marker points that are advected to update the cell shape and location. Each triangle is
assumed to remain flat upon deformation of the cell. The displacement field \( \mathbf{v} \) is assumed
to vary linearly within each triangular element, and is expressed in terms of linear shape
functions \( N_i \) as \( \mathbf{v} = N_i \mathbf{v}_i \), where the index \( i = 0, 1, 2 \) denotes the vertices of the triangle.
The shape functions can be evaluated by knowing the coordinates of the vertices. Once the
shape functions are known, the deformation gradient \( \mathbf{F} \) is obtained. Subsequently, \( \epsilon_1^2 \) and
\( \epsilon_2^2 \) which are the eigenvalues of \( \mathbf{F} \cdot \mathbf{F}^T \), and the principal stresses \( \tau_1 \) and \( \tau_2 \) are obtained.
Having the stress tensor \( \tau \) in each element evaluated, we obtain the resultant elastic force
at each node as
\[
f_e = \sum_n \int_{S_n} \frac{\partial \mathbf{N}}{\partial \mathbf{X}} \cdot \mathbf{P} \, dS, \tag{2.4}
\]
where \( \mathbf{N} \) is the vector of the shape functions, \( \mathbf{P} = \epsilon_1 \epsilon_2 \tau \cdot \mathbf{F}^{-T} \) is the first Piola-Kirchhoff
stress tensor, and \( S_n \) is the area of each of the \( n \) triangles surrounding the node. Further
details on the development of Eq. 2.4 can be found in prior works [47, 204].

The cell membrane also exerts a resistance against bending, and, hence formation of
high curvature. The bending resistance is modeled following Helfrich’s formulation for a
bending energy that is expressed as [211]
\[
W_b = \frac{E_b}{2} \int_S (2\kappa - c_o)^2 \, dS, \tag{2.5}
\]
where \( E_b \sim 2 \times 10^{-19} \) J is the bending modulus, \( \kappa \) is the mean curvature, \( c_o \) is the
spontaneous curvature, and \( S \) is the entire surface area of a cell. An expression for a force
density arising due to the bending resistance can be derived from Eq. 2.5 as
\[
f_b = E_b \left[ (2\kappa + c_o)(2\kappa^2 - 2\kappa g - c_o\kappa) + 2\Delta_{LB}\kappa \right] \mathbf{n}, \tag{2.6}
\]
where \( \kappa_g \) is the Gaussian curvature, \( \Delta_{LB} \) is the Laplace-Beltrami operator, and \( \mathbf{n} \) is the
normal vector. The above force expression, which can be easily implemented within the
IBM framework, is used here to model the bending resistance of the cell membrane. The
mean and Gaussian curvatures are evaluated at each vertex using a quadratic surface fitted to the vertex and its nearest neighboring vertices. Then, using the Gauss theorem \( \Delta_{LB} \kappa \) is approximated on a small surface patch \( dS \) as \( (1/dS) \int_l \nabla_S \kappa \cdot n_l dl \), where \( l \) denotes the patch boundary, \( \nabla_S \) the surface gradient, and \( n_l \) the unit normal to the boundary \( l \). The gradient \( \nabla_S \) on a surface triangle can be obtained either by a linear interpolation of the surface and \( \kappa \), or using the loop subdivision method.

The net membrane force at each Lagrangian node on the cell surface is the summation of the contributions from shear, area dilation, and bending,

\[
 f_m = f_e + f_b. \tag{2.7}
\]

With regard to the mechanical properties of the membrane used in the simulations, considered here is a membrane shear modulus \( (G_s) \) of \( 2.5 \times 10^{-6} \frac{N}{m} \), membrane bending stiffness \( (E_b) \) of \( 7 \times 10^{-19} \frac{J}{m} \), and fluid viscosities of 0.001 Pa-s, unless otherwise noted in the relevant section. With regard to the membrane constitutive law, Eq. 2.1 is used with the exception of the micropipette aspiration simulations Section 2.5.3 where Eq. 2.2 is used. The membrane viscosity is assumed to be negligible in the present work. However, it has been incorporated within this deformable cell methodology in a previous study [204].

The white blood cells are modeled using the similar capsule model, and using the constitutive law given by Eq. 2.1, with the membrane stiffness assumed to be 10 times higher than the RBC. Furthermore, they are assumed to be non-nucleated. It should be noted that there are many different WBC models that exist in the literature, for example: (1) liquid drop model without any membrane [91], (2) perfectly rigid sphere [99, 100], and (3) capsule without any nucleus [87, 63]. The WBC model here is similar to that of [87, 63], and is sufficient for the purpose of the present work to demonstrate that diverse types of cells can be considered. Inclusion of one or multiple nuclei is a rather trivial issue within the front-tracking method, and previous works on WBC adhesion have been performed where nucleated WBCs were considered using the same numerical method as described here [137, 138, 139].
2.3.2 Cell and flow coupling

The cell membrane is deformed by the fluid flow, and the membrane deformation in turn alters the flow. This two-way coupling between the membrane and the fluid is obtained via a continuous-forcing IBM by adding the membrane force \( f_m \) to the governing equations for fluid flow and spreading the singular force over a finite span of the surrounding fluid using a delta function. This approach allows a single set of fluid flow equations written for both fluids, internal and external to the cell, and solved on a fixed Eulerian mesh (Figure 2.1).

For microcirculatory flows, inertial effects are negligible, and hence the flow is governed by the unsteady Stokes equations, along with the incompressibility condition:

\[
\nabla \cdot \mathbf{u} = 0
\]

\[
\frac{\rho \partial \mathbf{u}}{\partial t} = -\nabla p + \nabla \cdot \mu \left[ \nabla \mathbf{u} + \nabla \mathbf{u}^T \right] + \mathbf{F} \tag{2.9}
\]

where

\[
\mathbf{F} = \int_S f_m \delta(\mathbf{x} - \mathbf{x}')d\mathbf{x}' \tag{2.10}
\]

is the membrane force distributed to the surrounding fluid, \( \delta \) is the three-dimensional Dirac-delta function, and \( \mathbf{x} \) and \( \mathbf{x}' \) are the locations in the flow domain and on the cell surface \( S \), respectively [187]. Thus the delta function vanishes away from the cell membrane. Following [187], a cosine function spanning four grid points around the cell boundary is used as a numerical approximation of the delta function

\[
\delta(\mathbf{x} - \mathbf{x}') = \frac{1}{64\Delta^3} \prod_{i=1}^3 \left[ 1 + \cos \frac{\pi}{2\Delta} (x_i - x'_i) \right] \tag{2.11}
\]

where \( \Delta \) is the Eulerian grid size. The method to solve the flow equations is described later.

Once the flow field is obtained at any time instance, the velocity \( \mathbf{u}_m \) of the marker points (Lagrangian nodes) on the cell surface is obtained by interpolating the Eulerian velocity \( \mathbf{u} \) using the delta function as given above. The membrane is then advected as \( \frac{d\mathbf{x}'}{dt} = \mathbf{u}_m \) to obtain the new deformed shape and position of the cells. It may be noted that \( \mu \) in Eq. 2.9 is a function of \( \mathbf{x} \) and time \( t \) due to the presence of multiple fluids (i.e. plasma and cytoplasm). Thus \( \mu \) has to be evolved with time as the flow field evolves. The method of evolving \( \mu \) is described next.
2.3.3 Numerical treatment of viscosity

The method used to evolve the viscosity field $\mu(x, t)$ is now discussed. As the deformable cells change shape and acquire new locations, the viscosity field must be evolved since the viscosity of the fluids interior and exterior to the cells are different. The technique given in [187] is followed in which $\mu(x, t)$ is written in terms of an indicator function $I(x, t)$ as

$$\mu(x, t) = \mu_p + (\mu_c - \mu_p)I(x, t) \tag{2.12}$$

where $\mu_p$ and $\mu_c$ are the viscosities of the plasma and cytoplasmic fluids, respectively. The indicator function is zero outside a cell and one inside. For the sake of brevity, it is assumed in Eq. 2.12 that only two fluids are present. However, the technique can be applied to any number of fluids, and, hence, to poly-disperse cell suspensions, by using multiple indicator functions. It can be shown that the indicator function follows a Poisson equation as

$$\nabla^2 I = \nabla \cdot G \tag{2.13}$$

where the $G(x, t)$ is an Eulerian variable constructed from the cell surface normals $n$ as in [187]:

$$G(x, t) = \int_S \delta(x - x') n \, dS. \tag{2.14}$$

The delta function, as before, is numerically approximated by the cosine function given by Eq. 2.11. Thus the indicator function and the viscosity field vary smoothly across a cell membrane. Eq. 2.13 is solved to obtain $I$ at each time step, and update $\mu$. The solution procedure for Eq. 2.13 is similar to that of the Poisson equation for the projection operator $\phi$ as described in Section 2.4.1.

The presence of multiple fluids with different viscosity also requires care in dealing with the diffusion terms in Eq. 2.20. The natural choice is to treat the diffusion terms in conservation form, due to the finite-volume nature of the staggered-grid arrangement. Considering the $x$-component of the fluid momentum equation, these terms are:

$$\{ \nabla \cdot [\mu(\nabla u + \nabla u^T)] \}_x = \frac{\partial}{\partial x} \left( \mu \frac{\partial u}{\partial x} \right) + \frac{\partial}{\partial y} \left( \mu \frac{\partial u}{\partial y} \right) + \frac{\partial}{\partial z} \left( \mu \frac{\partial u}{\partial z} \right)$$

$$+ \frac{\partial}{\partial x} \left( \mu \frac{\partial u}{\partial x} \right) + \frac{\partial}{\partial y} \left( \mu \frac{\partial u}{\partial x} \right) + \frac{\partial}{\partial z} \left( \mu \frac{\partial u}{\partial x} \right) \tag{2.15}$$
For a constant viscosity field, this reduces to:

$$\{ \nabla \cdot \left[ (\nabla u + \nabla u^T) \right] \}_x = \frac{\partial}{\partial x} \left( \frac{\partial u}{\partial x} \right) + \frac{\partial}{\partial y} \left( \frac{\partial u}{\partial y} \right) + \frac{\partial}{\partial z} \left( \frac{\partial u}{\partial z} \right)$$  \hspace{1cm} (2.16)

using $\nabla \cdot u = 0$. With a staggered-grid arrangement, the numerical evaluation of $\frac{\partial}{\partial x} \left( \frac{\partial u}{\partial x} \right)$, for example, on the U-grid using 2nd order central differencing proceeds as:

$$\left. \frac{D}{Dx} \left( \frac{Du}{Dx} \right) \right|_{I,J,K} = \frac{Du}{Dx}_{I+1/2,J,K} - \frac{Du}{Dx}_{I-1/2,J,K} = \left( \frac{u_{I+1,J,K} - u_{I,J,K}}{\Delta x} \right) - \left( \frac{u_{I,J,K} - u_{I-1,J,K}}{\Delta x} \right) \Delta x$$

$$= \frac{u_{I+1,J,K} - 2u_{I,J,K} + u_{I-1,J,K}}{\Delta x^2}$$

$$\hspace{1cm} (2.17)$$

which is identical to that which would have been obtained using a standard 2nd order central difference to evaluate $\frac{\partial^2 u}{\partial x^2}$ directly. Thus for a constant viscosity field, the resulting discrete form is identical whether the diffusion terms are evaluated in conservation or non-conservation form. The indices I,J,K denote Eulerian grid points in the x-, y-, and z-directions, respectively.

For a variable viscosity field, as in the present work, the conservative form is observed to significantly limit the time step size relative to the constant viscosity case. It is found that
this stability limit can be relaxed by using a non-conservation form of the variable viscosity terms. For example, for the diffusion terms in the $x$-component of the fluid momentum equation, we have

$$\{ \nabla \cdot [\mu (\nabla u + \nabla u^T)] \}_x = \mu \nabla^2 u + 2 \frac{\partial \mu}{\partial x} \frac{\partial u}{\partial x} + \frac{\partial \mu}{\partial y} \left( \frac{\partial u}{\partial y} + \frac{\partial v}{\partial x} \right) + \frac{\partial \mu}{\partial z} \left( \frac{\partial u}{\partial z} + \frac{\partial w}{\partial x} \right)$$  \hspace{1em} (2.18)

In the staggered-grid arrangement used here, $\mu(x,t)$ is defined as cell-center based as shown in Figure 2.3. Thus, an averaging scheme has to be used in evaluating the mixed derivative terms in Eq. 2.18. Consistent with typical staggered-grid averaging, the following is used:

$$\frac{\partial \mu}{\partial x}\bigg|_{I,J,K} \frac{\partial u}{\partial x} = \left( \frac{\mu_{I+1,J,K} - \mu_{I,J,K}}{\Delta x} \right) \cdot \left( \frac{u_{I+1,J,K} - u_{I-1,J,K}}{2\Delta x} \right)$$

$$\frac{\partial \mu}{\partial y}\bigg|_{I,J,K} \frac{\partial u}{\partial y} = \left( \frac{\mu_{I,J+1,K} + \mu_{I+1,J+1,K} - \mu_{I,J-1,K} - \mu_{I+1,J-1,K}}{4\Delta y} \right) \cdot \left( \frac{u_{I,J+1,K} - u_{I,J-1,K}}{2\Delta y} \right)$$ \hspace{1em} (2.19)

and similarly for the $z$-direction.

### 2.4 Modeling rigid interfaces

The methodology for simulating complex rigid interfaces, both stationary and moving, is now discussed, in addition to the overall computational framework into which each of the distinct interface types are incorporated.

#### 2.4.1 Flow solver

As noted in Section 2.3.2, the fluid flow is governed by the unsteady Stokes equations (Eq. 2.9). While there are several numerical methods available for a fast solution of the Stokes equations, here an approach is followed that is usually used for the full Navier-Stokes equations, and is very suitable for use with immersed boundary methods. In this approach, given the velocity and pressure fields at a time instance $n$, the governing equations are
solved to advance the fields to the next time instance \( n + 1 \), using a projection method. This method consists of first solving an advection-diffusion equation, and then solving a Poisson-type equation to enforce the conservation of mass. These steps can be represented in general form, as follows, treating the body force and off-diagonal viscous terms explicitly with a 2nd order Adams-Bashforth method, and the diagonal viscous terms semi-implicitly using the Crank-Nicholson method:

\[
\frac{\rho u_i^* - u_i^n}{\Delta t} = G_i + \frac{3}{2} \alpha_i^n - \frac{1}{2} \alpha_i^{n-1} + \frac{1}{2} (\beta_i^* + \beta_i^n) \tag{2.20}
\]

\[
\frac{\partial^2 \phi}{\partial x_i \partial x_i} = \frac{\rho \partial u_i^*}{\Delta t \partial x_i} \tag{2.21}
\]

\[
\rho u_i^{n+1} = \rho u_i^* - \Delta t \frac{\partial \phi}{\partial x_i} \tag{2.22}
\]

where

\[
\alpha_i = F_i + \frac{\partial}{\partial x_j} \left( \mu \frac{\partial u_i}{\partial x_i} \right)
\]

\[
\beta_i = \frac{\partial}{\partial x_j} \left( \mu \frac{\partial u_i}{\partial x_j} \right)
\]

Here it is assumed that the densities of the plasma and cytoplasmic fluids are the same, as is the case in blood flow, but their viscosities are different. The first step (Eq. 2.20) solves for an intermediate velocity field, \( u_i^* \), that is in general non-solenoidal. The projection step (Eq. 2.22) corrects \( u_i^* \) to be solenoideal by projecting it onto a divergence-free space using a projection operator \( \phi \) that is closely related to the pressure \( p \). The variable \( G_i \) in Eq. 2.20 is a placeholder for an approximation to the pressure gradient in the advection-diffusion step. Various authors have used different choices for \( G_i \), as summarized in [21]. The choice for \( G_i \) dictates the difference in magnitude between the intermediate velocity \( u_i^* \) and the physical velocity, \( u_i^{n+1} \), in addition to the relationship between \( \phi \) and \( p \). With projection methods the boundary conditions for the velocity are enforced at the advection-diffusion step on \( u_i^* \), not \( u_i^{n+1} \). The means of enforcing the boundary conditions is thus dependent on the choice of \( G_i \), and the relevance of this to the present work is discussed shortly. The body force term computed from Eq. 2.10 representing the deformable interfaces enters the discrete governing equations as \( F_i \) when solving Eq. 2.20 - 2.22. The complex rigid interfaces are simulated by enforcing specific constraints when solving these equations, as will be detailed later.
All spatial derivatives are evaluated using second-order differencing. For the viscous flows considered here, the semi-implicit treatment of the viscous terms in the advection-diffusion equation is desirable for numerical stability. To take advantage of the fast inversion of tri-diagonal matrices, the advection-diffusion equation is solved using an Alternating Direction Implicit (ADI) scheme. The ADI scheme provides a robust means of solving Eq. 2.20 when compared with an iterative method where the performance can vary based on the complexity of the immersed boundary. The ADI scheme implemented here solves the advection-diffusion equation in four steps, as follows:

\[
\frac{u_{i}^{****} - u_{i}^{n}}{\Delta t} = G_i + \frac{3}{2} \alpha_i^n - \frac{1}{2} \alpha_i^{n-1} + \frac{1}{2} \beta_i^n \tag{2.23}
\]

\[
\frac{u_{i}^{***} - u_{i}^{****}}{\Delta t} = \left. \frac{\partial}{\partial x_1} \left( \mu \frac{\partial u_{i}^{***}}{\partial x_1} \right) - \frac{1}{2} \frac{\partial}{\partial x_1} \left( \mu \frac{\partial u_{i}^{****}}{\partial x_1} \right) \right|_{i \neq 1} \tag{2.24}
\]

\[
\frac{u_{i}^{**} - u_{i}^{***}}{\Delta t} = \left. \frac{\partial}{\partial x_3} \left( \mu \frac{\partial u_{i}^{**}}{\partial x_3} \right) - \frac{1}{2} \frac{\partial}{\partial x_3} \left( \mu \frac{\partial u_{i}^{***}}{\partial x_3} \right) \right|_{i \neq 3} \tag{2.25}
\]

\[
\frac{u_{i}^{*} - u_{i}^{**}}{\Delta t} = \left. \frac{\partial}{\partial x_2} \left( \mu \frac{\partial u_{i}^{*}}{\partial x_2} \right) - \frac{1}{2} \frac{\partial}{\partial x_2} \left( \mu \frac{\partial u_{i}^{**}}{\partial x_2} \right) \right|_{i \neq 2} \tag{2.26}
\]

with the diffusion terms evaluated as discussed in Section 2.3.3. The first step (Eq. 2.23) handles the explicit terms, while the remaining three steps (Eq. 2.24 - 2.26) handle the implicit sweeps in the x, z, and y directions, respectively.

In order to satisfy the incompressibility condition, the Poisson equation (Eq. 2.21) for \( \phi \) must be solved implicitly. To attain a fast computation, the computational domain is assumed to be periodic in one direction, and the Fourier expansion is used. The 3D Poisson equation is then converted to a 2D problem in Fourier space which can be solved using fast, direct matrix inversion. Note that the periodic condition required for this spectral solver does not impose any limit on the geometric complexity of the immersed boundaries that can be considered.

The left hand side of Eq. 2.21 is arrived at by taking the divergence of the gradient of \( \phi \) (i.e. the divergence of Eq. 2.22). Analytically this is equivalent to the Laplacian of \( \phi \), as in Eq. 2.21, however the discrete form of this necessary to ensure the conservation of mass is satisfied to machine epsilon depends upon the discrete spatial arrangement of the variables. Specifically, the discrete form of the Laplacian must be the result of two applications of
the discrete first derivative. As was discussed in Section 2.2, one of the well established
effects of a staggered-grid spatial discretization is that the resulting discrete form of the
Laplacian is simply the standard 2nd order central difference for the 2nd derivative, i.e. it is
naturally compact. The Fourier expansion used here to attain a fast computation considers
the z-direction for the transformations, and thus the resulting discrete form of Eq. 2.21 at
Eulerian node \((I, J, K)\) is:
\[
\hat{\varphi}_{I-1,J,K} - \frac{2\hat{\varphi}_{I,J,K} + \hat{\varphi}_{I+1,J,K}}{\Delta x^2} + \hat{\varphi}_{I,J-1,K} - \frac{2\hat{\varphi}_{I,J,K} + \hat{\varphi}_{I,J+1,K}}{\Delta y^2} - \kappa_z^2 \hat{\varphi}_{I,J,K} = \text{RHS}_{I,J,K}
\]
where the \(\hat{\text{ }}\) indicates a variable in Fourier space, \(\kappa_z\) are the wave numbers, and \(\text{RHS}\) is the
right hand side of Eq. 2.21. As before, \((I, J, K)\) correspond to grid indices in the \((x, y, z)\)
directions, respectively. Thus Eq. 2.27 represents the 2D problem solved in Fourier space
for each \(z\)-index \(K\) using fast, direct matrix inversion.

2.4.2 Complex geometry

The methodology used to treat rigid boundaries of arbitrary complexity is now discussed.
Figure 2.4(A) shows an example of a complex microvascular network that can be considered
using the present methodology. The network is obtained from an \textit{in vivo} image of a human
cerebral microvasculature given in [116], and digitally rendered for use in the present context.
The walls of the vessels provide the boundaries for the fluid, and are taken to be stationary.
These boundaries are treated as sharp-interface immersed boundaries. Following the \textit{in vivo}
image, the digital vascular network is first created using a standard CAD software package.
The geometric data is then imported into the Gmsh mesh generating program [75] which is
used to generate a triangular mesh on the vascular surface. The surface mesh is shown in
Figure 2.4(C) for a small section of the network. This surface mesh is then used to define
the location of the sharp-interface boundary in the context of the GNIBM as described
below. While the surface mesh approach provides a convenient means of defining complex
surfaces, rigid boundaries of simpler geometry can also be represented analytically instead
of using a surface mesh.

The GNIBM allows the use of a non-body conforming Eulerian mesh within which the
fluid boundaries are embedded. In the present case, the entire domain encompassing all
immersed boundaries is discretized using the same rectangular Cartesian mesh (Figures 2.1 and 2.5). A staggered arrangement of the variables on the Eulerian domain is utilized in which the velocity components are defined at the faces of a computational cell, and pressure is defined at the cell center. Figure 2.5 shows a computational stencil near an arbitrary rigid object interface for the grids associated with each velocity component. Once the boundaries of the rigid surface have been defined, the Eulerian nodes inside and outside the

![Figure 2.4](image)

Figure 2.4: (A) An example of a complex geometry: a section of a microvascular network digitally rendered from an *in vivo* image of human cerebral microvasculature [116]. Blood vessels are shown in red. The network is characterized by highly tortuous, bifurcating and merging vessels. (B) A small part of the network is shown, as identified by the green box and arrow. (C) A zoomed-in view of the surface mesh on the vascular wall.
fluid domain are identified following the method in [124]. The nodes outside the fluid domain are identified as solid nodes (SN), and the solid nodes that have at least one neighboring fluid node are identified as ghost nodes (GN). After the GNs have been identified, the boundary-intercept (BI) point for each ghost node is determined by locating the nearest point on the rigid object surface. Following this, the image-points (IP) are determined for each GN, which are defined as the mirror image of the respective GN in the fluid domain, across the BI. Figure 2.5 illustrates the SN, GN, BI, and IP for an arbitrary rigid surface.

At the sharp-interface boundary, a no-slip condition has to be satisfied. The basic premise of the GNIBM is to enforce a velocity $u_{GN}$ at the GN such that a known boundary condition $u_{BI}$ is achieved at the BI. The value at the BI is taken to be the average of values at the GN and the IP. In general, the IPs do not coincide with the Eulerian nodes. A standard trilinear interpolant is used to obtain the velocity at the IP from the surrounding Eulerian nodes [124]. Thus, the boundary condition to be imposed at the GN becomes

$$u_{GN} = 2u_{BI} - \sum_{m=1}^{8} \beta_m u_m$$

(2.28)

Figure 2.5: Separate grids associated with each velocity component (i.e. U,V,W), as identified in the figure. Shown here is an X-Y plane view of the grids. An arbitrary surface is shown, and the grid points are identified as Ghost Nodes (GN), Solid Nodes (SN), or Fluid Nodes (FN), depending on their location relative to the surface. Also shown are the Boundary Intercept (BI) and Image Point (IP) for an example GN. The nodes used in the stencil associated with the GN constraint are given in red, while the nodes used in the interpolation scheme for the IP are denoted by the shaded blue region.
where $\beta_m$ are the weighing coefficients for the interpolation, determined as:

\begin{align}
\beta_1 &= (1 - x_0)(1 - y_0)(1 - z_0) \\
\beta_2 &= x_0(1 - y_0)(1 - z_0) \\
\beta_3 &= x_0y_0(1 - z_0) \\
\beta_4 &= (1 - x_0)y_0(1 - z_0) \\
\beta_5 &= (1 - x_0)(1 - y_0)z_0 \\
\beta_6 &= x_0(1 - y_0)z_0 \\
\beta_7 &= x_0y_0z_0 \\
\beta_8 &= (1 - x_0)y_0z_0
\end{align}

where $x_0 = \frac{x_{IP} - x_1}{\Delta x}$, $y_0 = \frac{y_{IP} - y_1}{\Delta y}$, and $z_0 = \frac{z_{IP} - z_1}{\Delta z}$. The interpolation scheme results in a second-order accurate velocity field [124], and this is verified in Section 2.5.1 for the present implementation.

As noted above, the no-slip condition has to be satisfied at the immersed boundary by enforcing the ghost node constraint (Eq. 2.28) when solving the advection-diffusion equation (Eq. 2.20). The approach developed to enforce this is now described. Implicitly imposing this constraint amounts to breaking the tri-diagonal structure of the matrices at the ADI
steps. Therefore, the following explicit form is used

\[ u_{GN} = 2u_{BI} - \sum_{m=1}^{8} \beta_m u^n_m \]  

(2.30)

where \( u^n \) is the known fluid velocity from the previous time level \( n \). A generic schematic depicting a three-dimensional view of the points involved with the constraint imposed for a GN on the U-grid is given in Figure 2.6. Since the ADI steps solve for the nonsolenoidal velocity \( u^* \), rather than the physical velocity, the boundary conditions must be expressed accordingly. In general, using Eq. 2.22 the nonsolenoidal velocity at a GN can be expressed in terms of the physical velocity as

\[ u^*_{GN} = u_{GN} + \Delta t \frac{\partial \phi}{\partial x_i}. \]  

(2.31)

Then, the determination of \( u^*_{GN} \) reduces to the determination of the second term on the right hand side of the above equation. This term depends on the specific choice for \( G_i \) in Eq. 2.20. The classical choices for \( G_i \) are:

\[ G_i = 0, \quad \text{and} \]

\[ G_i = \frac{\partial p^n}{\partial x_i}. \]  

(2.32)  

(2.33)

For the choice of \( G_i = 0 \), this term can be approximated as \( \Delta t(\partial \phi^n/\partial x_i) + O(\Delta t^2) \) [94]. It can be further shown that \( \Delta t(\partial \phi^n/\partial x_i) = u^*_{GN} - u^n_{GN} \), where \( u^*_{GN} \) is the * level value at a GN from the previous time step \( n \). We use this form to express the condition at the immersed boundary. For the choice of \( G_i = \partial p^n/\partial x_i \), it was shown in [16, 36] that \( \Delta t(\partial \phi/\partial x_i) = O(\Delta t^2) \). Following this, the condition at the immersed boundary can be expressed as \( u^*_{GN} \approx u^n_{GN} \). Numerical experiments performed in testing the present approach suggest that the use of either choice for \( G_i \) results in negligible differences.

### 2.4.3 Moving rigid bodies

For moving rigid bodies of arbitrary shape, a method is developed to couple the rigid-body dynamics to the fluid flow. In this approach, the Euler parameters [14] are used as generalized coordinates to evolve the orientation of the object with time, while a Verlet algorithm [2] is used to integrate Newton’s second law and determine the position of the object.
The translational acceleration $\mathbf{a}$ of a rigid object is obtained simply from Newton’s second law $\mathbf{a} = \mathbf{F}_0 / m$, where $\mathbf{F}_0$ is the net force exerted on the object by the surrounding fluid, and $m$ is the mass of the object. The position $\mathbf{x}_0$ and velocity $\mathbf{U}$ of the center of mass are computed by integrating $d\mathbf{U}/dt = \mathbf{a}$ and $d\mathbf{x}_0/dt = \mathbf{U}$. The method of computing $\mathbf{F}_0$ and the numerical integration to obtain $\mathbf{U}$ and $\mathbf{x}_0$ are described later.

The rotational motion of the object is governed by the conservation of angular momentum $\mathbf{H}$ as

$$T_0 = \frac{d}{dt} \mathbf{H} \tag{2.34}$$

where $T_0$ is the torque exerted on the object by the surrounding fluid. The angular velocity $\omega$ is

$$\omega = \mathbf{I}_0^{-1} \cdot \mathbf{H} \tag{2.35}$$

where $\mathbf{I}_0$ is the moment of inertia tensor. Note that Eq. 2.34 is written in a space-fixed coordinate system, whereas Eq. 2.35 is in the body-fixed system. The basis vectors in the two coordinate systems are related via a rotation matrix $\mathbf{R}_e$ which can be expressed completely in terms of the four Euler parameters [14]. The Euler parameters are defined as

$$e_0 = \cos \frac{\beta}{2}$$

$$\begin{bmatrix} e_1 \\ e_2 \\ e_3 \end{bmatrix} = \mathbf{n} \sin \frac{\beta}{2} \tag{2.36}$$

where $\beta$ represents a finite rotation about an arbitrary axis $\mathbf{n}$. The rotation matrix $\mathbf{R}_e$ in terms of the Euler parameters is

$$\mathbf{R}_e = \begin{bmatrix} e_0^2 + e_1^2 - e_2^2 - e_3^2 & 2(e_1 e_2 + e_0 e_3) & 2(e_1 e_3 - e_0 e_2) \\ 2(e_1 e_2 - e_0 e_3) & e_0^2 - e_1^2 + e_2^2 - e_3^2 & 2(e_2 e_3 + e_0 e_1) \\ 2(e_1 e_3 + e_0 e_2) & 2(e_2 e_3 - e_0 e_1) & e_0^2 - e_1^2 - e_2^2 + e_3^2 \end{bmatrix} \tag{2.37}$$

The angular velocity can then be written as

$$\omega = \mathbf{I}_0^{-1} \cdot (\mathbf{R}_e \cdot \mathbf{H}) \tag{2.38}$$
The Euler parameters are used as generalized coordinates to evolve the orientation of the object with time. In terms of the Euler parameters, the rotational equations of motion are:

\[
\begin{bmatrix}
\dot{e}_0 \\
\dot{e}_1 \\
\dot{e}_2 \\
\dot{e}_3
\end{bmatrix} = 0.5 \begin{bmatrix}
e_0 & -e_1 & -e_2 & -e_3 \\
e_1 & e_0 & -e_3 & e_2 \\
e_2 & e_3 & e_0 & -e_1 \\
e_3 & -e_2 & e_1 & e_0
\end{bmatrix} \begin{bmatrix}
0 \\
\omega_1 \\
\omega_2 \\
\omega_3
\end{bmatrix}
\] (2.39)

where \(\omega_1, \omega_2, \omega_3\) are the angular velocity components determined by Eq. 2.38. The numerical integration of Eq. 2.39 is described later.

To numerically compute the force \(\mathbf{F}_0\) and torque \(\mathbf{T}_0\), the object surface is discretized using triangular elements similar to that used for the deformable cells (Figure 2.2). At each surface element, the fluid stress tensor is computed from the known velocity and pressure of the surrounding fluid. The pressure is obtained from the projection operator \(\phi\) which was introduced before in the context of Eq. 2.20. As mentioned there, the relationship between \(p\) and \(\phi\) depends on the choice of \(G_i\). For the specific choices of \(G_i\) used here as given by Eqs. 2.32 and 2.33, the respective equations for pressure become [21, 147]:

\[
p = \phi - \frac{1}{2} \frac{\partial u^*_i}{\partial x_i}, \quad \text{and} \quad p^{n+1} = p^n + \phi - \frac{1}{2} \frac{\partial u^*_i}{\partial x_i}.
\] (2.40a, b)

Once the pressure field is known, the pressure at each surface element is computed by interpolating from the surrounding Eulerian nodes.

The computation of the surface stress tensor can be simplified if the object has an analytically defined shape, such as a sphere or spheroid. Since the rigid objects considered here are either spherical particles or platelets that have an oblate spheroidal shape, either the spherical or the oblate spheroidal coordinate system is used, respectively. This is because in such a coordinate system one of the basis vectors aligns with the surface normal vectors, and thus many terms drop out. As such, the major benefit to using such a coordinate system is that it minimizes both the amount of computation and number of interpolations. Furthermore, it permits a direct analytical evaluation of some of the velocity derivative terms. Details are provided here for computations in the spherical coordinate system. The
details behind the evaluation of forces in spheroidal coordinate systems are provided in Appendix A.

For computing the viscous stresses at the object surface of a rigid sphere, the traction vector is computed at each surface element from the stress tensor, $\sigma$, and normal vector, $n$. Considering a spherical coordinate system $(r, \theta, \phi)$ defined by the following transformation:

$$
\begin{align*}
x &= r \sin \theta \cos \phi \\
y &= r \sin \theta \sin \phi \\
z &= r \cos \theta
\end{align*}
$$

(2.41)

the outward normal vector at any point on the surface of the sphere is given by $n = e_r$. The traction vector is thus:

$$
\mathbf{t} = n \cdot \sigma
$$

(2.42)

and hence only three components of the stress tensor need to be computed. These are [136]:

$$
\begin{align*}
\sigma_{rr} &= -p + 2\mu \frac{\partial u_r}{\partial r} \\
\sigma_{r\theta} &= \mu \left( \frac{1}{r} \frac{\partial u_r}{\partial \theta} + \frac{\partial u_\theta}{\partial r} - \frac{u_\theta}{r} \right) \\
\sigma_{r\phi} &= \mu \left( \frac{1}{r \sin \theta} \frac{\partial u_r}{\partial \phi} + \frac{\partial u_\phi}{\partial r} - \frac{u_\phi}{r} \right)
\end{align*}
$$

(2.43)

Using Eq. 2.41-2.43, in the Cartesian coordinate system the components of the traction vector become:

$$
\begin{align*}
t_x &= \sigma_{rr} \sin \theta \cos \phi + \sigma_{r\theta} \cos \theta \cos \phi - \sigma_{r\phi} \sin \phi \\
t_y &= \sigma_{rr} \sin \theta \sin \phi + \sigma_{r\theta} \cos \theta \sin \phi + \sigma_{r\phi} \cos \phi \\
t_z &= \sigma_{rr} \cos \theta - \sigma_{r\theta} \sin \theta
\end{align*}
$$

(2.44)

The velocity derivatives with respect to $r$ in Eq. 2.43 are evaluated using second-order differencing. A three-point stencil is used with one end point located on the object surface and the other two points in the fluid domain. The velocity at the surface point is computed from the translational $(U_x, U_y, U_z)$ and rotational $(\omega_x, \omega_y, \omega_z)$ velocities of the object, while those at the other two points are interpolated from the surrounding Eulerian nodes. The
The velocity field from the fluid solution is in the Cartesian coordinate system \((u_x, u_y, u_z)\), so the components in the spherical coordinate system are determined as:

\[
\begin{align*}
    u_r &= u_x \sin \theta \cos \phi + u_y \sin \theta \sin \phi + u_z \cos \theta \\
    u_\theta &= u_x \cos \theta \cos \phi + u_y \cos \theta \sin \phi - u_z \sin \theta \\
    u_\phi &= -u_x \sin \phi + u_y \cos \phi
\end{align*}
\] (2.45)

and at the surface

\[
\begin{align*}
    u_x &= U_x + (z\omega_y - y\omega_z) \\
    u_y &= U_y + (x\omega_z - z\omega_x) \\
    u_z &= U_z + (y\omega_x - x\omega_y)
\end{align*}
\] (2.46)

The velocity derivatives with respect to \(\theta\) and \(\phi\) in Eq. 2.43 are evaluated at the sphere surface analytically by differentiating Eq. 2.45. After simplifying this becomes:

\[
\begin{align*}
    \frac{\partial u_r}{\partial \theta} &= U_x \cos \theta \cos \phi + U_y \cos \theta \sin \phi - U_z \sin \theta \\
    \frac{\partial u_r}{\partial \phi} &= -U_x \sin \theta \sin \phi + U_y \sin \theta \cos \phi
\end{align*}
\] (2.47)

Finally, the force vector \(\mathbf{F}\) at each surface element is obtained from the traction vector \(\mathbf{t}\) simply by multiplying by the element area. The force and torque are then used to evolve the position and orientation of the object. As mentioned, the details behind the determination of \(\mathbf{t}\) in spheroidal coordinate systems are provided in Appendix A.
(a) Integrating the translational and rotational equations of motion

Using the above equations, a procedure is developed to evolve the position and orientation of a rigid object discretely in time utilizing concepts presented in [2]. Beginning at an instance in time \( t \), the following is known:

- Object orientation, angular velocity, and linear velocity and acceleration of center of mass
- Fluid solution for velocity and pressure in the presence of the object at this initial orientation
- Value of the Euler parameters \( e_0, e_1, e_2, e_3 \) and the resulting rotation matrix \( R_e \) corresponding to the initial orientation

A Verlet algorithm is used to update the position and translational velocity of the object using the known object position \( x_0(t) \), translational velocity \( U(t) \), and acceleration \( a(t) \), in conjunction with the new acceleration \( a(t + \Delta t) \) computed from the net force exerted on the object by the surrounding fluid. Specifically, the procedure is as follows:

1. Compute the net force on the object, \( F_0 \), by summing the forces computed on each of the discrete surface elements using Eq. 2.44, and use this to compute \( a(t + \Delta t) = \frac{F_0}{m} \).

2. Update the position of the center of mass using the known acceleration and center of mass velocity:

\[
x_0(t + \Delta t) = x_0(\Delta t) + \Delta t U(t) + 0.5 a(t) \Delta t^2
\]  

(2.48)

3. Compute the new velocity of the center of mass:

\[
U(t + \Delta t) = U(t) + \frac{1}{2} \Delta t \left[ a(t) + a(t + \Delta t) \right]
\]  

(2.49)

The rotational equations of motion are integrated using a leapfrog scheme, and the procedure consists of the following steps. Note that values taken directly from the fluid solver are in a space-fixed coordinate system, while the integration is performed in a body-fixed coordinate system. Quantities in each of these coordinate systems are denoted by the subscripts \( s \) and \( b \), respectively.
1. Using the vector components of the calculated force at each element on the surface in space-fixed coordinates, \( F = F_x e_x + F_y e_y + F_z e_z \), compute the torque components \((T_x, T_y, T_z)\):

\[
T_x = r_y F_z - r_z F_y \\
T_y = r_z F_x - r_x F_z \\
T_z = r_x F_y - r_y F_x
\]  

(2.50)

where \( r = r_x e_x + r_y e_y + r_z e_z \) is the position vector from the center of mass to the point on the surface at which the force is computed. The net torque is taken to be the sum of the individual torques at each of the discrete elements on the surface.

2. Calculate the space-fixed angular momentum using this torque:

\[
H_s(t) = H_s(t - 0.5\Delta t) + 0.5\Delta t \cdot T_s(t)
\]  

(2.51)

3. Calculate the body-fixed angular velocity \( \omega_b(t) \) using Eq. 2.38 and use this to compute the time derivative of the Euler parameters \( \dot{e}(t) \) from Eq. 2.39

4. Using this, advance the Euler parameters to \( t + 0.5\Delta t \):

\[
e(t + 0.5\Delta t) = e(t) + 0.5\Delta t \cdot \dot{e}(t)
\]  

(2.52)

5. Advance the space-fixed angular momentum to \( t + 0.5\Delta t \) using Eq. 2.34, and then advance the body-fixed angular velocity using Eq. 2.38 with the updated rotation matrix \( R_e \) based on the Euler parameters \( e(t + 0.5\Delta t) \):

\[
H_s(t + 0.5\Delta t) = H_s(t - 0.5\Delta t) + \Delta t \cdot T_s(t)
\]  

(2.53)

\[
\omega_b(t + 0.5\Delta t) = I_0^{-1} \cdot [R_e(t + 0.5\Delta t) \cdot H_s(t + 0.5\Delta t)]
\]  

(2.54)

6. Compute the time derivatives of the Euler parameters \( \dot{e}(t + 0.5\Delta t) \) using Eq. 2.39, and use these to advance the Euler parameters to the next time step:

\[
e(t + \Delta t) = e(t) + \Delta t \cdot \dot{e}(t + 0.5\Delta t)
\]  

(2.55)

These updated Euler parameters define the new orientation of the object.
7. Compute the new rotation matrix \( R_e(t + \Delta t) \), update the angular momentum \( H_s(t + \Delta t) \), and use these to compute the new angular velocity of the object:

\[
\omega_b(t + \Delta t) = I_0^{-1} \cdot [R_e(t + \Delta t) \cdot H_s(t + \Delta t)]
\] (2.56)

8. Determine the space-fixed angular velocity used to compute the surface velocity at each elemental surface area:

\[
\omega_s(t + \Delta t) = R_e^T(t + \Delta t) \cdot \omega_b(t + \Delta t)
\] (2.57)

Thus, at \( t + \Delta t \), the new position, orientation, and translational and angular velocities of the object are obtained. These are then used in turn to apply the appropriate boundary conditions on the object surface (i.e. moving sharp-interface immersed boundary) as discussed in Section 2.4.2. Use of the Euler parameters provides a robust and efficient means of evolving the orientation of a rigid body with time. In this form the equations of motion are free of any singularities, which is not the case with other traditional approaches such as those involving the Euler angles.

### 2.5 Validation

A series of validation studies is considered to establish the accuracy of the methodology. These validation studies involve stationary rigid objects, moving rigid objects, and simulations that involve both complex rigid boundaries and deformable cells. Each of the cases was chosen to both demonstrate and test specific aspects of the methodology, as highlighted in Table 2.1 and discussed in the relevant sections. Results are compared with analytical solutions, experimental studies, and previously published numerical results. Since the interest here is in blood cell motion for which the inertial effect is negligible, validation studies to are limited to Stokes flow. It should be noted that validation of the deformable cell model in simple geometry has been considered in previous studies, e.g. [47, 203, 204, 40].

#### 2.5.1 Stationary rigid objects

The first validation study demonstrates the accuracy of the methodology for stationary rigid objects. Considered is the classical problem of a sphere subjected to a linear shear
Figure 2.7: Validation for stationary rigid body: (a) Schematic of a fixed rigid sphere subjected to a simple shear flow. (b) $L_\infty$ error norm of the velocity magnitude for $256^3$ Eulerian resolution with respect to the analytical solution. (c) $L_1$ and $L_2$ error norms as functions of Eulerian resolution varied as $64^3$, $128^3$ and $256^3$. 
flow given by

\[ \mathbf{u}^\infty = [\dot{\gamma}y, 0, 0] \] (2.58)

where \( \dot{\gamma} \) is the shear rate. The set up is schematically shown in Figure 2.7(a). The sphere is not allowed to translate and rotate. An analytical solution for this problem for an unbounded domain and in the absence of inertia can be derived as

\[
\begin{align*}
    u &= \frac{y\dot{\gamma}}{2} \left[ 1 - \left( \frac{r}{a} \right)^{-5} \right] + \frac{y\dot{\gamma}}{2} \left[ 1 - \left( \frac{r}{a} \right)^{-3} \right] - \frac{5}{2} \left( \frac{x}{a} \right)^2 y\dot{\gamma} \left[ \left( \frac{r}{a} \right)^{-5} - \left( \frac{r}{a} \right)^{-7} \right] \\
    v &= \frac{x\dot{\gamma}}{2} \left[ 1 - \left( \frac{r}{a} \right)^{-5} \right] - \frac{x\dot{\gamma}}{2} \left[ 1 - \left( \frac{r}{a} \right)^{-3} \right] - \frac{5}{2} \left( \frac{y}{a} \right)^2 x\dot{\gamma} \left[ \left( \frac{r}{a} \right)^{-5} - \left( \frac{r}{a} \right)^{-7} \right] \\
    w &= -\frac{5}{2} \frac{xyz\dot{\gamma}}{a^2} \left[ \left( \frac{r}{a} \right)^{-5} - \left( \frac{r}{a} \right)^{-7} \right]
\end{align*}
\] (2.59)

where \( r = \sqrt{x^2 + y^2 + z^2} \) and \( a \) is the sphere radius. The numerical results will be compared with this analytical solution.

In this simulation the sphere is represented as a sharp-interface immersed boundary, and in this context the sphere surface is defined by an analytical function. A cubic computational
domain is considered which is discretized by a rectangular Cartesian mesh. The domain edge length is taken to be $12a$. The Eulerian resolution is varied as $64^3$, $128^3$, and $256^3$. The boundary conditions applied at the $x$ and $y$ boundaries are the analytical solution given by Eq. 2.59, and the condition applied at the $z$ boundaries is the periodic condition. The domain edge length considered here was found to be sufficient to eliminate any boundary effect.

Figure 2.7(b) shows contours of the $L_\infty$ error norm of the numerical solution at $256^3$ resolution with respect to the analytical solution based on the velocity magnitude. The numerical result agrees very well with the analytical one as the maximum $L_\infty$ norm is $\sim 0.001$. As can be seen in the figure, the maximum error occurs near the sphere surface and decreases with increasing distance from the surface, a trend that is expected in an IBM. Figure 2.7(c) shows the $L_1$ and $L_2$ error norms of the three velocity components as functions of the Eulerian resolution. A second-order trend is evident here, providing a measure of the global accuracy of the method. The results of this section are used to establish a guideline for determining the Eulerian resolution to use with arbitrarily complex geometries.

With the sharp-interface method, the degree to which an object surface is resolved is directly controlled by the Eulerian resolution; a greater number of grid points, and hence ghost nodes, will result in a better representation of the surface curvature. For the present case of a stationary sphere the degree to which the surface is represented can be quantified by the number of Eulerian points across the sphere diameter. As the Eulerian resolution is increased from $128^3$ to $256^3$, the number of grid points across the sphere diameter changes from $\sim 20$ to $\sim 40$, and the maximum $L_\infty$ norm changes from $\sim 0.004$ to $\sim 0.001$. Thus 20–40 grid points across the sphere diameter keep the error within a reasonable limit. For the sphere, the number of Eulerian points across the diameter is a convenient metric for quantifying the resolution of the surface in terms of Eulerian mesh. For spheroidal geometries, this criteria is used in conjunction with the equivalent spheroid diameter in determining the appropriate resolution, as discussed later. For arbitrarily complex surfaces, this guideline is extended by examining the regions of highest curvature and selecting an appropriate Eulerian resolution in accordance. For complex microvascular networks, for example, the means by which this approach is extended is two-fold. First, the minimum vessel diameter
is looked at, and ensured that the number of grid points across is in accordance with the criteria. Second, the surface curvature relative to the Eulerian resolution is examined. A ray is extended across the regions where curvature is highest, and it is checked that the number of Eulerian grid points per unit length is also in accordance with the established criteria. In general, this criteria is used when selecting the Eulerian resolution to be used with the subsequent validation cases, and thus its use is verified by the accuracy of the results.

2.5.2 Moving rigid bodies

The accuracy of the methodology for moving rigid boundaries is now validated by considering four classical problems as follows.

(a) Spheroid in shear flow

The first problem considered is the unsteady motion of an oblate spheroid in a linear shear flow. The setup is schematically shown in Figure 2.8(a), and the imposed linear shear flow is given by Eq. 2.58. The oblate spheroid is free to translate and rotate by the action of the force and torque exerted on it by the surrounding fluid. The center of the spheroid is placed at the origin of the coordinate system so that there is no relative translational motion between the fluid and the spheroid. However, under the fluid torque, the spheroid executes an unsteady flipping motion in which its orientation changes with time. As before, it is assumed that inertial effects are negligible. In this limit, and with further assumption of an unbounded fluid domain, an exact analytical solution [88] describing the spheroid motion can be expressed as

\[
\theta(t) = \tan^{-1} \left( \alpha \tan \left[ \frac{t^\gamma}{\alpha + \frac{1}{\alpha}} \right] \right)
\]  

(2.60)

where \(\theta\) is the instantaneous inclination angle of the spheroid’s major axis, and \(\alpha\) is the ratio of the major axis to minor axis lengths. This exact solution is used to validate the immersed boundary simulation results.

In the numerical simulation, an oblate spheroid is considered of aspect ratio \(\alpha = 3\). While the object surface can be defined analytically, a surface Lagrangian mesh is needed.
for the force and torque computation. 1,280 surface triangles are used for this purpose which was observed to be sufficient after testing with various surface resolutions. While using a relatively coarse surface resolution obviously results in the surface curvature not being adequately represented, using an excessively fine mesh resolution results in an increased number of interpolations to be performed at each surface element. In general it was observed that a mesh resolution resulting in an average element side length on the same order of the Eulerian grid spacing was a good criterion for selecting a surface resolution. As noted in Section 2.4.3, an oblate spheroidal coordinate system is used for efficient computation of force and torque. A cubic computational domain with edge length \( L = 12r_{sp} \) is considered where \( r_{sp} \) is the radius of a sphere having the same volume as that of the spheroid. The Eulerian resolution used is \( 160^3 \), resulting in a resolution in accordance with the aforementioned criteria, based on the equivalent spheroid diameter. The domain is periodic in the \( x- \) and \( z- \)directions, and wall bounded in the \( y- \)direction. The influence of the domain size was tested, and \( L = 12r_{sp} \) is found to have no significant effect due to finite domain size.
The simulation result for inclination angle \( \theta(t) \) is presented in Figure 2.8(b) over one half period of flipping for \( \alpha = 3 \), and for three different time step sizes, namely \( \gamma \Delta t = 0.002, 0.001 \), and 0.0005. An excellent agreement with Eq. 2.60 is observed as \( \Delta t \) is decreased. The maximum absolute error in \( \theta(t) \) over one-half period for each of the time step sizes is 0.4, 0.052, and 0.014 radians, respectively, while the \( L_2 \) error norms are 0.167, 0.0257, 0.00755, respectively.

(b) Sphere moving near a wall

The next validation study considered for moving bodies is the motion of a sphere in a linear shear flow near a stationary plane wall, as shown in Figure 2.9(a). The sphere is free to translate and rotate by the action of the fluid force and torque. In the absence of inertia, the sphere moves parallel to the wall with constant translational and angular velocities. The translational and angular velocities decrease with decreasing distance between the sphere and the wall. Analytical solutions have been developed for this problem in the limit of negligible inertia [76, 192]. These classical solutions typically express the sphere’s translational velocity \( U \) and the angular velocity \( \Omega \) in terms of expansions in \( a/H \), where \( a \) is the sphere radius and \( H \) is the distance of the sphere center from the wall. A Padé approximation to the classical solution was obtained as

\[
U^* = \frac{U}{U_0} = \frac{\sum_{i=0}^{37} q_i(U) \left( \frac{a}{H} \right)^i}{\sum_{i=0}^{37} r_i(U) \left( \frac{a}{H} \right)^i} \tag{2.61}
\]

\[
\Omega^* = \frac{\Omega}{\Omega_0} = \frac{\sum_{i=0}^{37} q_i(\Omega) \left( \frac{a}{H} \right)^i}{\sum_{i=0}^{37} r_i(\Omega) \left( \frac{a}{H} \right)^i} \tag{2.62}
\]

where \( U_0 \) and \( \Omega_0 \) are the values in the absence of the wall, and \( q_i \) and \( r_i \) are the coefficients in the expansions [32]. The numerical results are validated against Eqs. 2.61 and 2.62.

Both the moving sphere and the stationary wall are simulated as sharp-interface immersed boundaries. The minimum distance between the sphere surface and the wall considered in the simulations is as small as \(<6\%\) of the sphere diameter. Thus, this validation study establishes the accuracy of the methodology when both moving and stationary immersed boundaries are in close proximity. In order to calculate the necessary parameters for the ghost-node identifications, the sphere surface is represented analytically. However, for
the purpose of force and torque computation, the surface is discretized by 1,280 triangles. The computational domain is cubic with edge length 13a, and the Eulerian resolution used is 160^3.

Simulations are performed for different values of a/H in the range of 0.3 to 0.9. The numerical results for the dimensionless translational and angular velocities, U* and Ω*, are compared with the analytical ones in Figure 2.9(b). All 38 terms in the analytical expression were used. In general, the two solutions agree very well as presented in the figure, even for a/H = 0.9 for which there are three Eulerian points between the sphere surface and the immersed wall. The absolute error for U* and Ω* ranges from 0.00027 to 0.0037, and 0.00037 to 0.0046, respectively, as a/H is increased from 0.3 to 0.9. One reason why error increases at higher values of a/H is that the analytical solution itself becomes inaccurate as a/H becomes large.
Figure 2.9(c) provides contours of the velocity magnitude and streamlines in the frame of reference of the sphere for $a/H = 0.9$. As can be seen here, flow variables vary smoothly around the sphere and near the wall. Consistent with the characteristics of Stokes flow, the flow field exhibits fore-aft symmetry. Similar smoothness in the flow field and symmetry in accordance with Stokes flow were verified for the validation studies presented earlier.

(c) Sphere moving in a tube

A sphere moving through a straight tube is simulated to examine the accuracy of the GNIBM for a situation in which there is both an external flow over an object (moving rigid sphere), and an internal flow through an object (stationary tube). For this case a rectangular computational domain is considered into which both the tube of radius $R$ and sphere of radius $a$ are immersed. The sphere is placed at the center of the tube as shown in Figure 2.10(A) below, and the case is considered where $R/a = 2\pi$. A constant force is applied to the sphere driving it in the $x$-direction. The simulation is set up such that the computational domain is wall-bounded at $y = 0$ and $L_y$, and is periodic in the $x$ and $z$ directions. With the present methodology a solution is achieved throughout the entire computational domain, which includes both the fluid and solid domains. In this case the fluid domain is bounded by the tube wall, and the solid domain, i.e. outside of the tube, crosses the computational domain boundaries. In the $y$-direction this is of no consequence as the no-slip condition is simply enforced at the top and bottom walls. In the $z$-direction, however, it is of particular interest considering the $z$-direction Fourier transforms inherent to the Poisson solver. Thus, an additional purpose of this case is to investigate the accuracy of the methodology for geometries resulting in a solid domain crossing the $z$-boundary.

An expression for the force exerted on a sphere moving with a constant velocity $U$ in the axial position of a tube can be derived as \[81\]

\[
F' = \frac{F}{-6\pi \mu a U} = 1/1 - 2.10444 \left(\frac{a}{R}\right) + 2.08877 \left(\frac{a}{R}\right)^3 - 0.94813 \left(\frac{a}{R}\right)^5 - 1.372 \left(\frac{a}{R}\right)^6 + 3.87 \left(\frac{a}{R}\right)^8 - 4.19 \left(\frac{a}{R}\right)^{10} + \ldots
\]

(2.63)
Here, the force $F'$ required to drive the sphere at a specified velocity $U$ is first computed from Eq. 2.63. The simulation is then started with an initial condition corresponding to that of a stagnant fluid, and this constant force $F'$ is applied to the sphere. As the sphere accelerates, the surrounding fluid exerts a force on the sphere in response to its motion, computed using the methodology of Section 2.4.3. In the simulation $U$ is taken to be the velocity scale for the problem, or $U_{ch}$. The velocity of the sphere when it reaches its final, steady value is compared with the desired value of $U' = \frac{U}{U_{ch}} = 1$.

The domain dimensions in the $y$- and $z$- directions are $L_y/a = L_z/a = 4\pi$. Eq. 2.63 is derived based on an infinite domain length in $x$, and thus in order to eliminate any boundary effect it is found that $L_x/a = 128\pi$ is sufficient. With regard to Eulerian resolution of the computational domain, 2650 grid points are used in the $x$-direction, and 80 grid points in both the $y$- and $z$- directions. Both the moving sphere and the stationary tube are simulated as sharp-interface immersed boundaries. In order to calculate the necessary parameters for the ghost-node identifications, the surfaces of both objects are represented analytically. For the purpose of force computation on the sphere, the surface is discretized by 1,280 triangles. The radius of the tube is taken to be $L_y/2a$, which tests the ability of the method to handle ghost and solid nodes on the $y$ and $z$ computational domain boundaries.
Figure 2.10(B) gives the simulation result for the sphere velocity, and as can be seen it settles on the desired value of \( U' = 1 \) to within 0.1% error. This indicates that the methodology is able to accurately model flows involving stationary and moving rigid objects where there is both an internal flow and an external flow. What this case also demonstrates is that while the *computational* domain is required to be periodic in one direction for the spectral Poisson solver (here in the \( z \)-direction), the *fluid* domain does not have to be. With the orientation of the tube in the present problem, the \( z \) domain boundary is within the *solid* region and the solution is highly accurate. This is important going forward, as it verifies that the periodicity requirement for the *computational* domain in one direction does not limit the types of complex geometries that can be considered.

**(d) Impulsively started sphere**

Lastly, the transient force on an impulsively started sphere in the vicinity of a plane wall is evaluated to further assess the performance of the simulation tool with regard to unsteady start-up flows. A sphere is placed in a stagnant fluid, as shown in Figure 2.11(A), and at an instant in time is given a constant translational velocity \( U \) while being prevented from rotating.

An analytical expression for the transient force acting on the sphere is given by [81]:

\[
F' = \frac{F}{6\pi\mu a U} = 1 + \frac{a}{\sqrt{\pi \nu t}} + \frac{9}{16} \frac{a}{H} K(\xi) \tag{2.64}
\]

where the dimensionless group \( \xi = \frac{H}{\sqrt{\nu t}} \), and \( K(\xi) \) is given by:

\[
K(\xi) = 1 - \frac{16}{9\sqrt{\pi}} \xi + \frac{8}{9\sqrt{\pi}} \xi^3 - \frac{1}{6} \xi^4 + O(\xi^5) \quad \text{for } \xi < 1 \tag{2.65a}
\]

\[
K(\xi) = \frac{1}{3} \xi^{-2} + \frac{4}{3\sqrt{\pi}} \xi^{-3} + O(\xi^{-4}) \quad \text{for } \xi > 1 \tag{2.65b}
\]

A cubic domain is considered that is periodic in the \( x \)- and \( z \)-directions, and wall bounded in the \( y \)-direction. The simulation domain is taken to have a side length \( L = 13a \), with an Eulerian resolution of \( 160^3 \). These were found to be sufficient to both achieve the conditions upon which the analytical solution is based and spatially resolve the computational domain. Both the moving sphere and the stationary wall are simulated as sharp-interface immersed boundaries. The sphere surface is represented analytically with the GNIBM, and
Figure 2.11: Impulsively started sphere near a plane wall, $a/H = 0.3$. (A) Simulation schematic (B-D) Transient force exerted on sphere for timestep sizes $\Delta t = 0.002, 0.001, 0.0005$, respectively. The solid line gives the simulation result, and the dashed line gives the analytical result from Eq. 2.64.

is discretized by 1,280 triangles for the force computations. The transient force acting on the sphere as it is started is compared with the force given by Eq. 2.64. Three timestep sizes, $\Delta t = 0.002, 0.001, 0.0005$, are considered for the case in which $a/H = 0.3$. The velocity scale is taken to be the translational velocity of the sphere $U$, while the length scale is taken to be the sphere diameter $D$. With this scaling the dimensionless force computed by the simulation code is $F' = \frac{F}{\nu UD^2}$, where $\nu$ is the kinematic viscosity, and the viscous scale is used for time, or $t' = \frac{t}{D^2/\nu}$.

Figure 2.11(B-D) provides a comparison between the numerical result and the analytical solution given by Eq. 2.64. For each of the timestep sizes, an excellent agreement with the analytical solution is observed after a period of time. The duration of this period of time is directly proportional to the timestep size, as can be seen in these figures. For each
\(\Delta t\) considered, there is an initial oscillation that settles into a smoothly decaying trend, matching that of the analytical solution. For \(\Delta t = 0.002\) the trend becomes smooth by \(t' \sim 0.125\), while for \(\Delta t = 0.001\) and \(0.0005\) this occurs by \(t' = 0.07\) and \(0.04\), respectively.

### 2.5.3 Micropipette aspiration of a red blood cell

The next validation study deals with a deformable interface in the presence of a complex stationary boundary. Specifically simulated is the experiment of [196] in which an RBC was aspirated into a micropipette by applying a pressure difference \(\Delta P\). The RBC exhibited a large deformation as it was partly drawn into the pipette, and the length \(L\) of the RBC inside the pipette was measured as a function of \(\Delta P\). The purpose of this case is to demonstrate, in a quantitative manner, the accuracy of the methodology in capturing the extreme deformation of an individual cell, in addition to the short range interaction between the two types of interfaces. This is one case for which reliable experimental results exist, and thus provides a good benchmark for the accuracy of the method.

The setup for the simulation is shown in Figure 2.12(a), where the RBC and micropipette are immersed in a viscous fluid. The pipette itself is a cylinder of small but finite thickness with a rounded inlet edge. Numerically it is modeled as a rigid object using the GNIBM. The inside diameter is \(1.8 \mu m\) with a thickness of \(0.8 \mu m\), while the length is \(4.3 \mu m\). The computational domain into which it is immersed has dimensions \(8.6 \mu m \times 11.5 \mu m \times 11.5 \mu m\), in the x-, y-, and z-directions, respectively, and the cylinder axis is oriented in the x-direction. The outlet face of the cylinder coincides with the outlet of the computational domain, and pressure boundary conditions are applied at the bounds of the domain in the x-direction in accordance with the applied pressure difference. The domain is wall bounded in the y-direction and periodic in the z-direction, with lengths taken so as to eliminate any effect on the result. The deformable RBC is modeled using the FEM as described in Section 2.3, with the membrane strain energy modeled by Eq. 2.2. As the deformation of the RBC is strongly influenced by the micropipette geometry, this problem involves a close interaction between the deformable cell membrane and the sharp-interface rigid boundary.

Figures 2.12(a) and (b) provide snapshots from a simulation at the beginning and at a later time after a steady state has been reached. The initial shape of the RBC at the
Figure 2.12: Validation for interaction between deformable and rigid interfaces: Micropipette aspiration of an RBC. (a) The undeformed RBC (red) at the beginning of aspiration. The pipette is modeled as a cylinder of finite thickness (grey). Both the cell and the pipette are immersed in a viscous fluid. (b) Snapshot from the simulation after the steady state is reached. A portion of the cell is drawn into the pipette. (c) Comparison of the present simulation results (●) and experimental data (□, [196]). Here $L^* = L/r_p$ is the dimensionless length of the cell drawn inside the pipette, and $ΔP^* = Δp(r_p/2G_s)$ is the dimensionless pressure, where $r_p$ is the inside radius of the pipette. (d) Sensitivity of the results to the Lagrangian resolution on the RBC surface. 2D contours of the cell volume residing inside the pipette are shown for three different Lagrangian resolutions by varying the number of surface elements as 20480 (—), 32000 (—), and 49152 (—).
beginning of the simulation is the biconcave discocyte. With the applied pressure, a part of
the cell volume begins entering the pipette. Eventually a steady state is reached under the
balance of the applied pressure and the tension generated in the cell membrane. The large
deformation and an extended length of the cell inside the pipette is evident in Figure 2.12(b).
Also noteworthy is the smoothness of the RBC surface even after the extreme deformation.
The numerical results are compared with the experimental data of [196] in Figure 2.12(c)
where the cell length $L$ inside the pipette is plotted as a function of the applied pressure
difference $\Delta P$. Good agreement between the two studies is observed. It should be noted
that the results are sensitive to the the actual values of the model parameters used for the
RBC membrane. For the numerical data shown here we used $G_s = 7 \times 10^{-6}$ N/m as noted
in [196], and $C_3 = G_s / 30$ as noted in [122]. Also discussed in [122] is that use of Eq. 2.2
is well suited for matching experimental data for large deformation, and provides a much
better match with experiments using this equation over lower order ones of the same type.
With regard to the common types of strain energy model typically utilized in numerical
methods, for this case it was found that Eq. 2.2 better predicts the experimental results
than Eq. 2.1.

Sensitivity of the results to the Lagrangian resolution on the surface of the RBC is
shown in Figure 2.12(d) where 2D contours of the cell volume residing inside the pipette
are shown. The resolution criteria for deformable cells has been established in prior works
involving the implemented cell model here [47, 203]. The general criteria is that the average
side length of an element of the Lagrangian mesh is on the same order as the spacing of
the Eulerian mesh. Simulations are performed with three different Lagrangian resolutions,
namely 20480, 32000, and 49152 triangular elements on the RBC surface. While the shape
obtained with 20480 elements lacks smoothness at the pipette entrance, those with 32000
and 49152 elements are smooth and indistinguishable. The sensitivity to the Eulerian
resolution is also tested using $96 \times 128 \times 128$ and $192 \times 256 \times 256$ grids, and the difference
was observed to be negligible.
Figure 2.13: Validation study for multiple deformable interfaces in presence of rigid boundaries: Flow of deformable RBCs in a bifurcating and merging channel. (a) Geometry of the channel modeled in the simulation. (b)-(c) Snapshots from one simulation showing the flow of deformed RBCs through the channels. The arrows indicate the flow directions. The feeding vessel (left) bifurcates into two daughter vessels of unequal cross-sections. $Q_0$ and $Q_1$ are the flow rates and $N_0$ and $N_1$ are the RBC number densities, in the feeding vessel and in branch 1, respectively. Note that the left and right boundaries are periodic.
2.5.4 Multiple deformable RBCs in complex geometry

The next validation study considers multiple deformable interfaces in the presence of non-moving rigid boundaries. The specific example considered is the flow of multiple deformable RBCs in a bifurcating and merging rectangular channel (Figure 2.13). It is well known in microcirculatory physiology that when a suspension of RBCs reaches a vascular bifurcation, it does not split in proportion to the flow rates in the two daughter branches. Rather, the branch with the higher flow rate gets a disproportionately greater number of cells. This phenomenon, known as the Zweifach-Fung (Z-F) effect, is believed to be one reason why blood cell distributions are not uniform across different vessels in the microcirculation [145, 71, 153]. In this section the Z-F effect is simulated, and the numerical results are compared against published experimental results.

The geometry considered for the simulations is shown in Figure 2.13(a). A microfluidic channel of rectangular cross-section is modeled that bifurcates into two daughter branches of unequal cross-sections. After a certain distance, the daughter branches again merge to form one channel. The cross-sections of the feeding branch (Branch 0) and one daughter branch (Branch 1) are fixed at 12 × 12μm² and 12 × 9.3μm², respectively, while that of Branch 2 is varied from 12 × 3.7μm² to 12 × 7.5μm². Thus, the flow rates in the daughter branches are varied by adjusting the cross-sectional area of Branch 2. The entire length of the device is 158 μm. The microfluidic geometry is modeled as a sharp-interface immersed boundary object, with its surface defined using a triangular mesh that is comprised of about 1.7 million triangles. The computational domain is 158 × 49 × 14 μm³ which is discretized by 580 × 180 × 51 Eulerian points. Each RBC surface is discretized by 5,120 Delauney triangles, and the number of RBCs considered for this problem is about 50. The flow is driven by a pressure differential between the inlet and outlet. Periodic boundary conditions are assumed for the velocity.

Snapshots from one simulation are shown in Figures 2.13(b)-(c). As the cells reach the bifurcation they split into two daughter branches. Deformation of the RBCs is evident in the figures where many of them assume the so-called slipper shape and parachute shape as observed in experiments. Obtained from the simulations are the ratio of the flow rates.
Figure 2.14: Multiple RBCs flowing in a bifurcating channel. Comparison of the present numerical results (●) with previous experimental measurements: *in vivo* data from Pries et al [151], and microfluidic measurements of Yang et al [202]. \( N_1/N_0 \) versus \( Q_1/Q_0 \) shows a half-sigmoidal variation and represents the Zweifach-Fung effect.
$Q_1/Q_0$, and the ratio of the RBC number densities $N_1/N_0$, where $Q_0$ and $Q_1$ are the flow rates in the feeding vessel and Branch 1, and $N_0$ and $N_1$ are the RBC number densities. Generally, the flow rates and number densities vary with time, so time averages are done in computing the ratios once the flow has reached a quasi-steady state. Figure 2.14 presents $N_1/N_0$ as a function of $Q_1/Q_0$. If the cells were to distribute in proportion to the flow rates, the plot of $N_1/N_0$ versus $Q_1/Q_0$ would be a straight line with a slope of unity. Instead, a nonlinear variation in the form of a half-sigmoidal curve is noted. Such a sigmoidal curve is the result of a disproportionate splitting of the RBC suspension at the bifurcation, and hence, of the Z-F effect. At $Q_1/Q_0 \approx 0.85$, $N_1/N_0$ becomes one, i.e. all RBCs are flowing into Branch 1 while only plasma flows into Branch 2. Behavior like this is an origin of the term \textit{plasma skimming}, which is often used to describe general disproportionate distributing of cells and flow. Overall these results show that the numerical methodology is able to predict this characteristic behavior of the Z-F effect.

In Figure 2.14, the data from two experimental studies are also presented in addition to the numerical results: one is the \textit{in vivo} measurement by Pries et al who considered blood flow through arteriolar bifurcations in the rat mesentery [151], and the other is the microfluidic measurements by Yang et al [202] using rigid spheres. The blood vessel diameters considered in the \textit{in vivo} measurements, and the sphere to channel size in the microfluidic experiments were in the same range as considered here. The results from each of these experiments provide an example of a typical manifestation of the Z-F effect in the form of the sigmoidal variation of $N_1/N_0$ versus $Q_1/Q_0$. The results obtained from the simulations clearly capture this sigmoidal relation.

### 2.5.5 Comparison with a numerical study

In the previous sections the methodology was validated against analytical results and experimental studies. In this section the methodology is validated against a previous numerical study. Furthermore, the specific example considered here validates the methodology in the presence of sharp rigid corners. [140] used a spectral boundary integral method to study the deformation of a capsule moving through a constricted microchannel. The conditions of this previous work are recreated, and the results attained with the present methodology
Figure 2.15: Validation with numerical results: Initially spherical cell moving through a microchannel constriction. (a) shows snapshots from the present simulations at three time instances. (b) compares the capsule lengths in three directions obtained using the present methodology (---) and a spectral boundary integral method [17] (□ x, ○ y, ∆ z). Here $X_C$ is the instantaneous location of the cell center, and $R$ is the initial radius.

are compared. A microchannel of square cross-section with a rectangular constriction of height and length $2H_c$ is considered as shown in Figure 2.15. The microchannel geometry is modeled using the sharp-interface immersed boundary method, with the surface defined using a triangular mesh of about 1.5 million elements. This geometry is immersed within a bounding computational domain $20H_c \times 4.5H_c \times 5H_c$. The Eulerian resolutions used are $400 \times 90 \times 100$ and $800 \times 180 \times 200$. An initially spherical cell is considered, with Skalak et al.’s model (Eq. 2.1). The cell surface is discretized using 5,240 or 20,480 triangles. The capillary number, defined as $Ca = \mu_p U_c / G_s$, was 0.1, where $U_c$ is the average velocity in the unconstricted part of the channel in absence of the cell. Three values of the ratio of the fluid viscosity internal and external to the cell, $\mu_c / \mu_p$, are considered as 0.1, 1, and 5. The ratio of the initial cell radius to the half-width of the constriction, $R/H_c$ is varied as 0.6, 0.9 and 1. Snapshots from a simulation ($R/H_c = 1$, $Ca = 0.1$, $\mu_c / \mu_p = 1$) are presented in Figure 2.15(a) which shows the squeezing of the cell through the constriction. Quantitative comparison with [140] is presented in Figure 2.15(b) for a case of $R/H_c = 1$, $Ca = 0.1$, 


\[ \frac{\mu_c}{\mu_p} = 0.1 \] where deformed lengths of the cell in three directions are plotted as it squeezes through the constriction. Good agreement is observed between the results achieved using the different numerical methodologies for the specific case shown in the figure, as well as for varying parameters. Differences observed with different Eulerian and Lagrangian resolutions were negligible. The Eulerian resolution used for this case is slightly higher than that used with other cases, on account of the sharp corners of the constriction geometry. Thus the limiting factor with regard to mesh resolution was the sharp-interface geometry for this case, not the deformable cell.

### 2.5.6 Additional considerations

With the current methodology, a uniform rectangular Eulerian mesh is used to discretize the flow domain. As such, a natural consequence of arbitrary rigid boundaries immersed into the domain is that the degree of boundary alignment with the mesh can vary. The impact this may have on the results has been tested, considering two different notions of alignment.

The first notion of alignment is in the sense of symmetry of interfaces with respect to a natural centerline. For example, the case studied in Section 2.5.5 considered a centrally placed deformable cell flowing through a channel with a symmetric constriction. Analytically both the velocity field and evolution of the cell shape as it passes through the constriction will be symmetric about the centerline. Numerically speaking, with a symmetric shape like the constriction geometry it can be immersed into the domain such that the location of the Eulerian mesh points relative to the interface will be symmetric relative to the channel centerline. It can also be immersed in such a way that these relative locations are asymmetric. Cases for both of these configurations have been tested, and both the resulting velocity field and the shape evolution of the cell passing through the constriction were compared. For the fluid velocity fields, differences were observed to be less than 0.1%. It is noted that in comparing the two cases, Eulerian fluid mesh points are not located at the same physical points in space, so an interpolation was used when comparing the results. This <0.1% difference could therefore be attributed to the error in the interpolation used for comparison. In comparing the shape of the deformable cell, a negligible difference
was also observed. It is noted that as the Eulerian mesh resolution becomes more coarse, these differences may be more pronounced. However in all of the simulations fine enough resolutions are used to ensure relevant aspects of the flow are adequately resolved.

The second notion of alignment is in the sense that for rectangular rigid geometries, such as that considered in Section 2.5.5, the rectangular Eulerian mesh can nicely align with the rigid interface. The majority of the validation cases in Section 2.5 involve rigid interfaces with curvature, thus testing this notion of alignment. In performing these cases, however, the effect of the symmetry of alignment was also tested. For the stationary sphere case (Section 2.5.1), for example, at coarser mesh resolutions the error increased, as noted in the section. The location of the maximum error, at the coarser resolutions, was observed to shift to one side when the location of the sphere relative to the Eulerian mesh was slightly shifted. While the location shifted, the differences in the magnitude of the error were insignificant. So at the coarser resolutions, differences were observed in the symmetry of the error location, not in the magnitudes. This same general theme was observed for the other cases as well. At the finer Eulerian mesh resolutions, such as that of Figure 2.7, insignificant differences were observed in both the location and the magnitude.

In selecting the appropriate resolutions, the first part involves selecting an Eulerian resolution such that the relevant features of the flow will be resolved. Since the Lagrangian mesh size is on the same order as the Eulerian mesh, as the cells deform, the degree to which the surface deformation is resolved is on the same order as the degree to which the surrounding flow is resolved. The validation cases show that the method is able to capture the essential mechanisms needed to understand flows in microvascular networks and microfluidic devices: the mechanics of overall cell populations (Section 2.5.4), and extreme deformation of an individual cell (Section 2.5.3). For the case presented in Section 2.5.3, the differences in result using different Lagrangian resolutions were demonstrated.

As an example, the cells in Figure 2.14 are highly deformed, and the scale of the membrane deformation is small. However, this does not necessarily imply that the Eulerian resolution does not resolve the flow structures associated with this. In transferring information between the membrane and surrounding fluid, the scale of resolution is of the same order for each of the meshes associated with this. So they are consistent with one another.
In other words, the deformation resolved on the Lagrangian mesh is consistent with the flow structure resolved on the Eulerian mesh.

Another important issue is the cell volume and surface area preservation. This issue has been addressed in previous works involving the cell model implemented here [47, 203, 204, 40]. Specifically, the cell surface area and volume change over time were shown in [40] in the Supplemental Materials. The change in cell volume is within 0.1% as noted therein. Note that the incompressibility condition is satisfied at every Eulerian node up to machine epsilon. The change in cell surface depends on the specific constitutive law. The model of Skalak et al (Eq.2.1) is nearly area preserving. The area dilation in this model is controlled by the parameter $C$ in Eq. 2.1. For the RBCs, the area change is kept within 0.1%.

### 2.6 Demonstration of computational capability

This section presents a demonstration of the capability of the methodology to simulate multiple deformable cells and heterogeneous suspensions moving in highly complex geometries ranging from physiologically realistic microvascular networks to geometrically complex microfluidic devices. The focus here is to show that the methodology can reproduce some well-known but complex microphysiological and biomicrofluidic phenomena. Each case has been selected to demonstrate specific aspects of the methodology, as outlined in Table 2.2. Together these studies show the versatility of the methodology in addressing a diverse set of problems related to microvascular blood flow and microfluidic blood handling.

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Table 2.2: Specific objective of each of the demonstration studies considered
2.6.1 Flow of RBCs in a microvascular network

The first demonstration involves the flow of many deformable RBCs in a complex microvascular network as shown in Figure 2.16. The vascular network is numerically generated as described in Section 2.4.2, following an in vivo image of human cerebral microvasculature given in [116]. The network considered in the simulation is comprised of 23 vessels of circular cross-section, with multiple bifurcations, trifurcations, and mergers, while several vessels are highly winding. The diameter of the vessels ranges from 11 to 17 µm, and the length of the vascular segments between two branch points ranges from approximately 18 to 70 µm. The walls of the vessels are not deformable, and are treated as sharp-interface immersed boundaries with the entire surface represented by approximately 1.25 million triangular elements. The computational domain is $131 \times 109 \times 65 \, \mu m^3$, and the Eulerian resolution used is $480 \times 400 \times 240$. Multiple inlet and outlet vessels are present: the inlets are at the right and top boundaries of the domain, and the outlets are at the left and bottom boundaries. The flow is driven by pressure differences at the inlets and outlets. Periodic boundary conditions are assumed for the velocity. Cells leaving the outlets are also put back at the inlets. Each cell surface is discretized by 5120 triangular elements, and at any instance the network contains approximately 300 RBCs.

A snapshot of the simulation at one time instance is shown in Figure 2.16. Extreme deformation of the cells is evident in this figure. Also noted are the parachute and slipper shapes which are the well-known characteristic shapes of RBCs flowing in capillary vessels. The simulation is conducted over a dimensionless time of $\gtrsim 800$, and the cell distribution in different branches evolves naturally. As can be seen in the figure, distribution of blood cells is highly nonhomogeneous across the network: some branches are filled with cells while others have only a few cells. For example, the hematocrit in Vessel 15 is 12% while that in Vessel 7 is 30%. This inhomogeneity in cell distribution is a hallmark of blood flow in the microvasculature. Also, in several branches the cell distribution over a cross-section of the vessels is not symmetric. This asymmetric distribution is due to the disproportionate distributioning of cells at bifurcations, which is predicted here and also earlier in Section
Figure 2.16: Demonstration of computational capability: Simulation of many deformable RBCs flowing in a microvascular network. The top figure is a view along the $y$ axis, and the bottom figure is an isometric view. Some vessels are identified by numbers as needed for the discussion.
2.5.4. Such asymmetric distributioning is another hallmark of microvascular blood flow that the current simulation is able to predict.

The simulation platform has the potential to be used as a virtual framework to understand many microcirculatory processes with cellular scale details in physiologically realistic vascular architecture. As an illustration, the time-averaged velocity contours are extracted over the cross-sections of certain branches as shown in Figure 2.17. A wide variability in the average velocity is observed among different vessels in the network. In certain vessels, e.g. Branches 5 and 24, a nearly axisymmetric but “blunt” (non-parabolic) velocity profile is observed, which is a well-known characteristic of blood flow in small vessels. In contrast, however, the velocity profiles in several other vessels, for example Branches 11 and 17, are highly non-axisymmetric. Such non-axisymmetric velocity profiles are observed in post-bifurcation daughter branches. The non-axisymmetry is also observed in the cell-free region along the vascular walls. This is due to the RBCs flowing along one side of a vessel after they split at the bifurcation, and such behavior has been noted in prior experiments (see e.g. [145, 151, 131]).

As mentioned previously, most computational studies of cellular-scale blood flow have considered flow in unbranched, straight vessels in which the average velocity profile and cell-free region appear to be axisymmetric. In contrast, the present simulations show that these hemodynamic quantities are non-axisymmetric in many vessels depending on the architecture of the network, as has been observed in vivo [131]. Such non-axisymmetric profiles may have a significant effect on wall shear stress and, hence, on endothelial cell response, as well as deposition of drug and other particulates. The present methodology can be used to address these critical microhemodynamic issues.

2.6.2 Platelet and RBC interaction in a microvascular network

This section demonstrates the capability of the simulation methodology to deal with multiple deformable cells and moving rigid particles in a complex microvascular network. The specific example is the flow and interaction of RBCs and platelets in a network. As noted before, RBCs are highly deformable, while inactivated platelets behave as rigid particles. Normal platelets are of an oblate spheroidal shape with a major diameter of $\sim 3.6 \, \mu m$ and
Figure 2.17: Streamlines, and time-averaged velocity contours at vessel cross sections in certain selected vessels for the microvascular network simulation. Also shown are the average velocity profiles across radial directions as indicated by the black lines. Well known ‘blunt’ velocity profiles, as well as radially non-axisymmetric profiles are noted.
a minor diameter of $\sim 1.1 \mu m$. Platelets are modeled here as moving rigid objects using the GNIBM as described in Section 2.4.3. Each platelet surface is represented by the analytical equation for a spheroid, and discretized using a surface mesh of 1,280 triangular elements for the force and torque computations. Each RBC surface is discretized by 5,120 triangular elements. The computational domain is taken to be $65 \times 59 \times 33 \mu m^3$, and is discretized using $240 \times 216 \times 120$ Eulerian points. The vascular network is immersed in the domain. Vessel surfaces are treated using the GNIBM and discretized by approximately 325,000 triangular elements.

A snapshot from the simulation is shown in Figure 2.18(a). Because of their deformation, RBCs flowing in a vessel experience a hydrodynamic lift and migrate laterally towards the center of the vessel. The interaction between the RBCs and platelets causes the latter to marginate towards the wall. Platelet margination is the first step in the formation of a blood clot. Rigorous hydrodynamic analyses of platelet margination and the role of RBCs is emerging only recently, and has been limited to simple linear flows and in straight tubes. It is relatively unknown how vascular bifurcations and mergers influence platelet margination, especially in tortuous vessels. The representative simulation shown in Figure 2.18 would allow such an analysis to be performed. As an illustration, platelet trajectories have been extracted from the simulation, and the distance between the platelets and the vascular wall is plotted over time in Figure 2.18(b). The platelets considered in this figure were released near the center of a vessel. It is observed that the wall-to-platelet distance decreases over time as the platelets marginate towards the wall. Therefore, the present methodology can successfully predict RBC-induced margination of platelets in a microvascular network. The methodology can be readily extended to study other similar problems of immense physiological significance, such as margination of white blood cells and circulating tumor cells, as well as RBC-induced drug deposition in realistic vascular geometry.

### 2.6.3 Microfluidic cell sorting

The previous two demonstrations have considered physiological scenarios with internal viscous flows. The next demonstration deals with a microfluidic device involving external flows and includes deformable interfaces, moving rigid bodies, and non-moving boundaries.
Specifically considered here is a microfluidic cell sorting technique. Cell sorting is a common microfluidic technique used to separate different types of biological cells, such as circulating tumor cells and blood cells. One such device is an array of rigid cylinders of micrometer size [118, 128]. The basic idea behind such devices is to exploit different trajectories that flowing cells take based on their size and deformability. In this section the ability of the simulation tool to predict cell separation in such a device is demonstrated.

The geometry considered is an array of 16 cylindrical posts with central axis perpendicular to the plane of the fluid motion (Figure 2.19). The diameter of each post is 14μm and with a length of 16μm. The computational domain is taken to be approximately 98 × 98 × 16μm³, and the Eulerian resolution used is 360 × 360 × 60. The domain is periodic in two directions and wall bounded at the ends of the cylinders. The flow is driven by a mean pressure gradient and is normal to the cylinder length. The rigid cylinders are modeled as sharp-interface immersed boundaries, with each surface represented by the analytical equation for a cylinder. The cell suspension contains three different types of cells:
deformable RBCs, rigid platelets, and a third type of cell that is stiffer than an RBC and bigger in size (12 $\mu$m in diameter). The latter type is representative of both white blood cells (WBC) and circulating tumor cells (CTC). The resolution used for each cell is the same as that in the previous two examples.

A snapshot from one simulation is shown in Figure 2.19(a). The cells move around the posts as they are driven by the flow, and large deformations can be observed in each of the RBCs. The streamlines and velocity magnitude at the central $x$-$z$ plane are shown in Figure 2.19(b) in absence of the cells, and a symmetric flow structure around each cylinder is observed as is the case for a Stokes flow. The interaction of the cells with the posts affects their trajectories, which are monitored in the simulation. Figure 2.19(c) compares the trajectories of an RBC, a platelet, and a WBC/CTC, each with the same initial position. The direction of the mean fluid flow is also shown. It is readily seen that the deviation of a cell trajectory from the flow direction increases with increasing cell size. The platelets, being the smallest cells, nearly follow the mean fluid path, while the WBC/CTCs follow a distinctly different path. As can be seen, the trajectory of the WBC/CTCs quickly separates from that of the RBCs and platelets. Over a time of approximately 0.02 seconds, more than 100 $\mu$m of separation between the WBC/CTC and the RBC is observed. These results demonstrate that the simulation tool can be used to design microfluidic cell sorting devices that exploit the deformability and size/shape-dependent sorting of cells in suspension.

2.6.4 Geometrically complex and integrated lab-on-chip devices

Microfluidic lab-on-chip devices often integrate many geometrically complex features in order to perform a complete analysis of a biological cell suspension [118, 43]. The final demonstration of the numerical methodology is in resolving deformable cell motion in such a complex device. A lab-on-chip device is modeled as depicted in Figure 2.20(a). The device combines various geometrical features commonly utilized, such as a winding passage, sudden expansion, obstacles of different shapes, and channel bifurcations. The length of the device is approximately 250$\mu$m, and it is immersed in a $250 \times 100 \times 10$ $\mu$m$^3$ computational domain that is discretized using $900 \times 390 \times 35$ Eulerian points. The walls of the device are modeled as sharp-interface immersed boundaries and discretized by approximately 2.1
Figure 2.19: Simulation of cell sorting: flow of a suspension of heterogeneous cells through an array of cylindrical posts. (a) A snapshot from the simulation. Three types of cells are considered: deformable RBC (red), white blood cells (WBC) and circulating tumor cells (CTC) (blue), and rigid platelets (green). Flow is along the $x$-$z$ plane. (b) Streamlines and velocity magnitude at the central $x$-$z$ plane. Velocity magnitude range in arbitrary dimensionless units is 0 (blue) to 0.6 (red). (c) Trajectories of an RBC (—), a WBC/CTC (—), and a platelet (—). The arrow indicates the mean flow direction.
million triangular elements. Flow is driven by an applied pressure difference at the inlet and outlets. Two different types of deformable cells, namely RBCs and WBC/CTCs, are injected at the inlet. Figure 2.20(b) shows a snapshot from the simulation with the distribution of highly deformable RBCs and relatively stiff WBC/CTCs. Large deformation of the cells can also be noted here as they flow through the winding passages and around the obstacles. Also shown is the trajectory of each cell which can be analyzed further to assess cell separation efficiency for the present device or similar devices. This example further demonstrates the capability of the present methodology to resolve flows of multiple heterogeneous and deformable cells in highly complex geometry such as that often encountered in integrated lab-on-chip devices. Another feature of this example is that it demonstrates the capability of the methodology to simulate flows involving boundaries with discontinuities in the surface curvature. Specifically, this simulation involves an internal flow through a geometry with sharp corners, in addition to an external flow around objects such as the rectangular and triangular obstructions. The ability to simulate flows around sharp-edged obstructions such as these further highlights the versatility of the methodology with regard to boundary complexity.

2.7 Fluid leakage considerations with increasingly complex sharp-interface geometries

With immersed boundary methods such as those presented here, the desired conditions at the immersed surfaces are approximately achieved. For the front-tracking method used with the deformable cells, this is formulated before the governing equations are discretized, and thus both the no-slip and no-penetration conditions are inherently achieved within the accuracy of this method. For the GNIBM described to model rigid interfaces, this is based on imposing constraints on the variables of the discretized governing equations (i.e. it is formulated after the governing equations are discretized). So in this sense the no-slip and no penetration conditions are approximately achieved by constraining the variables in the framework of the method. To put this in the proper context, it is instructive to consider that the boundary conditions imposed for the computational domain are also enforced by constraining the discrete variables. Specifically, the no-slip condition is enforced in the
Figure 2.20: Simulation of the flow of a suspension of deformable RBCs and WBC/CTCs in a geometrically complex lab-on-chip device. (a) 3D view of the device modeled. The mean flow is from left to right. The device consists of winding channels, a sudden expansion, obstacles of different shapes, and bifurcations. (b) A snapshot from the simulation. RBCs are shown in red, and WBC/CTCs are in blue. Sharp-interface boundaries are in white. Trajectories of a few cells are shown in yellow.
momentum-forcing step (Eq. 2.20), and the incompressibility condition is enforced when solving the Poisson equation (Eq. 2.21). With the scheme here, the no-slip condition is satisfied to second-order accuracy, while the no-penetration condition is satisfied to machine epsilon within the bounding computational domain. This latter condition is important because it ensures that the volume of fluid remains constant within the overall boundaries of the flow solver.

The basis of the GNIBM described in Section 2.4.2 for rigid interfaces was centered on enforcing the no-slip condition at the immersed surfaces, without directly enforcing the no-penetration condition. With the staggered-grid discretization, it was observed that the momentum-forcing alone did an excellent job of also enforcing the no-penetration condition on the immersed rigid surfaces, albeit indirectly. This is verified by the accuracy demonstrated with the various validation cases. However, because this condition is not directly enforced it was observed that as as the complexity of the rigid interfaces became significant, the degree to which this no-penetration condition was satisfied decreased.

It is noted that when considering such leakage, with the present methodology the fluid is not actually ‘lost’ because, as mentioned, the total fluid volume within the bounding computational box is maintained constant to machine epsilon. What this means, though, is that when considering the separate fluid and solid domains that comprise the computational domain for the GNIBM, there can be an exchange of flow between the fluid and solid domains. Although insignificant for the validation cases, a primary purpose of the method developed here is to simulate flows within highly complex physiological geometries. Thus, this warrants investigation, and is the subject of this section.

One established means of directly imposing the no-penetration condition is to enforce the standard Neumann condition in an immersed boundary method sense [124] when solving the Poisson equation. However, this requires breaking the structure of the linear system required to efficiently solve Eq. 2.21 with the spectral method previously discussed in Section 2.4.1. As such, an alternate means of solving Eq. 2.21 must be implemented, and an iterative method is described in Section 2.7.1 below to do so. The implementation is first validated by comparing with the results of Section 2.5.1 for flow around a stationary sphere. It is shown that while the accuracy achieved with the two approaches is similar, the CPU
time with the iterative solver is approximately 4 times greater than with the spectral solver.

Leakage considerations are subsequently examined in Section 2.7.2. Results are compared between the approaches for flow through a geometry of modest complexity, namely, a tube with a constriction. It is shown that the overall fluid leakage for both approaches is small, but is greater without any direct measure for imposing the no-penetration condition. Due to the increased CPU time with the iterative solver, a novel method is detailed in Section 2.7.2 to mitigate fluid leakage in a way that the fast spectral solver can be used. It is shown that this approach reduces the leakage to roughly that achieved with the iterative solver. Finally, it is shown that for a highly complex geometry, namely, a microvascular network, the flow leakage is negligible with the novel method, while significant without any direct no-penetration measure.

2.7.1 Iterative Poisson solver

For the projection method implemented here, the Neumann condition is imposed on the projection operator $\phi$, and takes the form $\mathbf{n} \cdot \nabla \phi = 0$ [147], where $\mathbf{n}$ is the normal vector to the surface. To achieve this in an immersed boundary sense, following [124] ghost nodes are identified on the Eulerian $\phi$ grid, and are used to directly enforce $\mathbf{n} \cdot \nabla \phi = 0$ at the BI point for each GN. Since the vector from the BI to the IP for each GN is normal to the surface, and the BI is the midpoint between the IP and the GN, this condition is approximated with a central difference as:

$$\phi_{GN} - \phi_{IP} = 0$$

(2.66)

As before in Section 2.4.2, the value at the image point is approximated based on the 8 surrounding grid points, and thus the constraint enforced at each GN is:

$$\phi_{GN} - \sum_{m=1}^{8} \beta_m \phi_m = 0$$

(2.67)

where the second term on the LHS of this equation approximates $\phi_{IP}$, and $\beta_m$ are determined from by Eq. 2.29. As mentioned, imposing this constraint at each GN amounts to changing the structure of the linear system such that the spectral solver cannot be used.

To impose Eq. 2.67 when solving Eq. 2.21, the Generalized Minimum Residual (GMRES) method [159] is employed. Within the GMRES framework, application of a geometric
multigrid V-cycle at the preconditioning step effectively results in a preconditioner that varies as the solution progresses and is specifically tailored to the immersed boundary geometry. To this end, the method employed is the Flexible GMRES (FGMRES) method on account of the varying preconditioner. FGMRES is an iterative method where each ‘iteration’ represents an additional dimension in a Krylov subspace whose basis vectors are used to form an approximation to the solution. The Arnoldi iteration is used to find these basis vectors, which are in turn combined with the solution to a least squares problem efficiently solved by making use of the Givens rotation. Thus the solution with this method is given by the vector in a Krylov subspace with minimum residual.

The discrete form of Eq. 2.21 to be solved is written at Eulerian node \((I, J, K)\) as:

\[
\frac{\phi_{I-1,J,K} - 2\phi_{I,J,K} + \phi_{I+1,J,K}}{\Delta x^2} + \frac{\phi_{I,J-1,K} - 2\phi_{I,J,K} + \phi_{I,J+1,K}}{\Delta y^2} + \frac{\phi_{I,J,K-1} - 2\phi_{I,J,K} + \phi_{I,J,K+1}}{\Delta z^2} = \frac{1}{\Delta t} \left( \frac{u^*_I,J,K - u^*_I,J,K}{\Delta x} + \frac{v^*_I,J,K - v^*_I,J,K}{\Delta y} + \frac{w^*_I,J,K - w^*_I,J,K}{\Delta z} \right)
\]

(2.68)

and modified at each GN by Eq. 2.67. In a more general form, this linear system can be represented as:

\[
A\phi = b
\]

(2.69)

where \(A\) is the linear operator corresponding to the left hand side of Eq. 2.68 modified by the GN constraint, and \(b\) is the right hand side. As with any iterative method, a convergence criteria is specified to identify the point at which the linear system is deemed solved. Specifically this criteria is the value of the minimum residual, however when using preconditioning the definition of the residual depends on the form of the preconditioner applied to the original linear system. For the present work, the right-preconditioning form is used:

\[
AM^{-1}\gamma = b, \quad \gamma = M\phi
\]

(2.70)

for some preconditioning matrix \(M^{-1}\), as this minimizes the same residual as in the original linear system (i.e. \(\text{res} = b - A\phi\)) [159]. This is important because in this form the convergence criteria directly specifies the degree to which \(\mathbf{n} \cdot \nabla \phi = 0\) is approximated in the context of the GNIBM.
The FGMRES algorithm is implemented as detailed in [159]. Within the algorithm, an application of one multigrid V-cycle is used to determine the preconditioned vectors $M_j^{-1}q_j$ at the preconditioning step of each $j$ dimension, where $q_j$ is the $j^{th}$ normalized residual. A red-black Gauss-Seidel smoother is used during the restriction and prolongation steps, with a specified number of smoothing steps. A constant-type prolongation operator is used in which the values of the coarse grid cells are simply assigned to the corresponding fine grid cells, as discussed in [197]. The restriction operator corresponding to this prolongation operator is its adjoint with a scaling factor of $\frac{1}{8}$. Figure 2.21 below depicts typical operations between two grid levels.

![Figure 2.21: Prolongation and restriction operations](image)

Zero initial conditions and boundary conditions are used within the V-cycle, as is appropriate when using a V-cycle preconditioner with a Krylov method [120]. Accordingly, at each grid level ghost nodes are identified and a zero value is enforced. For computational cells intersected by an immersed boundary, the prolongation and restriction operations are modified to only act on fluid nodes. A two-dimensional diagrammatic representation of this between three grid levels is provided in Figure 2.22.

At the coarsest grid level, an ‘exact’ solution is achieved using direct matrix inversion, as required when using a multigrid V-cycle as a preconditioner [120]. Since each FGMRES iteration represents an additional dimension in Krylov subspace, the size of each new basis
The implementation of this within the main fluid flow solver is validated by considering the flow around a stationary sphere as in Section 2.5.1. Table 2.3 presents the maximum $L_{\infty}$ error norm as determined using each method by comparing the numerical result with Eq. 2.59. Data is given for three Eulerian domain resolutions, namely $64^3$, $128^3$, and $256^3$. vector grows as the dimension increases. On account of this, a ‘restart’ version of the method is implemented in which the main algorithm is restarted after a specified number of dimensions, using the solution at the maximum dimension as the initial guess during the restart. The specified maximum restart dimension resulting in the minimum computation time will vary based on the linear system (i.e. the immersed boundary geometry), and thus is fine-tuned to each specific problem. Since the linear operator is extremely sparse, the compressed sparse row (CSR) format is used to most efficiently handle the data arrays. The general structure of the algorithm follows various recommendations for minimizing the memory footprint while maximizing speed [159, 120, 133, 56]. Overall, use of this preconditioner has been found to significantly speed up convergence, and thus enables a relatively fast and efficient solution of the linear system.

(a) Flow around a stationary sphere

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Also included is the CPU time required to complete 10000 timesteps. As can be seen, the

<table>
<thead>
<tr>
<th>Domain Resolution</th>
<th>Poisson Solver</th>
<th>CPU Time (seconds)</th>
<th>Maximum $L_\infty$ norm</th>
</tr>
</thead>
<tbody>
<tr>
<td>$64^3$</td>
<td>Spectral</td>
<td>123.1</td>
<td>0.0169</td>
</tr>
<tr>
<td></td>
<td>MG-FGMRES</td>
<td>523.6</td>
<td>0.0147</td>
</tr>
<tr>
<td>$128^3$</td>
<td>Spectral</td>
<td>1210.8</td>
<td>0.0042</td>
</tr>
<tr>
<td></td>
<td>MG-FGMRES</td>
<td>4346.1</td>
<td>0.0037</td>
</tr>
<tr>
<td>$256^3$</td>
<td>Spectral</td>
<td>15267.7</td>
<td>0.0011</td>
</tr>
<tr>
<td></td>
<td>MG-FGMRES</td>
<td>60302.9</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

Table 2.3: Comparison of results using spectral and iterative (MG-FGMRES) Poisson solvers for flow around a stationary sphere (Section 2.5.1). Given is the maximum $L_\infty$ norm and CPU time to complete 10000 timesteps for three different Eulerian resolutions.

error with the iterative Poisson solver is slightly less than that obtained with the spectral solver, although both are of the same order. With regard to computational time, the spectral Poisson solver is roughly four times faster for the cases considered, thus offering a significant speed improvement over the iterative solver. The second order accuracy as in Figure 2.7(C) is also verified for this implementation. Figure 2.23 provides additional qualitative comparisons between the two approaches.

One benefit to using an iterative solver solver with the present method is the size of the linear system can be reduced by restructuring the system so as to not include any solid nodes, which was done with the present implementation. In contrast, with the spectral Poisson solver, all nodes (i.e. fluid and solid) must be included in the linear system. In spite of this, for the iterative method implemented here for the problems considered, the spectral Poisson solver was faster. Modifications to the iterative method, including different types of preconditioning, or different means of parallelization (OpenMP is used here with 16 cores), could potentially speed up the routines, but this was not investigated here. It is noted, however, that the iterative solver was tested with an ILU preconditioner, but this multi-grid preconditioner was observed to be orders of magnitude faster. Furthermore, it was also tested without any preconditioning, but this was found to be even slower than the ILU preconditioner.

With the implementation validated, the next section investigates fluid leakage, which is the main purpose here.
Figure 2.23: Qualitative comparisons between results with the spectral and iterative Poisson solvers. (A,B) Pressure contours on an X-Y plane through the sphere center. (C,D) Rotated views of v-velocity component contours on an X-Y plane through the sphere center. For each quantity plotted, (A,C) gives the result with the spectral solver, and (B,D) gives the result with the iterative solver.

2.7.2 Solid-constraint method for reduced fluid leakage

Given the increase in computational time associated with the iterative Poisson solver, a novel alternate approach is first described here to enforce the no-penetration condition. This approach circumvents modifying the structure of the linear system and thus permits the use of the fast, spectral Poisson solver. Following this, flow leakage comparisons are made between the different approaches.
The idea behind this alternate approach is that with the spectral solver, the values of the intermediate velocity (i.e. \( u^*_i \) in Eq. 2.21) within the solid domain are actually used when solving the Poisson equation. In contrast, with the iterative solver the values at the solid nodes will not come into play due to the way the linear system is restructured by the GN constraints. A generic schematic depicting the different types of nodes comprising the computational domain, namely the fluid, ghost, and solid nodes (or FNs, GNs, and SNs, respectively), are provided in Figure 2.24(A). As shown, the ghost and solid nodes comprise the solid domain, and the fluid nodes comprise the fluid domain. With the GNIBM as described in Section 2.4, Eq. 2.28 are enforced at the GNs and the flow develops in the fluid domain. The flow also develops, however, within the domain represented by the SNs, although nothing is done with this solution. The basic idea here thus involves specifying constraints on not just the GNs, but the SNs as well.

By allowing the flow to develop within the solid domain, this potentially creates conditions within this domain that are conducive to fluid leaking through the immersed surface. So the idea is then to first, ensure that if any leakage does occur, it is negligible, and second, to ensure that any flow developing in the solid domain is consistent throughout the
solid domain, regardless of the geometry. A natural first choice is to just constrain the physical velocity to be zero at all SNs by imposing the proper values on $u^*_i$ when solving Eq. 2.20. This would prevent any flow from developing in the solid domain, and essentially impose conditions there that are truly ‘solid’. When tested, however, this was observed to be severely unstable numerically. These instabilities occurred right at the interface between the GNs and the SNs, due to the differences between the constraints enforced at these different types of nodes that are next to one another. This instability was remedied by allowing the flow to develop within a thin region beyond the GNs into the solid domain, and then constraining the velocity to be zero at all other SNs not in this region. With this, the solid domain is broken into ‘primary’ solid nodes, where the velocity is constrained to be zero, and ‘secondary’ solid nodes where the flow is allowed to develop. A schematic depicting this is shown in Figure 2.24(B). In the numerical experiments performed in testing this, various thicknesses of this thin region were utilized. It was found that a thickness of two grid points was optimal to minimize any fluid leakage and retain the numerical stability. This is represented in Figure 2.24(B).

All geometries in the previous sections were used were used for these tests, as well as those presented below.

(a) Flow through a tube with a constriction

The fluid leakage is first tested through a geometry of modest complexity, namely a tube with a constriction. The geometry is shown in Figure 2.25(A), and the flow is driven by an applied pressure difference between the inlet and outlet faces in the x-direction. Simulations are performed using each of the three Poisson solvers, referred to here as MG-FGMRES, non-constrained spectral, and solid-constraint spectral. The tube length is $5R$, where $R$ is the radius of the tube, the length of the constricted region is $1.4R$, and the minimum radius within this region is $0.3R$. The Eulerian resolution is such that approximately 35 grid points are considered across $R$, and the boundaries of the constricted tube geometry are represented within the GNIBM by an analytical function. Over the straight portion of the tube this is simply the equation of a straight tube, while over the constriction region
the following function is used:

\[ r = R - b(\cos(kx) + 1) \]  \hspace{1cm} (2.71)

where \( r \) is the radius within the constriction region, and \( b \) and \( k \) are selected to give the aforementioned minimum radius and a constriction region that smoothly merges with the straight portion of the vessel.

Simulations are performed using each of the three Poisson solvers, and run until a steady-state is reached. The total fluid leakage is then determined by evaluating the volume flux through the surface, \( Q_{surf} \). This is done by calculating the velocity normal to the surface at each BI point by interpolating from the steady state velocity field, and summing over all points:

\[ Q_{surf} = \sum_{k=1}^{N} u \cdot n \, dA \]  \hspace{1cm} (2.72)

where \( N \) is the total number of BI points, \( u \) is the interpolated velocity vector at each BI point, \( n \) is the outward normal vector to the surface at the BI point, and \( dA \) is the elemental area. Also calculated is the average fluid leakage per BI point, determined as \( \bar{Q}_{surf} = Q_{surf}/N \). Both of these values are given in Table 2.4 as computed from each of the simulations, as well as the CPU time required to complete 5000 timesteps. As can be seen, while the leakages are very small for each case, they are largest for the non-constrained spectral solver and smallest for the MG-FGMRES solver. Furthermore it is shown that using the solid-constraint method with the spectral solver reduces the leakage to be nearly that of the iterative solver. With regard to the CPU time, the spectral solvers are roughly six times faster than the iterative one. The solid-constraint solver offers a slight improvement over the non-constrained one because there are less operations required to enforce a node to be zero than to solve the fluid flow equations on it.

To further investigate the differences between each of the three Poisson solvers, Figure 2.25 provides additional qualitative results. Streamlines through the constriction as well as contours of the velocity magnitude are shown in Figure 2.25(B), on a plane through the tube centerline. Negligible differences were observed between the cases when considering the results in this manner. Since the leakages were, overall, very small, differences did not manifest prominently in the velocity field. Differences in the \( \phi \) field, however, were more
Figure 2.25: Flow through a tube with a constriction. (A) Rotated view of geometry. (B) X-Y plane view of velocity magnitude contours on a plane through the vessel centerline, including streamlines. The flow direction is from left to right. (C) Contours of the $\phi$ field in arbitrary units on the same plane as in (B). (D-F) Zoomed in view showing $\phi$ contours within the boxed region denoted in (C), using each of the three Poisson solvers. (D) gives the result using MG-FGMRES, (E) gives the result for non-constrained spectral, and (F) gives the result for solid-constraint spectral. Contours are re-scaled to better illustrate the variations, with values cut-off below 5.0 in the arbitrary scale used.

<table>
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<tr>
<th>Poisson Solver</th>
<th>CPU Time (seconds)</th>
<th>$Q_{surf}$</th>
<th>$\bar{Q}_{surf}$</th>
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</thead>
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<tr>
<td>Non-Constrained Spectral</td>
<td>294</td>
<td>$1.2 \times 10^{-6}$</td>
<td>$3.9 \times 10^{-11}$</td>
</tr>
<tr>
<td>MG-FGMRES</td>
<td>1736</td>
<td>$1.3 \times 10^{-9}$</td>
<td>$4.2 \times 10^{-14}$</td>
</tr>
<tr>
<td>Solid-Constraint Spectral</td>
<td>273</td>
<td>$1.1 \times 10^{-8}$</td>
<td>$3.5 \times 10^{-13}$</td>
</tr>
</tbody>
</table>

Table 2.4: Comparison of fluid leakage and CPU times between each Poisson solver for flow through a tube with a constriction. Times are based on that required to complete 5000 timesteps, $Q_{surf}$ gives the total leakage as a fraction of the inlet flow, and $\bar{Q}_{surf}$ gives the average leakage per BI point.

apparent, and this is shown in Figures 2.25(C-F). Figure C provides $\phi$ contours on the same plane as in Figure B for the MG-FGMRES case. A zoomed-in view of the field within the denoted region is presented in Figure D, along with the results from the non-constrained spectral case (Figure E) and solid-constraint spectral case (Figure F). To highlight the
differences in results, the contours are re-scaled from that in Figure C, with values cut-off below 5.0 in the arbitrary scale used.

The smoothness of the $\phi$ field in (D) as attained with the MG-FGMRES solver is noted, along with the behavior near the immersed surface (black line). For the result with the non-constrained spectral solver in Figure E, a notable jaggedness appears in the contours, and the behavior near the wall is such that the value steeply drops. Figure F shows that by using the solid-constraint spectral solver, the contours very closely resemble that attained with the MG-FGMRES solver shown in Figure D. In spite of these differences observed in the $\phi$ field, the effect on the velocity field, and thus the fluid leakage, was not significant. It will be shown in the next section, however, that when considering highly complex geometries, these considerations become important, and the fluid leakage can be significant if appropriate measures are not taken.

(b) Flow through a complex microvascular network

With highly complex geometries, the fluid leakage through the immersed rigid surfaces can become significant. To demonstrate this, flow through a complex microvascular network is considered in this section using both the non-constrained and solid-constraint spectral approaches to solving Eq. 2.21. The network geometry used for the simulations here is given in Figure 2.26, and details on the construction, design, flow conditions, etc. can be found later in Chapter 3. This is one of the networks that is used to later study RBC behavior in in vivo-like geometries (Chapters 3-6).

Figure 2.26(A) provides an X-Z plane view of the network through which flow is driven. There is one main inlet (lower left) and outlet (upper right), and pressure is applied at the inlet and outlet faces to drive the flow. The black arrows give the flow direction, and each simulation is run until a steady state is reached. Figure 2.26(B) provides a rotated view depicting the bounds of the computational domain (rectangular box) into which this complex geometry is immersed. In each of these figures the red vessels enclose the fluid domain, and the region between this and the bounds of the computational domain is the solid domain.
Figure 2.26: Simulation geometry for flow through a complex microvascular network. (A) X-Z plane view of the geometry. The red vessel walls enclose the fluid domain, the black arrows give the flow direction and identify the main inlet and outlet vessels, and the grey space around the vessels gives the solid domain. (B) Rotated view of geometry depicting the computational domain (rectangular box) into which the network is immersed.

First considered is the simulation using the solid-constraint spectral solver, and results are given in Figure 2.27. Contours of the velocity magnitude are shown in Figure 2.27(A) on a plane through the centerline of the geometry, including both the fluid and solid domain regions. Due to the enforced solid constraint, velocities are zero within the solid domain (i.e. constant dark blue) and non-zero elsewhere. Figure 2.27(B) provides a zoomed-in view of the denoted region in Figure A, and shows both contours of the velocity magnitude as well as streamlines. The streamlines nicely follow the general direction of the vessels, even ones in close proximity to the vessel walls. Figure 2.27(C) provides contours of $\phi$ in both the fluid and solid domains for a portion of the region in Figure B. The black lines denote the vessel walls, and the blue arrows give the flow direction as well as denote the fluid domain. As can be seen, within the fluid domain the contours show $\phi$ as constant over cross sections, and decreasing downstream along the vessel lengths. Constant contour levels can be seen to extend out normal from the vessel surface and into the solid domain, and form the patterns shown. These results are representative of that observed in other areas of the network, and provide a measure of the degree to which the solid-constraint enforces the no-penetration condition at the boundaries.
Figure 2.27: Simulation results using the solid-constraint Spectral solver. (A) Contours of velocity magnitude on an X-Z plane through the network centerline. Contours are included for both the fluid and solid domains, the latter of which is given by the solid dark blue regions, indicative of the zero velocity there. (B) Zoomed-in view of the denoted region in (A), also showing streamlines. (C) Pressure contours of the denoted region in (B), including both the fluid and solid domain. The black arrow at the top identifies the corresponding solid region in (B), the black lines denote the vessel walls, and the blue arrows give the flow direction.

With significantly complex geometries such as the network considered here, what has been observed in the numerical experiments performed for the present work is that significant flows can develop within the solid region when using the Spectral solver without enforcing the solid constraints. For the microvascular network geometry, velocity magnitude contours are given in Figure 2.28. These are analogous to Figures 2.27(A,B), except here based on the velocity field as computed with the non-constrained spectral solver. As is evident in Figure 2.28(A), significant flows develop within the solid regions. Figure 2.28(B) provides a zoomed-in view of the same streamlines as seeded in Figure 2.27(B), and it is evident from this that significant leakage occurs. The computational boundary coincides
with the left edge of Figure 2.28(B), and fluid enters the computational domain with a relatively large velocity and leaks into the vessels shown. Fluid leakage from vessel to vessel via the solid domain is also evident in this figure. As shown in Figure 2.26, the solid domain crosses the computational domain boundary at all areas except the main fluid inlet and outlet faces. As mentioned earlier, flow rates across the computational domain boundaries are conserved to machine epsilon. When significant flows develop in the solid region, this can create conditions favorable to fluid leaking across the immersed rigid boundaries and in-to or out-of the solid domain, as occurs here.

![Figure 2.28](image)

**Figure 2.28**: Simulation results using the non-constrained Spectral solver, analogous to that presented in Figure 2.27(A,B). (A) Velocity magnitude contours generally show the significant flows that develop within various regions of the solid domain. (B) Zoomed-in view of the denoted region, with the computational domain boundary on the left-most side. Streamlines are shown as seeded in 2.27(B), which here flow through the immersed surfaces and are indicative of significant leakage occurring.

The overall fluid leakage for the simulation with the non-constrained spectral solver was such that the flow rate at the main exit vessel was approximately 53% greater than at the main inlet. This is compared with a flow rate difference of 0.064% between the same vessels as computed for the simulation that used the solid-constraint spectral solver. As the flow traverses the network, any fluid that crosses the immersed rigid surfaces does so by going either in-to or out-of the fluid domain. The total leakage thus represents the cumulative effect of this. For the non-constrained spectral solver, as indicated in Figure 2.28(B), any leakage will then in turn move throughout solid domain. In contrast, the negligible leakage
with the solid-constraint spectral solver is essentially confined to the thin region in the solid domain bordering the vessel walls.

These results show that use of the solid-constraint method provides a direct measure of imposing the no-penetration condition at immersed rigid surfaces. It maintains fluid leakage at a negligible level with highly complex geometries, and does not require modifying the linear system to impose the \( \mathbf{n} \cdot \nabla \phi = 0 \) condition. As such, the spectral-based approach can be used, which provides a fast and efficient means of solving Eq. 2.21.

As mentioned, the basic idea behind the solid-constraint is to prevent any flow from developing within the solid region, thereby forcing all fluid to remain within the fluid domain. It is reiterated that simply enforcing all solid nodes to a zero velocity does not work due to numerical instability, and the key to making this work is to allow flow to develop within a thin region of SNs adjacent to the GNs. There is a velocity specified at each GN in accordance with the method for the no-slip condition, but in general the magnitude of the value is relatively small, and the direction is typically perpendicular to the surface normal. The velocities allowed to develop at the secondary SNs are then such that velocity field gradually decreases from that of the GN to the zero value specified at the primary SN. This mitigates the numerical instability, and reduces any fluid leakage across the immersed rigid surfaces to negligible levels.

### 2.8 Additional discussion and conclusions

The present methodology provides a novel means of simulating both deformable and rigid cells flowing within arbitrarily complex geometries. It seamlessly integrates different modeling components dealing with rigid non-moving boundaries, rigid moving boundaries, and highly deformable interfaces governed by complex nonlinear elasticity. In addition, multiple fluids with different viscosity can be considered. A finite-element method is used to deal with the deforming interfaces, and the coupling between the fluid flow and interface deformation is obtained via the continuous-forcing IBM. A sharp-interface ghost-node IBM is used to treat the vascular walls and moving rigid bodies. A novel technique to couple
the rigid body dynamics with the fluid flow was also presented. Additionally, a novel technique to ensure fluid leakage remains negligible with highly complex rigid boundaries was developed.

A series of validation studies was presented to establish the accuracy of the methodology against analytical theory, experimental data, and previous numerical results. The overall goal of these was to systematically test the ability of the methodology to accurately capture the wide range of phenomena commonly encountered in the complex biological flows considered. As such, each case was studied with a specific purpose in mind, as summarized in Table 2.1. The accuracy of the rigid interface methodology was first verified by modeling a rigid stationary sphere in a shear flow. This case was also used to establish a general mesh resolution criteria for rigid interfaces. The accuracy of the moving rigid interface methodology was then established under a wide range of scenarios by considering four classical problems. The accuracy of the methodology for simulations involving both rigid and deformable interfaces was then studied. A red blood cell aspirated into a micropipette was first modeled, and results were compared with experimental data. An excellent agreement between the two was observed, demonstrating the ability to resolve the close interaction of a rigid boundary with a deforming interface under extreme deformation of a cell. Multiple deformable RBCs flowing through a bifurcating channel were then simulated. A good agreement was shown with experimental data thus demonstrating the ability of the methodology for high hematocrit flows. Lastly a simulation previously performed using an alternate numerical method in which a capsule flows through a rectangular constriction was recreated. It was shown that the present method is able to capture the transient cell dynamics with the same degree of accuracy.

The method has been shown to be highly versatile and able to model very complex geometries, as evident from the extensive list of demonstrations. Each demonstration case had specific objectives that served to highlight different features of the methodology, as outlined in Table 2.2. RBCs flowing in a microvascular network were simulated as a demonstration of the ability to model physiologically realistic microvascular networks with highly deformable cells. RBCs and platelets interacting in microvascular network flow were also simulated, demonstrating the ability to handle both rigid and deformable cells flowing in
such complex geometries. Going beyond microvascular flows, the ability of the methodology to be extended to complex microfluidic devices handling diverse types of cells has been shown. These demonstrations collectively established the versatility of the numerical tool to address a diverse range of problems.

With each of these demonstrations it was shown that the methodology can predict several complex microhemodynamic phenomena observed in vascular networks and microfluidic devices. These included the Zweifach-Fung effect, platelet margination, and deformability-and size-based cell separation. It is noted that for each case it is possible to conduct an extensive hemodynamic study, however the purpose of Section 2.6 was just to demonstrate the wide range of potential the present methodology offers. Detailed quantitative investigations into a number of hemo- and hydro-dynamic phenomena that arise when considering cellular-scale blood flow in complex microvascular networks are presented in Chapters 3 - 6.

As the validation and demonstration cases show, a major advantage of the current methodology is that it is not limited to any specific geometry; as such, vessels with multiple bifurcations and mergers, as well as tri- and multi-furcations, can be easily modeled. The ability to model fully three-dimensional cellular-scale blood flow in such arbitrary and highly complex geometry while simultaneously resolving the details of the deformation and dynamics of every cell represents the forefront of the current state-of-the-art. As such, it provides a means of performing simulations that are the first of their kind. The present methodology is robust and versatile, and has the potential to scale up to extremely large microvascular networks at organ levels.

While the approach taken is based on immersed boundary methods, there are various other approaches that may be considered for simulating the types of interfaces modeled here. In the context of finite-difference based methods, perhaps the most direct approach is to use a boundary-fitted computational mesh to discretize the flow domain. Benefits of this approach with regard to accuracy are straightforward. All boundaries align with the computational grid, and thus the accuracy of the method is simply in accordance with the discretization scheme. Modeling arbitrarily complex boundaries, however, can significantly hinder the performance and limit the overall robustness, especially when considering moving
complex boundaries. The benefits of using IBMs, or others, in lieu of this approach have been well documented, and owe mainly to the significant increase in computational efficiency outweighing decreases in accuracy, if any.

Common alternatives to IBMs for modeling interfaces such as those considered here are boundary integral methods, stochastic particle methods, and Lattice Boltzmann methods. A detailed review on each of these methods for modeling blood flow was performed in [65], and the salient features on each have been used here in the subsequent discussions. Boundary integral methods have been shown to be highly efficient and accurate in simulating multi-phase flows, although they are strictly limited to linear flows and can present difficulties with regard to specifying boundary conditions. While the level of accuracy achieved using these approaches is typically higher than that of IBMs, it is unclear if a method of this type can be efficiently extended to model the large-scale highly complex three-dimensional geometries considered here. Most studies using boundary integral methods are limited to simple geometries.

Dissipative particle dynamics (DPD) provides the most common basis for stochastic particle methods. It has been used to simulate blood cells within various types of geometries [112, 55, 209], and has been shown to be highly efficient. However, the means by which no-slip conditions are achieved at solid boundaries requires attention with DPD, as particle repulsions generally cannot achieve this alone. Thus extra measures must be taken in order to accurately impose no-slip conditions. The order of accuracy of this method for commonly used Verlet-type integrators tends to be first-order [109], while generally speaking the error order is unclear on account of the random and dissipative forces in the integration algorithm [78]. In addition, both the accuracy of the flow solver and the smoothness of resolution of the deformable cell interfaces are of a lower order than with the IBM approach. Also, most studies in the literature offer little information on the implementation of multiple fluids of different viscosity with this or other particle-based methods. In contrast, implementing multiple fluids of different viscosity is straightforward using a front-tracking method, as is evident from many works in the literature using this approach [111, 47, 203, 187, 40]. The degree of geometric complexity that can be achieved with DPD seems to be on the same order as with the IBM approach presented here.
Lattice Boltzmann (LB) methods involve a particle-based, meso-scale approach and are well suited to modeling complex geometries, in addition to being efficiently parallelized. Simulation of complex boundaries using LB methods is typically done using either IBMs or other approaches, and are typically simulated to first-order accuracy. As the theoretical basis on which these methods are founded naturally results in compressible fluids being modeled, care must be taken in order to simulate incompressible flows approaching zero inertia. On the other hand, with a finite-volume based IBM approach such as that presented here, both zero and finite inertia flows can be simulated with ease.

Evidently, the methodology developed offers an efficient, and often better, alternative to these other commonly used methods. It can be employed in a relatively straightforward manner, and has been shown in this work to be both versatile and accurate through the extensive validation and demonstration cases. It provides a viable means of bridging the gap between resolving the sharp features of extreme cell deformation and modeling flows through large-scale complex geometries.
Chapter 3

Simulation of RBCs in 3D microvascular networks: analysis of some general hemo- and hydro-dynamics

3.1 Overview

Using the methodology detailed in Chapter 2, this chapter presents the 3D direct numerical simulation and analysis of RBCs flowing in physiologically realistic microvascular networks. Three different vascular networks are designed following \textit{in vivo} images and data, and are comprised of bifurcating, merging, and winding vessels. As discussed in Chapter 2, the numerical model resolves the large deformation and dynamics of each individual red blood cell flowing through the networks with high fidelity, while simultaneously retaining the highly complex geometric details of the vascular architecture.

This chapter studies some general hemo-and hydro-dynamics that arise in the simulations. After describing the details associated with the design of the networks, quantitative comparisons are made with \textit{in vivo} data, and predicted RBC shapes are compared with experimental images. Following this, the subsequent sections detail the quantitative exploration of the cellular-scale dynamics that naturally arise in a complex network, and their connection to observed hemo- and hydro-dynamical behavior. In so doing, several novel and unusual phenomena with potentially significant physiological consequences are predicted. These anomalies are absent in blood flow in simple geometries, and are the direct result of the interaction between the discrete cells and the complex network architecture. This underscores the importance of utilizing realistic physiological geometries in conjunction with cellular-scale microphysics to better understand microvascular hemodynamics.
3.2 Simulation details

Microvascular networks have been constructed in silico following published in vivo images [29, 208, 17] and data [115, 71]. Three different networks are considered, and are shown in Figure 3.1. As can be seen, all networks include bifurcating, merging, and winding vessels as observed in vivo. Each network has one main inlet and outlet, and is composed of arterioles, capillaries, and venules. Considering all three networks, there are in total 138 vessels and 45 bifurcations. The vessel diameters range from 6 to 24 µm, and the lengths range from 25 to 165 µm. The average overall path length from inlet to outlet ranges from 500 to 620 µm, and the overall volumes of the regions simulated are \( \sim 1.6 \times 10^6 \mu m^3 \). The average diameter and length of the capillary vessels are 6 and 68 µm, and the average diameter and length of all vessels are 9 and 65 µm, in agreement with in vivo data [71, 167, 29]. In general, the network design utilizes the in vivo data in conjunction with Horton’s law, which describes the relationships between vessel diameters at bifurcations and mergers. This law is defined as:

\[
\frac{D_n}{D_{n-1}} = 10^b
\]  

(3.1)

and a topology following this law is fractal in nature [29]. The empirical constant \( b \) is taken as 0.1582, \( D \) is the vessel diameter, and the subscript \( n \) corresponds to the vessel order in the Strahler ordering system [29]. For \( b = 0.1582 \) the diameter ratio is approximately 1.43, however no distinction is made between the arterial and venous sides of the network in [29]. Since vessels of order \( n \) on the venous side are usually larger in diameter than their counterparts on the arterial side, this is taken into account by using:

\[
\frac{D_n}{D_{n-1}} \bigg|_{arterial} \approx 1.2 \quad \frac{D_n}{D_{n-1}} \bigg|_{venous} \approx 1.5
\]  

(3.2)

Within the Strahler ordering system the numbering begins at the capillaries, which are taken to be order 0. As the hierarchy proceeds upstream and downstream of these vessels, the order number increases to \( n+1 \) when two vessels of the same order connect with each other. In many instances, connecting vessels are of the same order but have different diameters. In such cases an averaging is used in conjunction with the above diameter ratios to determine the appropriate vessel size. A similar approach is taken when connecting vessels are of a different order.
Figure 3.1: Snapshots from the direct numerical simulations of RBCs flowing through microvascular networks. Each of the three network geometries are shown in Figures A-C. Inlet and outlet vessels are marked by arrows giving the flow direction, and the scale bar (–) represents 10 μm.

In each network the hierarchical structure is such that three orders of the Strahler ordering scheme are spanned on both the arterial and venous sides. At the capillary level,
across each of these topologies the number of upstream bifurcations ranges anywhere from 2 to 12. The vessels are nondeformable with circular areas, but they generally have variable cross sections along their length.

The network geometries are implemented following the procedure described in Section 2.4.2. They are constructed using a standard CAD software, and a triangulated mesh is then generated on the vessel surfaces using Gmsh [75]. The total number of RBCs in the three networks considered is \( \sim 1550 \). The hematocrit is initially maintained in the main feeding artery at \( \sim 30\% \), and the subsequent cell distribution throughout the networks naturally develops and evolves. Before simulation data are recorded for analysis, an initializing simulation is performed. RBCs are initially placed randomly throughout each network, and then they deform as they flow through each network. When they reach the outlet, they are re-directed to the network inlet via a shifted periodicity. During the initialization simulation, cells are repeatedly added to maintain the hematocrit in the main feeding artery at around 30\%. Once the network is filled with cells and a quasi-steady state is reached, simulation data are stored for analysis. The overall physical time during which data were stored is approximately 0.7s.

Simulations are performed in which flow is driven through the networks with either fixed pressure-boundary conditions or fixed flow-rate conditions. For pressure-boundary conditions, the overall pressure difference between the inlet and outlet is specified in accordance with published in vivo data as \((0.3 - 1.0) \text{ Pa}/\mu\text{m} \times (3 - 10) \times 10^3 \text{ cm H}_2\text{O}/\mu\text{m}) [71, 115]\). For flow-rate boundary conditions, the mean flow rate in the main feeding artery is specified as \((2 - 4.6) \times 10^{-13} \text{ m}^3/\text{s}\), also in agreement with in vivo data [71, 115]. In total, 12 simulations are performed resulting in \( \sim 550 \) time-averaged vessel measurements. Considering the number of RBCs passing through each of the networks over the course of the simulations, there are \( \sim 20,000 \) data points utilized for studying RBC behavior at vascular bifurcations.

Table 3.1 shows the observed range of average flow rates at the simulation boundaries when the pressure drop is specified, and conversely, the observed range of pressure drops between the simulation boundaries when the flow rate is specified. As can be seen, the flow rate specified in the second set of simulations is identical to the average flow rate that is observed in the first set of simulations for the midrange-specified pressure drop. Also,
the resulting pressure drop in the second set is similar to those specified in the first set of simulations. Thus, there is no significant difference in terms of average pressure drop or flow rate in the two sets of simulations. Furthermore, any observed trends, phenomena, or conclusions drawn, were the same regardless of the type of boundary conditions specified. The exact time-dependent quantities, however, are different in each case because of the stochastic nature of particulate flow.

<table>
<thead>
<tr>
<th>Specified $\Delta P'$ $Pa/\mu m$</th>
<th>Resulting $Q$ $(m^3/s) \times 10^{13}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Network A</td>
<td>0.340 3.426</td>
</tr>
<tr>
<td></td>
<td>0.450 4.627</td>
</tr>
<tr>
<td></td>
<td>0.663 7.278</td>
</tr>
<tr>
<td>Network B</td>
<td>0.528 2.073</td>
</tr>
<tr>
<td></td>
<td>0.696 2.839</td>
</tr>
<tr>
<td></td>
<td>1.018 4.131</td>
</tr>
<tr>
<td>Network C</td>
<td>0.525 1.469</td>
</tr>
<tr>
<td></td>
<td>0.698 2.055</td>
</tr>
<tr>
<td></td>
<td>1.018 3.344</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specified $Q$ $(m^3/s) \times 10^{13}$</th>
<th>Resulting $\Delta P'$ $Pa/\mu m$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Network A</td>
<td>4.627 0.429</td>
</tr>
<tr>
<td>Network B</td>
<td>2.839 0.712</td>
</tr>
<tr>
<td>Network C</td>
<td>2.055 0.777</td>
</tr>
</tbody>
</table>

Table 3.1: Information on the two different boundary condition types used in the simulations: specified pressure drop and resulting average flow rate, and specified flow rate and resulting average pressure drop between the simulation boundaries.

The RBCs are modeled following that presented in Section 2.3, with the shearing deformation and area dilation described following the strain energy function of Eq. 2.1. The surface of each cell is discretized using 5120 Delaunay triangles. Under healthy conditions, the viscosity of plasma is close to that of water, and the hemoglobin viscosity is approximately 5 times greater. This ratio is the relevant parameter input into the simulations, with the viscosities of each of these phases taken to be 0.0012 and 0.006 Pa s, respectively [70]. The shear elastic and bending moduli are taken to be $5 \times 10^{-6} N/m$ and $7 \times 10^{-19} J$, respectively. The higher bending modulus is used for numerical stability as it helps prevent mesh breakdown on the surface of the cells undergoing extreme deformation while squeezing through capillary bifurcations. The microvascular networks are modeled as rigid stationary
Figure 3.2: Schematic depicting various simulation components. 
(A) Microvascular network simulation. (B) Lagrangian mesh on which finite element computations are performed for RBC deformation (C) Mesh generated on the surface of a vascular network defining vessels walls when solving the governing fluid flow equations (D) Eulerian mesh (for one of the velocity components) on which the governing equations are solved. Eulerian mesh nodes are identified as Solid Nodes (SN), Ghost Nodes (GN), and Fluid Nodes (GN). Additional points utilized with the GNIBM are identified as Boundary Intercept (BI) and Image Points (IP).

Some limitations of the network model against actual physiological conditions may be noted. For example, the vessels in the networks are to be assumed non-deformable and circular in cross-section, which is usually not the case in vivo. Additionally, the presence of the endothelial surface layer is neglected, which has been shown to influence the blood flow in vivo [101]. Furthermore, the layout of each of the simulated networks is planar in nature. While there is a physiological basis for this, for example, networks found in muscles [6] or in
the retina [113], many in vivo networks have 3D topology. Data analysis and interpretation are, however, easier for the planar networks. Finally, this work does not consider leukocytes, which would likely have a considerable impact on the behavior. Since RBCs significantly out-number leukocytes in healthy blood [70], this work is thus representative of a period of time when leukocytes are not present in the part of the microvasculature of interest. Despite these limitations, the present DNS provides to-date the closest in silico model to actual in vivo geometry.

3.3 Results

Snapshots of the simulations for each of the networks are shown in Fig. 3.1. As can be seen, the virtual microvascular networks are highly complex in geometry and representative of realistic in vivo situations. Cell distributions naturally develop in the networks based on the architecture. Some vessels are observed to be filled with RBCs, whereas others have a reduced number of cells, as is the case in vivo. Extreme deformation and a wide range of RBC shapes are observed as they flow through the networks. In the smallest capillary vessels, cells are observed to assume elongated bullet/parachute and slipper shapes, and flow in a tight-filled, single-file manner. The shapes are never axisymmetric, due to the geometric effects. Two- and multi-file motions are observed in larger vessels. In the main feeding and collecting vessels, discoid shapes are often observed. Formation of cell-free regions near vascular walls, and plasma skimming at arterial bifurcations, are observed here. The predicted shapes of individual cells in capillary vessels agree well with experimentally observed shapes, and are compared in Section 3.3.2 below.

3.3.1 Comparison with in vivo data

Figure 3.3(A) provides a quantitative comparison of vascular flow resistance determined from the simulations against in vivo data [115] obtained in the mesentery of a cat. The simulation data reported is from all three networks with each of the considered boundary conditions. Data is time-averaged over ~0.7 s, during which time the transient patterns in flow properties in each of the network vessels are in a quasi-steady (cyclic) state. Each
simulation data point in the figure is the time-averaged data from one vessel, with the corresponding vessel diameter on the abscissa. The time-averaged flow resistance per unit length of a vessel is defined as \( R = \Delta P' / Q \), where \( \Delta P' \) and \( Q \) are the time-averaged pressure drop per unit length and flow rate, respectively, in each vessel. A good agreement between

Figure 3.3: (A) Comparison of predicted time-averaged vascular resistance \( R \) per unit length (red symbols (in \( Pa/(m^3/s)/\mu m \times 10^{-11} \)) against in vivo data (black circles) and fourth-order power law (line) fit of in vivo data [115]. (B and C) Time-averaged pressure drop per unit length \( \Delta P' \) (in \( Pa/\mu m \)) and hematocrit in different vessels across the networks.

the simulations and the in vivo data is noted. The resistance is maximum at the capillaries and decreases on both the arterial and venous sides with a fourth-order dependence on vessel diameter, as in a Poiseuille’s law relationship.

Figure 3.4 provides additional quantitative comparisons between results obtained from the simulations and the in vivo data of [115]. Specifically compared in this figure is \( \Delta P' \), wall shear stress (\( \tau_w \)), and blood viscosity (\( \mu \)). The wall shear stress and viscosity are determined in an averaged sense per vessel, as in [115]:

\[
\tau_w = \frac{\Delta P' \cdot D}{4} \tag{3.3}
\]
\[
\mu = \frac{\Delta P' \cdot D^2}{\bar{V}} \tag{3.4}
\]

where \( D \) is the vessel diameter and \( \bar{V} \) is the time-averaged bulk fluid velocity in the vessel. As is evident, these quantities also agree well with in vivo data.
Figure 3.4: Additional comparisons between simulation results (red, filled circles) and in vivo data (open black circles) from [115]. (A) $\Delta P'$, Pa/µm; (B) $\tau_w$, Pa; (C) $\mu$, cP

Comparisons are made with in vivo data to generally show that predictions from the in silico networks are quantitatively very similar to what has been observed in vivo. It is noted that in physiology the architecture of a network is organ-specific, and thus the simulated networks for this work are more of an average representation of a network structure or hierarchy. As such, the simulation results presented in the subsequent sections are not intended to be representative of what would be found only in the network of a particular organ. Rather, the conclusions and observations represent commonalities associated with general microvascular network topology.

A hallmark of microvascular blood flow is heterogeneity. Prior in vivo studies have reported wide variations of hemodynamic quantities across different vessels within a network [71, 115]. The simulation data reveal a similar heterogeneity. Figure 3.3(A) shows that
the flow resistance can vary by a factor of 4 in vessels of the same diameter within a network. Time-averaged pressure drop per vessel length is presented in Figure 3.3(B), which shows nearly an order-of-magnitude variation across capillaries of similar diameters, implying a high-degree of heterogeneity. Figure 3.3(C) presents the distribution of time-averaged hematocrit. A high degree of heterogeneity is also observed here, where \( H_t \) is seen to range from \( \sim 0.04 \) to 0.35 in the capillaries. This observation also qualitatively agrees with \textit{in vivo} studies reporting that whereas some capillary vessels are filled with cells, some are almost devoid of cells. Interestingly, it is also noted that the degree of heterogeneity decreases with increasing vessel diameter. This is expected, as it is shown later that the underlying mechanism of heterogeneity is the particulate nature of blood, which has a diminishing effect with increasing vessel diameter. A similar high degree of heterogeneity is also observed in the time-averaged wall shear stress, and blood viscosity, as predicted by the simulations and shown in Figure 3.4, as well as in the time-averaged flow rate as shown in Figure 3.5.

3.3.2 Comparison of predicted RBC shapes with experimental images

A wide variety of RBC shapes is observed in the simulations as the cells traverse the networks and undergo significant deformation. A few representative examples are provided in Figure

![Figure 3.5: Arterio-venous distribution of time-averaged flow rates, \( Q \), in \( m^3/sec \times 10^{13} \)]
3.6, along with images from the experimental work of [73]. As can be seen, various RBC shapes predicted by the simulations match well with those observed in the experiments, providing additional qualitative validation.

![Figure 3.6: Comparison of various observed RBC shapes in the simulations with the experimental images of [73]. For each comparison, the simulation image is on the right.](image_url)

### 3.3.3 Temporal heterogeneity

The heterogeneity discussed in prior *in vivo* studies and shown in Figures 3.3-3.5 from the simulations represents spatial heterogeneity, i.e., the data for each vessel is averaged over time. In addition to this spatial heterogeneity, the simulations reveal a temporal
heterogeneity. That is, hemodynamic quantities show a high degree of variation over time even within one vessel in a network. Variations of flow resistance and hematocrit over time are shown in Figure 3.7(A,B) for a specific vessel. As seen here, over time Ht varies from \( \sim 0.13 \) to 0.41, and R varies from \( \sim 650 \) to 3200 Pa/(m\(^3\)/s)/\( \mu \text{m} \times 10^{-11} \) (500-2400 mm Hg/(mm\(^3\)/s)/\( \mu \text{m} \)) in the specific vessel considered. Similar temporal fluctuations in pressure drop and flow rate are also observed, as shown Figure 3.8(A,B).

To quantify the degree of temporal heterogeneity, the amplitude of fluctuation is measured, defined as the difference between the maximum and minimum of flow quantities over time.
the entire simulation time. The amplitudes are then plotted scaled by the mean quantities for each vessel in the networks. Figure 3.7(C,D) shows distributions of the hematocrit amplitude $\Delta H_t$, and resistance amplitude $\Delta R$. As seen here, the amplitudes exhibit large variations within individual vessels of similar size. $\Delta H_t$ varies from $\sim 0.35$ to 5, implying that $H_t$ in a specific vessel at some instances is five times higher than the average value. Distribution of $\Delta R$ is even more dispersed as it varies from $\sim 0.35$ to $> 100$, implying that in a specific vessel, flow resistance at certain time instances can be more than 100 times the average value. Temporal heterogeneity is also observed in pressure drop and flow rate, and is given in Figure 3.8(C,D). Flow-rate and pressure-drop amplitudes are observed to be as high as 180 and 600%, respectively, of the average values. The magnitude of the time-dependent variable amplitudes is, therefore, significant. Such temporal heterogeneity could be more severe than the spatial heterogeneity when the figures in this section compared with their time-averaged counterparts in Section 3.3.1. Similar to the spatial heterogeneity, the temporal heterogeneity is maximum in the capillary vessels, and decreases with increasing vessel diameter. The temporal heterogeneity is entirely due to the particulate nature of the blood, which becomes more pronounced in smaller vessels. It would not occur in absence of the cells, and the flow would remain steady.

Note that temporal fluctuations in flow quantities are also present in long, straight vessels, but with significantly smaller amplitudes, often in the range of a few percentage of the mean. In contrast, temporal fluctuations observed in the network simulations exhibit amplitudes that are several factors, and often, orders higher than the mean. As shown later, such temporal fluctuations have severe consequences in pressure-flow and hematocrit-resistance correlations.

### 3.3.4 RBC jamming at vascular bifurcations

The origin of this significant temporal heterogeneity in the networks is found to be the dynamics of the cell suspension near vascular bifurcations. At all of the vascular bifurcations in the three networks considered, RBCs tend to linger for a while before eventually flowing into the daughter vessels. This is shown in Figure 3.9(A), with additional examples provided in Figure 3.10 for capillary bifurcations, as well as in Figure 3.11 for bifurcations associated
with larger sized vessels. Although lingering is observed at all bifurcations, it is most

pronounced at the capillary bifurcations. During such events, cells near the bifurcations significantly stretch and straddle around the entrance to both daughter vessels, causing incoming cells to pile up and partly block the entrance. Consequently, the flow rates in the daughter vessels are reduced. Lingering is a dominant event observed in the simulations. In extreme cases, the lingering is observed to be so severe that it can jam a bifurcation and nearly stop the flow in the affected branches. Figure 3.12 shows that upon such a severe event the flow rates in the daughter vessels nearly become zero.

Figure 3.9: (A) RBCs are observed to linger (or, jam) at capillary bifurcations. (B and C) The RBC residence time $\tau_r$ (dimensionless) and frequency of lingering $n_r$ at bifurcations.

Figure 3.10: Additional examples of RBC lingering occurring at capillary bifurcations. Arrows are used to show the lingering events
Figure 3.11: Examples of lingering events occurring at bifurcations associated with larger sized vessels. (A) mother vessel with 14 µm diameter and daughter vessels with 11.5 µm diameters; (B) mother vessel with 16 µm diameter and daughter vessels with 12 µm diameters.

To quantify the lingering phenomenon, the dimensionless residence time $\tau_r = t_r/t_0$ for each cell is computed, where $t_r$ is the time spent by an RBC lingering at a bifurcation and $t_0$ is the time taken by an RBC to pass through the bifurcation without lingering. Also computed is the frequency $n_r$ of lingering as the ratio of the number of cells lingering for an extended time to the total number of cells passing through a bifurcation over the entire simulation time. These quantities are plotted in Figure 3.9(B,C) as functions of arterial diameter. As seen here, on average the maximum $\tau_r$ varies between roughly 4 and 6 over the entire range of diameters considered. This means that at all vascular bifurcations cells can linger 4-6 times longer than the time it would take without lingering. Therefore, the lingering time is significant, and it occurs in all arterial bifurcations. Furthermore, the frequency of lingering is the highest in the capillary vessels and decreases with increasing vessel diameter. Thus, the lingering events are more frequent at the capillary bifurcations.

It is found that during a lingering event, the cells at the bifurcation can straddle the daughter vessels either symmetrically or asymmetrically (Figure 3.13). In many bifurcations, it is found that the cell lingering occurs in a periodic manner in which the cells straddle more near one daughter vessel at one time, but near the other daughter vessel at other times (Figure 3.13(B,C)). This is because when cells linger asymmetrically, the hematocrit is reduced in the branch that is partially blocked, but is increased in the other branch. As hematocrit builds up, cells start to straddle the second branch, freeing up the
first branch which was blocked before. This periodic change in asymmetric lingering favoring one branch or the other requires a continuous influx of cells in the mother vessel. If for any reason hematocrit in the mother vessel is significantly reduced, an asymmetric lingering favoring one daughter vessel can last much longer. Often times it is found that as an asymmetric lingering switches from one side to the other, a symmetric lingering can occur in between (Figure 3.13). It is further found that a symmetric blockage lasts for a longer time, whereas an asymmetric lingering occurs more frequently.

Experimental images of RBC lingering are provided in Figure 3.14, taken from the *in vivo* work of [20] at a frame rate of 3700 fps. These specifically show blood cells flowing through a capillary bifurcation in a microvascular network of a frog. The arrows provided give the flow direction, and significant RBC lingering at the bifurcation can be observed in each figure.

### 3.3.5 Cell lingering results in hematocrit reduction upstream and downstream

An immediate consequence of the cell lingering is a reduction of hematocrit in daughter vessels. The hematocrit reduction is manifested by formation of voids in the RBC train, i.e. vessel segments that are devoid of cells (see Figure 3.13(A-C)). For a symmetric lingering,
voids are formed in both daughter vessels, whereas for an asymmetric lingering void formation switches between one branch and the other depending upon which daughter vessel is temporarily blocked. During the periods of time when asymmetric lingering events are predominantly occurring, the flow rates between the two daughter branches tend to be imbalanced. Conversely, when symmetric lingering events are occurring, the flow rates tend to be balanced. Such cycling can be observed in the time-dependent flow rate ratios during
Figure 3.14: Experimental images of RBC lingering from the *in vivo* work of [20], based on a frame rate of 3700 fps. The arrows provided give the flow direction, and significant RBC lingering at the bifurcation can be observed in each figure. The numbers in these figures are identifiers used in [20], and are not relevant here.

Symmetric and asymmetric lingering events, as shown for two daughter branches in Figure 3.13(D).

Cell lingering at bifurcations not only reduces hematocrit in the daughter vessels, it can also reduce hematocrit in the mother vessel by forming voids. This rather unusual event is shown in Figure 3.13(E). Cell lingering at the specific bifurcation considered here increases the local pressure, as shown in Figure 3.13(F). Consequently, the pressure difference along the mother vessel decreases. Due to the reduced pressure gradient, RBCs from the main feeding arteriole cannot enter the mother vessel, which leads to the formation of a void.

RBC voids, therefore, are the footprints of cell lingering at bifurcations. The significant temporal heterogeneity as noted earlier is a direct consequence of cell lingering, or alternatively, void formation. In general, voids are present in many vessels throughout the networks (e.g. Figures 3.1, 3.10,3.11), but are not always the result of cell lingering at bifurcations. Another mechanism of void formation is depicted in Figure 3.13(G). This mechanism is observed when two capillary vessels emanate from the same side of a larger arteriole. If cells are drawn in to the first capillary, an enhanced cell-free layer is formed along that side of the arteriole. If the distance between the two side branches is not large, the cell-free layer persists, resulting in the formation of a void in the second capillary.
The implications of cell lingering and void formation are significant, and are discussed next in terms of the relationships between different hydrodynamic quantities.

3.3.6 Negative pressure-flow correlation

First considered is the relationship between flow rate \( Q \) and pressure drop per unit length \( \Delta P' \) in each vessel in the networks. For a long, straight vessel, this relationship is expressed in terms of the well-known Poiseuille’s law as

\[
\Delta P' = R \cdot Q
\]

where \( R \) is the hydrodynamic resistance per unit length of the vessel. Although valid for long, straight vessels, this relationship is often used in analyzing \textit{in vivo} data, and also in lower-dimensional modeling of microvascular networks, as noted previously. Poiseuille’s law implies a positive correlation between pressure drop and flow rate, i.e., an increase in pressure drop results in an increase in flow rate, and vice versa.

To investigate if the simulations also yield positive pressure-flow correlations, the pressure drop-flow rate correlation coefficient \( C_{\Delta P'-Q} \) is computed, defined as

\[
C_{\Delta P'-Q} = \frac{\langle [\Delta P'(t) - \langle \Delta P' \rangle] \cdot [Q(t) - \langle Q \rangle] \rangle}{\sqrt{\langle [\Delta P'(t) - \langle \Delta P' \rangle]^2 \rangle \cdot \langle [Q(t) - \langle Q \rangle]^2 \rangle}}
\]

where \( \Delta P'(t) \) and \( Q(t) \) are the time-series pressure drop per unit length and flow rate data in each vessel, and \( \langle \rangle \) represents a time-averaged quantity. This correlation coefficient is presented in Figure 3.15(A). As seen in the figure, for most vessels \( C_{\Delta P'-Q} \) is positive, confirming the validity of Poiseuille’s law for capturing the general behavior of blood flow in microvessels. However, it can also be noted that for many vessels, the correlation coefficient is very weak. Most strikingly, for several vessels the coefficient is negative. This implies that, for these vessels, an increase in pressure drop is accompanied by a decrease in flow rate, which is in stark contrast to the positive pressure-flow correlation implied by Poiseuille’s law.

The origin of these negative correlations is the RBC lingering phenomenon at vascular bifurcations. Due to cell jamming at a bifurcation, the flow rate into the daughter vessels decreases, while at the same time the pressure at the entrance of the daughter vessel
increases, resulting in an increase in pressure drop. A time series of $\Delta P'(t)$ and $Q(t)$ for one such vessel is shown in Figure 3.15(B,C). It is readily seen here that large increases in $\Delta P'(t)$ at $\sim 0.16$, $0.3$, and $0.4$ s are accompanied by large drops in $Q(t)$. As is evident from the behavior in this vessel, the magnitudes of these temporary increases in $\Delta P'(t)$ and reductions in $Q(t)$ can be significant, and in vessels where such events occur frequently, a negative pressure-flow correlation results. As noted in Figure 3.15(A), large negative correlations are observed in the smallest diameter capillaries, because it is there that the jamming events are most severe. Large negative correlations are also observed in capillary vessels that directly discharge into venules of much larger diameter. Further insights into the negative $\Delta P' - Q$ correlation can be obtained by plotting $\Delta P'(t)$ versus $Q(t)$ and analyzing the nature of the data scatter. This is shown in Figure 3.15(D) for a specific vessel, and data points are obtained at $0.0005$ s intervals. The magnitude and frequency of the pressure drop and flow rate pulses causing the negative correlation are evident here. The lower-right portion of the figure showing a dense clustering of data points suggests that for most of the simulation, a positive correlation exists. On the other hand, the data points associated with the lingering events causing a negative correlation appear in the middle to upper-left of the figure. Whereas the range over which these data points appear is much greater in magnitude, indicating the severity of the lingering events, the reduced density of
the data cluster is indicative of the reduced frequency with which they occur. Additional data on \( \Delta P' - Q \) correlations from other representative vessels are given in Figure 3.16.

Figure 3.16: Additional examples of vessels with negative \( \Delta P' - Q \) correlations. For each vessel, the time series of \( Q \ (m^3/s \times 10^{13}) \) and \( \Delta P' \ (Pa/\mu m) \) are plotted on the left. Red arrows indicate temporal increases in \( \Delta P' \) corresponding to decreases in \( Q \). On the right, for each vessel, data scatter of \( Q(t) \) vs. \( \Delta P'(t) \) is provided. Red circles indicate data points corresponding to negative correlations, while the green circles indicate data points corresponding to positive correlations.
3.3.7 Temporal spikes in vascular resistance

An important consequence of the negative pressure-flow correlation is significant temporal spikes in vascular resistance. Regardless of the correlation behavior, as the flow rate through a vessel decreases the hydrodynamic resistance increases. However, as is clear from Eq. 3.5,

\[ \Delta P' \]

an increase in \( \Delta P' \) corresponding to a decrease in \( Q \) results in a much more significant increase in resistance than in a vessel with a positive \( \Delta P' - Q \) correlation. The time-dependent resistance \( R(t) \) of one vessel is shown in Figure 3.17, which shows spikes where the resistance increases by as much as 50 times the average value. The source of this significant increase in the vascular resistance is the cell lingering at bifurcations. Because of the cell lingering, the flow rate into the daughter vessel decreases whereas the pressure near the entrance to the daughter vessel increases. Consequently, the pressure drop in the daughter vessel increases. This, together with the decrease in flow rate, results in a large increase in resistance. Additional data is given in Figure 3.18.

3.3.8 Negative hematocrit-resistance correlation

In microvascular blood flow, and particulate suspension flows in general, the flow resistance increases with increasing hematocrit, or particulate volume fraction. Thus, in general, a positive correlation exists between the vascular resistance and hematocrit. Indeed, empirical
Figure 3.18: Additional examples of temporal spikes in hydrodynamic resistance as a consequence of the negative $\Delta P' - Q$ correlations. For each vessel, $R \ (Pa/(m^3/s)/\mu m \times 10^{-11})$ is plotted vs. time. Red arrows draw attention to examples of “spikes” caused by lingering.

relations exist based on *in vivo* and *in vitro* data relating these two quantities [154]. To see if the simulated networks yield a positive correlation between the time series of vascular resistance $R(t)$ and hematocrit $Ht(t)$, a hematocrit- resistance correlation coefficient $C_{R-Ht}$ is computed, defined in a similar manner to Eq. 3.6. This coefficient is plotted in Figure 3.19(A) for all vessels in the networks. As can be seen in this figure, on average most vessels yield a positive correlation, implying the usual trend that the vascular resistance increases with increasing hematocrit. However, in several vessels the correlation coefficient is either very small or, interestingly, is negative. This reveals a rather unusual phenomenon: in these vessels, resistance increases with decreasing hematocrit, or vice versa.
As with the $\Delta P' - Q$ correlation, the origin of the negative $R$–Ht correlation is the cell lingering at bifurcations. It was noted earlier that the lingering events result in hematocrit and flow-rate reductions in the daughter vessels. At the same time, pressure increases significantly around the bifurcation region, resulting in an increase in the pressure drop in the daughter vessels. Consequently, resistances in these vessels go up despite reductions in hematocrit, resulting in the negative correlation. Figure 3.19(B,C) shows one such example for a specific vessel. Here Ht(t) drops from 0.4 to 0.12 at $\sim$0.15-0.16 s, but $R(t)$ increases by nearly 50 times, resulting in a large negative correlation during this event. At other times, e.g. around 0.12, 0.14, and 0.18 s, Ht(t) increases to 0.4, but $R(t)$ does not show a significant jump, implying that at these times there is also not a strong positive correlation between the two quantities. Additional data on $R$–Ht correlations are given in Figure 3.20.

An interesting feature of the negative $R$–Ht correlation is that it takes on a different meaning based on the location of the vessel in the network hierarchy. For capillaries or other vessels on the arterial side (i.e. daughter branches or mother vessels), the negative correlation implies an increase in resistance accompanied by a decrease in hematocrit. That is, it occurs as a direct result of the RBC void formation due to lingering, as previously discussed. For vessels on the venous side however, a negative correlation results from an opposite trend: the resistance decreases with increasing hematocrit. This is observed to
Figure 3.20: Time series of resistance \( (Pa/\left( m^3/s/\mu m \right) \times 10^{-11}) \) and hematocrit in three different vessels to further illustrate the relationship between the two quantities. Red arrows denote times of negative correlations. Black arrows indicate times of weak positive correlations.

This latter behavior is observed in venules that are fed by two merging vessels each with distinctly different RBC patterns. For example, if one feeding vessel has a steady flow of RBCs and the other has a very intermittent flow, then this form of negative correlation occurs. A prominent cause of intermittent flow is the RBC voids generated due to lingering at the bifurcation feeding that vessel. As these voids migrate through the capillary and enter the venule into which it merges, this type of negative correlation results. The hydrodynamic explanation behind this is that in the outlet venule the hematocrit increases with an increase in \( Q \) and small change in \( \Delta P' \) (i.e. increase in Ht with decrease in R). The first event in
the development of this negative correlation is the formation of a void in the vessel feeding the venule. Following this, the void moves through the capillary and into the venule. Thus there is a volume flow-rate contribution to the discharge venule, without a hematocrit contribution. In the downstream vessel this ultimately results in an increase in volume flow rate with little change in $\Delta P'$. Figure 3.21 illustrates this process in a representative vessel.

![Figure 3.21](image)

Figure 3.21: (A) Time-dependent hematocrit and resistance in outlet venule (shown in B) as an indirect result of void formation in the upstream capillary bifurcation. (B) Void formed in capillary, eventually traverses the vessel and discharges into the outlet venule. Yellow arrows give the flow direction.

### 3.4 Discussion and conclusions

This chapter has presented, to our knowledge, the first 3D simulations studying blood flow in microvascular networks that capture both the cellular-scale microphysics and the highly complex physiological architecture. The number of vessels and bifurcations considered, and the network volumes simulated, as well as the amount of time-averaged data obtained are comparable to the typical volume of data utilized with in vivo analyses. Whereas time-averaged hemodynamic quantities agree quite well with published in vivo data, the simulations also elucidate cellular-scale events at small timescales that are usually not captured in experiments. To our knowledge, several novel and unexpected phenomena are observed
from such time-resolved simulations that are the result of the complex interactions between the RBCs and the vascular geometry.

Prior *in vivo* studies have shown that the distribution of hemodynamic quantities across a microvascular network is heterogeneous; quantities vary across different vessels of similar size (see e.g. [145, 45, 153]). The heterogeneity referred to in many of these studies is spatial heterogeneity, as quantities are averaged in time. Similar spatial heterogeneity is observed in the simulations. However, a more severe type of heterogeneity is revealed by the simulations when time dependent data is considered. It is shown that within the same vessel, hemodynamic quantities can greatly vary over time. Amplitudes of these temporal variations could be several factors and even orders of magnitude higher than the average values. This high degree of temporal heterogeneity is absent in blood flow in straight tubes where fluctuations in hemodynamic quantities occur solely due to cell-cell interactions.

In terms of quantifying heterogeneity in microvascular networks, various *in vivo* works have been performed in which velocities in capillaries were utilized. Considering all of the capillary vessels from each network simulation, the average velocity was \( \sim 0.7 \text{ mm/s} \). This is generally in agreement with the *in vivo* work of [101], who measured the average velocities in the neocortical capillaries of a rat to be in the range of \( 0.5 - 1.6 \text{ mm/s} \). Similar values have been reported in other *in vivo* works as well [115, 89, 161, 20]. With regard to the time-dependent velocities in all of the capillary vessels from the simulations, these were observed to fluctuate by as much as 2 mm/s, which is also in general agreement with the *in vivo* work of [186], who found velocities in capillaries to vary by as much as 1.6 mm/s. Various other *in vivo* studies on capillary blood flow have been performed [191, 141, 31] in which velocity ranges have been reported to be on the same order as that computed in the simulations.

It is shown that a major cause of the temporal heterogeneity is the piling-up (i.e. lingering) of RBCs near vessel bifurcations. RBC lingering has been qualitatively observed in prior *in vivo* works (e.g. [186, 149, 20]), as well as computational works [12]. Often, RBC lingering in the simulations here occurs in a cyclical manner, resulting in a quasi-periodic variation in hemodynamic quantities that is completely independent of the cardiac cycle. It is also shown here that lingering can reduce the hematocrit and flow rate not
just in the daughter vessels, but also in the mother vessels. Significant transient events are known to occur when considering the flow of whole blood [164, 72]. Periodic oscillations have been predicted in lower-dimensional theoretical modeling of microvascular networks [125, 45, 74], and observed both in vivo [93] and in microfluidic networks [60]. Specifically, the experimental studies in [93, 60] considered whole blood, and Forouzan [60] ascribed such oscillations to capillary blockage by leukocytes. In general, inactivated leukocytes are much stiffer than the RBCs and have a much larger transit time through a capillary vessel [15]. Thus, oscillations resulting from leukocyte blockage are likely to have a lower frequency than those resulting from RBC lingering. [60] also presented power spectra of time-series data, and found different maxima depending on the presence of RBCs only, or RBCs with leukocytes. The data here also shows the maxima to occur at the lower end of the frequency spectrum, with the magnitude of the total power fraction on the same order as in [60]. However, the range of frequencies in the two studies is significantly different. The simulations here represent 0.7 s of flow, during which ~1500 samples are taken. The range of frequencies obtained in the simulations is on the order of hundreds of Hz. Thus the fluctuations in flow quantities in the capillaries, such as flow rate, directly correspond to individual RBC behavior as each passes through an individual bifurcation. In contrast, in [60], measurements were made over a time interval of 5 min with a sampling frequency of 100 Hz, resulting in a frequency range of < 1 Hz. So the fluctuations are more associated with that of either bulk RBC motion, or events that occur over much longer times, such as capillary blockage by white blood cells. Nonetheless, RBC lingering serves as a major cause of microvascular heterogeneity, and is observed throughout the simulations at all bifurcations. Under extreme circumstances it may cause temporary flow stoppage, as also observed in the simulations.

An interesting question concerning the nature of heterogeneity is whether it is a stochastic phenomenon. On the one hand, in a more general sense, heterogeneity can be viewed as deterministic. First, the RBC lingering events were directly linked here to being the cause of the prominent temporal fluctuations. Second, the frequency of these events was linked to vessel size. So in this sense, the degree of heterogeneity is dictated by vessel size, and thus
it can be viewed as a deterministic phenomenon. On the other hand, the underlying mechanisms behind each of these time-dependent events that give rise to such heterogeneity do resemble that of a stochastic phenomenon. The nature of the process that led to the RBCs being in their particular configuration and deformed states that caused them to pile-up in a manner resulting in this temporary blockage can be viewed as stochastic in that all of the subsequent RBC interactions leading up to this are too complex to discern a pattern. Thus, heterogeneity can be considered a stochastic phenomenon if one considers the individual events that comprise the averages in quantities.

Vascular resistance is an important quantity that directly controls the amount of blood flow in specific vessels. Blood viscosity measured \textit{in vivo} was shown to be higher than that measured \textit{in vitro} using long, straight tubes [154, 153]. Accordingly, the \textit{in vitro} viscosity law would underpredict the network flow resistance. The higher \textit{in vivo} resistance is attributed in part to the presence of the glycocalyx layer on the surface of endothelial cells lining the blood vessels [150]. The present simulations provide another mechanism for increased flow resistance in a network. It is shown that the cell lingering causes large temporal spikes in vascular resistance. In some instances, magnitudes of these spikes are observed to be orders larger than the mean. This result is in agreement with a prior \textit{in vitro} study that reported an order-of-magnitude increase in pressure gradient at a bifurcation while flowing deformable disk-shaped particles [92]. The lingering mechanism, therefore, can account for the higher \textit{in vivo} flow resistance.

The cell lingering as observed here may have far-reaching consequences. It is shown that in several vessels it results in negative pressure-flow correlations, meaning that an increase in pressure drop is accompanied by a decrease in flow rate, in stark contrast to the positive pressure-flow correlation implied by Poiseuille’s law. In a tube flow, the pressure loss is synonymous with the shear stress and the flow rate is synonymous with the rate of strain. The negative correlation then implies that an increase in stress results in an increase in fluid viscosity. Thus, the blood behavior in these vessels resembles that of a shear-thickening fluid as opposed to a shear-thinning fluid.

An important point to note, however, is that the negative pressure-flow correlation happens only during the periods of time when the lingering events occur. Outside of these
events, conditions follow the positive pressure-flow correlation. What this suggests is that in vessels with negative correlation coefficients the average behavior is dominated by the pulses in flow properties resulting from RBC lingering. If the magnitude of these pulses and/or the frequency with which they occur is significant enough, then negative correlation coefficients result. Although events of this nature are observed in all capillary vessels, the severity of these events varies from vessel to vessel.

The pulses in flow properties caused by the cell lingering would also result in similar time-dependent behavior in the wall shear stress. It is known that both the average and time-dependent variations of the wall shear stress affect the endothelial cell response triggering diverse physiological events. The present findings suggest that in a microvascular network the nature of the time dependence may be dominated by the lingering-induced pulses in the shear stress. Negative correlations are also found between vascular resistance and hematocrit in several vessels, implying that the flow resistance increases in these vessels whereas hematocrit decreases. This also defies the principle of particulate suspension flow, and is a result of the lingering events that are severe in nature. It is observed here that the negative resistance-hematocrit correlation serves as a feedback mechanism; cells in the feeding artery can sense the lingering occurring in a downstream bifurcation via the fluid pressure, and be temporarily rerouted avoiding the mother vessel. This autoregulatory function provides a mechanism for efficient distribution of the cells across the network.

Cell lingering is observed to result in the formation of RBC voids in daughter and mother vessels. In prior studies using simple geometry, such as straight tubes, it has been observed that RBCs naturally form clusters and voids purely by cell-cell hydrodynamic interactions [121, 185]. In fact, in the present simulations voids are also observed to form as a result of cell-cell interactions just as they would in a straight tube. However, when this occurs, a positive resistance-hematocrit correlation is observed. The additional interaction with the vascular geometry is also required for a negative correlation to manifest.

As noted before, these anomalous results cannot occur in flow through straight tubes, and they underscore the importance of considering realistic physiological geometry and cellular interactions in modeling microvascular hemodynamics. These anomalies may become even more severe when whole blood is considered due to both RBC lingering and leukocyte...
blockage [164]. Additionally, diseased RBCs are known to have widely different rheological properties, which can also enhance such events. The magnitude and frequency of these events as observed in the present simulations warrants further study into the impact of them on important physiological phenomena, such as the adaptation mechanisms in the microvasculature at the cellular scale, oxygen and nutrient transport, and efficiency of drug delivery.

For this work RBC membrane properties have been utilized that are typical of an average, healthy cell. The effects of the cell properties on the network hemodynamics are not considered here. Specifically, the model does not consider membrane viscosity, which has been a subject of interest in some recent works [184, 148]. In prior works involving the present RBC model but including membrane viscosity [204, 41], it was shown that its usual value does not change the qualitative nature of the RBC deformation; rather, it changes the timescale of transient recovery. Thus, inclusion of membrane viscosity would not alter the occurrence of the phenomena that are observed in the present simulations, such as RBC jamming. Of course, in the extreme case of unusually large membrane viscosity, the jamming effect could be very severe.

For the present work the effect of the $b$ exponent used in Equation 3.1 in designing the microvascular networks was not investigated. The values of $b$ used are average, not extreme values within the physiological range. As such, the networks are representative of “average” physiological microvascular networks. To this end, the results presented in this chapter are related in a more general way to the topology of the network, rather than being related to the geometry of a very specific type of network. That is, the results are not intended to be representative of what would be found, for example, only in a capillary network in the kidney of a rat. Rather, the conclusions and observations represent commonalities associated with general microvascular network topology, and offer insight in a more general way into the hemodynamic mechanisms present in cellular-scale network blood flow. Different values of $b$ would result in networks with different diameter ratios between the mother and daughter branches of bifurcations. However, it is not believed that any of the conclusions or general observations would be different, barring drastic changes to this $b$ exponent representative of that beyond the physiological range, or of geometric
anomalies in microvascular architecture. In light of this, an investigation into the effects of $b$ could be of interest. However, a significant computational undertaking would be required to properly study this issue, which is beyond the scope of this thesis.
Chapter 4

Analysis of RBC partitioning at bifurcations in simulated microvascular networks

4.1 Overview

Partitioning of RBCs at vascular bifurcations has been studied over many decades using \textit{in vivo}, \textit{in vitro}, and theoretical models. These studies have shown that RBCs usually do not distribute to the daughter vessels with the same proportion as the blood flow. Such disproportionality occurs whereby the cell distribution fractions are either higher or lower than the flow fractions, and have been referred to as classical partitioning and reverse partitioning, respectively. This chapter presents a study of RBC partitioning based on the data generated from the microvascular network simulations described in Chapter 3. This provides, for the first time, a 3D DNS-based analysis of such partitioning as it arises with a cell suspension flowing through modeled vascular networks that are comprised of multiple bifurcations and have topological similarity to microvasculature \textit{in vivo}.

The focus of this chapter is on the detailed analysis of the RBC partitioning, based on the DNS data, as it develops naturally in successive bifurcations, and the underlying mechanisms. Results are provided in terms of both time-averaged and time-dependent behaviors of cell partitioning. Specific cellular-scale mechanisms that cause such time-dependent behaviors are identified, and it is shown how they cause the partitioning to oscillate between the diverse types over time. The major factors giving rise to these cellular mechanisms are also identified. By considering the cell behavior at bifurcations, this provides a direct, simulation-based analysis of how the sequential nature of bifurcations results in a positively or negatively skewed hematocrit profile and how this skewness leads to specific partitioning
types. Lastly, the classic plasma skimming and cell screening components causing the ob-
served disproportionate partitioning are quantified. Characteristic mechanisms associated
with each of these separate components are analyzed, and their significance is elucidated.

4.2 Results and discussion

4.2.1 RBC partitioning: time-averaged results

First, the time-averaged behavior of cell partitioning is considered. Figure 4.1(A) presents
the DNS data from all 45 bifurcations in the 12 simulations. Plotted here is the blood
volumetric flow rate ratio ($Q^*$) between a daughter vessel and the feeding vessel of each
bifurcation versus the erythrocyte flux ratio ($N^*$). These quantities are defined as

\[
Q^* = \frac{\int_d U \cdot dA}{\int_f U \cdot dA}
\]

\[
N^* = \frac{N_d(\tau)}{N_f(\tau)}
\]

where the subscripts $d$ and $f$ refer to a daughter vessel and feeding vessel, respectively, $U$ is
the fluid velocity in the respective vessel cross section, $N$ refers to the number of RBCs that
passed through the bifurcation via the denoted vessel over a time window $\Delta \tau$ centered on
time $\tau$, and the over-bar denotes the time-averaging. The choice of $\Delta \tau$ is further discussed
in Section 4.2.2.

As noted before, a hallmark of microcirculatory blood flow is the disproportionate par-
titioning of red blood cells at vascular bifurcations. If the RBCs were to distribute in
proportion to the blood flow, a linear relationship given by the straight line $N^* = Q^*$ would
result. It can be observed in Figure 4.1(A) that at most bifurcations in the simulations the
disproportionate partitioning of RBCs is predicted, i.e. $N^* \neq Q^*$ for $Q^* \neq 0.5$. This is in
general agreement with previous experimental findings.

One way that the disproportionality manifests is for the daughter vessel that receives
the greater fraction of the blood flow to receive an even greater fraction of the erythrocytes,
i.e. $N^* > Q^*$ for $Q^* > 0.5$. Similarly then, due to the conservation of respective flow rates,
the daughter branch that receives the lower fraction of the blood flow receives an even lower
fraction of the RBC flux, i.e. $N^* < Q^*$ for $Q^* < 0.5$. This type of behavior is termed here
as classical partitioning. It is evident from Figure 4.1(A) that most of the bifurcations in the simulations exhibit this type. However, an opposite trend is also observed at a number of bifurcations which manifest as either $N^* < Q^*$ if $Q^* > 0.5$ or $N^* > Q^*$ if $Q^* < 0.5$. At such bifurcations, the daughter branch that gets the higher fraction of the flow actually gets a lower fraction of the RBCs, or vice versa. This specific behavior, termed as reverse partitioning, has also been observed in prior studies (e.g., [163, 151, 170, 169]). To more clearly illustrate the two types of partitioning, $N^* - Q^*$ versus $Q^*$ is plotted in Figure
4.1(B). As evident in this figure, for the bifurcations exhibiting the classical partitioning, \( N^* - Q^* > 0 \) and for the reverse behavior \( N^* - Q^* < 0 \).

It may be noted that Figure 4.1 presents the aggregate of all data irrespective of different boundary conditions and network architectures used. The objective in this chapter is not to study the influence of different boundary conditions or network architectures. Indeed individual RBC deformation and trajectories would be different for different boundary conditions and networks. Given the presence of many bifurcations in any simulated network, and the presence of many RBCs, the state of an individual cell at any time can be viewed as stochastic in the sense that it cannot be directly correlated to the boundary conditions or network architectures. Thus, the values of \( Q^* \) and \( N^* \) at a specific bifurcation in such networks vary under different boundary conditions without any specific trend. Therefore, it is appropriate to consider the aggregate data as presented in Figure 4.1.

Furthermore, many of the aforementioned \emph{in vivo} studies reported results for individual bifurcations over a large range of \( Q^* \) (\( 0 < Q^* < 1 \)). In such studies, \( Q^* \) was typically varied at each bifurcation by modifying the geometry, for example, by occluding a daughter vessel. Such data generally led to sigmoidal-type relationships between \( N^* \) and \( Q^* \). The goal here is not to develop such relations. Rather, the intent is observe and study cell partitioning that naturally develops at each bifurcation in the simulated networks. That the simulation approach can predict the experimentally observed sigmoidal relationships has been demonstrated in Section 2.5.4.

### 4.2.2 Time-dependent RBC partitioning

To understand the means by which the time-averaged behaviors arise, the time-dependent results are now examined. The time-dependent flow ratio \( Q^*(t) \) and RBC flux ratio \( N^*(t) \) at each bifurcation are utilized to create plots analogous to Figure 4.1(A). Such plots would represent how cell partitioning evolves in a time-dependent manner at a specific bifurcation. Before presenting this data, a few words are warranted. Considering the RBC flux in a time-averaged sense is analogous to the RBCs being treated as a continuum. In reality, RBCs are of finite size and flow as discrete objects in small vessels. The actual time-dependent signal for RBC flux appears as a binary type signal that is not conducive to analysis. In order to
get a useful time-dependent flux, the binary signal must be averaged over an appropriately chosen and small time window such that the resulting fluctuation frequencies match that of the whole blood flow rate. On average, these windows were on the order of 50-100ms. This was selected based on the fact that the fluctuations in the whole blood flow rate are caused by the motion and deformation of the cells themselves. In testing this criteria, the time signal for \( N^*(t) \) derived from a specified window size was compared with visual observations of the simulations to ensure that what was being represented by this time signal was an accurate reflection of what was being observed with regard to time-dependent RBC motion.

In general, it was observed that small changes to the window size (i.e. \( \pm 20\text{ms} \)) usually did not result in fundamentally different behaviors.

Figure 4.2: Time-dependent cell partitioning. (A) \( N^*(t) \) versus \( Q^*(t) \) for two selected bifurcations. For one bifurcation, the average partitioning is the classical type (black symbols), while for the other it is the reverse type (red symbols). The straight line represents \( N^* = Q^* \). (B,C) Time sequence of \( N^*(t) \) (dotted line) and \( Q^*(t) \) (solid line) for the two bifurcations (black and red), respectively. The classical partitioning occurs when \( N^*(t) > Q^*(t) \) for \( Q^*(t) > 0.5 \) and vice versa, while the reverse type occurs when \( N^*(t) < Q^*(t) \) for \( Q^*(t) > 0.5 \) and vice versa. Time in (B,C) is scaled by \( \mu_0 a_0/Gs \), where \( \mu_0 \) is the plasma viscosity, \( a_0 \) is the undeformed RBC radius, and \( Gs \) is the membrane elastic modulus.

The time-dependent partitioning is shown in Figure 4.2(A) by plotting \( N^*(t) \) versus \( Q^*(t) \) for two selected bifurcations, and appears as a scatter plot. The time-averaged behavior in one bifurcation is of the classical type, while it is of the reverse type in the other. It is evident from this figure that while the time-averaged behavior could be either
of the classical or reverse types, the time-dependent data are scattered above and below
the straight line given by $N^*(t) = Q^*(t)$. This is also evident from the time sequences of
$Q^*(t)$ and $N^*(t)$ shown in Figures 4.2(B,C), where it can be seen that for each bifurcation
considered there are periods in time when $N^*(t) > Q^*(t)$ for $Q^*(t) > 0.5$ and $N^*(t) < Q^*(t)$
for $Q^*(t) > 0.5$ and vice versa. Therefore, in a time-dependent sense, the cell partitioning
at a given bifurcation cycles between the classical and reverse types. The time-averaged be-
behavior then depends on how frequently these time-dependent behaviors occur. The results
further suggest, and it has been verified from the simulation data, that the bifurcations
that exhibit a proportional cell partitioning in a time-averaged sense (i.e. $N^* = Q^*$) also
periodically oscillate between the classical and reverse type partitioning. The scatter plots
additionally reveal that for either bifurcation under consideration, multiple values of $N^*(t)$
occur for the same $Q^*(t)$, and, conversely, the same value of $N^*(t)$ may occur for multiple
values of $Q^*(t)$.

Most previous studies have considered cell partitioning in a time-averaged sense. The re-
sult in Figure 4.2 shows the dynamic nature of cell partitioning. It shows that a bifurcation
which, on average, directs more cells to the high flow rate branch (i.e. classical partition-
ing) can have intermittent events of the opposite nature (i.e. reverse partitioning) and vice
versa. Interestingly, [163] developed a 1D model for capillary blood flow, and using a cell
distribution function determined from their in vivo data, they predicted time-varying dis-
proportionate partitioning. However, it was not as a result of cell-cell and cell-vasculature
interactions, but rather it was caused by the temporary increase in resistance associated
with the passage of white blood cells. In general, it is observed that the time scales associ-
ated with fluctuation frequencies are related to both the cell residence time at bifurcations
as well as the passage time of the cells through the vessels. The passage time through the
bifurcations, however, is observed to be dominant. This is because the events occurring at
the bifurcations, such as the temporary RBC jamming, result in the most severe temporal
fluctuations in the hydrodynamic quantities. On the other hand, the origin of the fluctua-
tions coming from cell passage through the vessels is rooted in the temporary imbalances in
resistance between the daughter branches. These primarily occur due to differences in cell
distribution between the branches, as well as geometrical differences between the branches.
Although less severe, these will also contribute. Thus, bifurcations that have similar occurrences of each of these contributing factors are also commonly observed to exhibit similar frequencies in fluctuations.

4.2.3 Cellular mechanisms

This section investigates how instantaneous cell dynamics at bifurcations lead to a specific type of partitioning, and also cause a distribution to oscillate in time between the classical and reverse types. In describing the underlying mechanisms, the terms “left” and “right” used below are meant to be with respect to the direction of the flow in a vessel (i.e. looking downstream). The main focus is on mechanisms which directly give rise to periods of reverse partitioning. By extension then, the behavior analogous to the inverse of the described mechanisms gives rise to periods of classical partitioning. The first mechanism leading to the reverse type partitioning is presented in Figure 4.3(A). For the bifurcation of interest, the RBCs flowing in the feeding vessel are skewed toward the right of the vessel. This skewed distribution arises because of the way cells are partitioned at the upstream bifurcation. For the feeding vessel, the left side is plasma-rich, and the flow of cells lags that of plasma. The skewed distribution of the RBCs continues throughout the length of the feeding vessel. As a result, branch A receives a higher fraction of RBCs but a lower fraction of the blood flow, while branch B receives a lower fraction of RBCs but a higher fraction of blood flow, resulting in the reverse partitioning.

The second mechanism leading to reverse partitioning is shown in Figure 4.3(B). The underlying cell dynamics for this mechanism results from the piling-up of the RBCs at the upstream bifurcation, causing temporary and partial obstructions to the flow. Such piling (or lingering) of cells at bifurcations was discussed in Section 3.3.4. As a result of this behavior, RBCs enter the feeding vessel by moving around these temporary obstructions. For the time instant considered in Figure 4.3(B), a temporary pile-up in the upstream bifurcation causes the cells entering the feeding vessel to be shifted to the left side. The skewed distribution continues throughout the length of the feeding vessel, and the flow of cells lags that of the plasma. As a result, branch A receives a higher fraction of cells but a lower fraction of the blood flow, resulting in the reverse partitioning. The snapshots in
Figure 4.3: Mechanisms leading to reverse partitioning at two bifurcations selected from the microvascular networks. The bifurcation of interest, the feeding and daughter vessels, and the upstream bifurcation are marked. The arrows indicate the flow direction. (A) The first mechanism in which cells in the feeding vessel are skewed to the right resulting in a higher RBC fraction entering into branch A. (B) The second mechanism in which a piling-up of cells at the upstream bifurcation causes other cells entering the feeding vessel to be shifted to the left side, and consequently, a higher fraction of RBCs for branch A.

Figure 4.3 are during time windows when reverse partitioning occurs. As noted before, the time-dependent partitioning can switch between the classical and reverse types, and the time-averaged partitioning depends on how frequently each occurs.

These first two mechanisms are essentially associated with an asymmetry of the RBC distribution over the cross section of the feeding vessel as a result of the specific ways the cells are partitioned at the bifurcation that is immediately upstream. Therefore, while these two mechanisms are related to specific hematocrit patterns in the feeding vessel, they arise from the cellular interactions at an upstream bifurcation. Thus, in order to observe them, multiple bifurcations in sequence need to be considered as done in the present study. That upstream bifurcations can disturb the cell distributions entering a bifurcation downstream and cause reverse partitioning behavior has also been observed in vivo, e.g. [151, 163], and in vitro, e.g. [26, 157, 170].

Next, another mechanism that is directly related to cell-cell and cell-vasculature interactions is identified. This type of interaction was previously identified in [13] for a single, isolated bifurcation. They observed that either each RBC would enter a separate daughter vessel or each RBC would enter the same vessel, resulting in either a balance or imbalance in the hematocrit distribution. In the present simulations, during periods when RBCs on
Figure 4.4: Mechanism caused by cell-cell and cell-vasculature interactions in smaller capillaries leading to periods of classical and reverse type partitioning. A selected bifurcation from the simulated networks is considered. (A,B) Instances when cell partitioning is the reverse type. (C) Time history of blood flow ratio \( Q^*(t) \) (black line) and RBC flux ratio \( N^*(t) \) (red line) in branch A. The periods corresponding to (A,B) are marked in (C) using gray shades.

average enter separate branches, the time-dependent partitioning behavior is observed to be closer to proportional. In contrast, when RBCs on average enter the same branch the disproportionality temporarily increases. This latter behavior is a component to the mechanism described next, and it typically arises at bifurcations associated with the smaller capillaries. This is illustrated in Figure 4.4 for a selected bifurcation. First, it is noted that on average branch A gets 56% of the flow and 70% of the RBCs. Thus this bifurcation exhibits, on average, the classical partitioning. However, there are periods of time when branch A is congested with RBCs, but the flow rate is temporarily reduced due to the partial blockage of the branch by the cells, resulting in a reverse type partitioning. This is illustrated in Figure 4.4(A). Also shown is the time-dependent RBC flux ratio \( N^*(t) \) and blood flow ratio \( Q^*(t) \) for branch A in Figure 4.4(C), where this period of time is the first region shaded in gray. As evident in this figure, during this period, \( Q^*(t) < 0.5 \) but \( N^*(t) > Q^*(t) \) in branch A. However, as branch A continues to be blocked, the flow resistance in this branch increases. The flow is then diverted to branch B. Subsequently the cells are drawn into branch B while branch A frees up, as shown in Figure 4.4(B). As more cells are drawn to branch B, the resistance increases and the flow rate drops in that branch. At this moment, branch A receives a higher fraction of flow, but a lower fraction of cells, resulting in another time window of the reverse partitioning. This time window is marked in Figure 4.4(C) by the second shaded region, and it is evident from the figure that for this period \( Q^*(t) > 0.5 \) but \( N^*(t) < Q^*(t) \) in branch A. Outside these windows, the partitioning is the classical
type, i.e. \( N^*(t) > Q^*(t) \) when \( Q^*(t) > 0.5 \). In short, this specific mechanism is caused by temporary bursts of RBC flux that can occur in a branch as the direct result of cell-cell and cell-vasculature interactions. These in turn give rise to periods of classical and reverse partitioning behaviors.

These temporary bursts of RBC flux and their effect on the time-dependent partitioning are similar in spirit to that observed in [163]. In their analytical model, such behavior was predicted due to a temporary increase in resistance due to the passage of a WBC through a single bifurcation. Here it is shown how this can occur with RBCs alone by considering the 3D cellular-scale details and interactions caused by complex network geometries. As previously mentioned, this action of RBCs entering the same daughter branch is also similar to that observed in [13]. Therein such behavior was termed either “herding” or “following,” with the distinction between the two dependent on differences in behavior between simulations with one cell or two cells. These interactions predominantly occurred only when the cells were initially close to each other in the feeding vessel. Since the present simulations involve many cells passing through a bifurcation, the behavior similar to either “herding” or “following” can occur not only when the cells are close to each other in the feeding vessel but also when they are initially separated, depending on the interactions involving other cells. At the same time, however, multiple cell-cell and cell-vasculature interactions can also result in departures from the “herding” or “following” behavior.

![Figure 4.5: Flow-balancing mechanism caused by RBCs piling up in smaller capillary bifurcations. A selected bifurcation from the simulated networks is considered. (A,B) Instances when temporary flow-balancing occurs. (C) Time history of the flow rates in branch A \((Q_A(t), \text{solid line})\), and branch B \((Q_B(t), \text{dotted line})\). The periods corresponding to (A,B) are marked in (C).](image-url)
The fourth mechanism identified is a temporary flow balancing mechanism. It provides a means for initiating a transition between different time-dependent partitioning behaviors at an individual bifurcation. It is directly associated with the aforementioned piling-up of RBCs that is observed to occur within bifurcations and temporarily causes the flow to be equally distributed between each daughter vessel. This predominantly occurs at the smallest capillary bifurcations where the confinement effects are most pronounced so that when the piling-up occurs the flow is simultaneously reduced into each branch and the flow distribution is temporarily equalized. As previously mentioned, one observation in [13] involved each cell entering a separate daughter branch, which they termed a “trade-off” interaction. A byproduct of the fourth mechanism involves similar behavior in that following the temporary flow balancing we do observe that the RBCs can distribute in sequence to separate daughter branches. To some degree, this mechanism has also been observed in studies that used a continuum description of the blood flow, such as [93] or in [28] where the result of the splitting of an idealized hematocrit slug at a bifurcation was shown to initiate a transition from one state to another.

Snapshots from two representative bifurcations at times when this mechanism is manifesting are shown in Figures 4.5(A,B). The temporary congestion of cells within the bifurcation is evident, on account of the smaller vessel sizes causing a more pronounced confinement as the cells flow into the bifurcation. The time-dependent flow rates in each daughter vessel are shown in Figure 4.5(C), and the points in time associated with these events are labeled. The temporary balancing of the flow is evident from the flow rate signals temporarily overlapping.

Note that the selected bifurcations in Figures 4.3-4.5 provide representative examples. Each of the identified mechanisms is observed to occur, with varying frequency, at many bifurcations throughout the networks. While at a particular bifurcation one mechanism may predominantly occur more than another, the fraction of the total time is generally divided between each. This is illustrated for a few representative bifurcations in Table 4.1, which gives a breakdown, for each bifurcation, of the fraction of total time each component is active. Outside of these mechanisms, the partitioning behavior is either of the classical disproportionate type or else it falls into a category not captured by the present classification.
<table>
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<tr>
<th>Bifurcation Type</th>
<th>Classical Partitioning</th>
<th>Reverse Partitioning</th>
<th>Mechanism 1</th>
<th>Mechanism 2</th>
<th>Mechanism 3</th>
<th>Mechanism 4</th>
</tr>
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<td>0.10</td>
<td>0.61</td>
<td>0.02</td>
<td>0.00</td>
<td>0.00</td>
<td>0.26</td>
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<td>0.01</td>
<td>0.24</td>
<td>0.13</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
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<td>0.43</td>
<td>0.03</td>
<td>0.04</td>
<td>0.24</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Capillary</td>
<td>0.51</td>
<td>0.01</td>
<td>0.20</td>
<td>0.08</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
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<td>0.02</td>
<td>0.00</td>
<td>0.17</td>
<td>0.61</td>
<td></td>
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</tbody>
</table>

Table 4.1: Fraction of total time partitioning components is active at a few representative bifurcations. The bifurcation type is listed as Capillary for terminal bifurcations on the arterial side and as Arterial for all others.

scheme. For completeness, data are provided for all bifurcations in Section 4.2.3a, along with an additional discussion.

An interesting question arises as to whether the mechanisms described can occur in single bifurcation models. As noted before, Mechanisms 1 and 2 depend on what happens at an upstream bifurcation. So they would not be observed in a single bifurcation model unless the effect of the upstream bifurcation on the feeding vessel is somehow modeled. In contrast, Mechanisms 3 and 4 were in fact observed in a single bifurcation model, as noted earlier. To appropriately compare the probability of either mechanism occurring in a single bifurcation model, the issue of boundary conditions will come into play. With the network simulations, the velocity and pressure fields are not fixed at the bifurcation inlet/outlet, but rather they arise naturally and are highly time dependent. This affects the means by which these mechanisms manifest and would have to be considered when selecting the boundary conditions to prescribe in a single bifurcation model. Any fixed pressure or flow boundary conditions may bias the results being compared and cause departures from the naturally developing conditions captured in the network simulations.

Concerning the nature of these mechanisms, a point of distinction is that these are not meant to be predictive in nature but are really more observational. To some extent, their existence depends on subtle details in the complex cell-cell and cell-vasculature interactions which cause the mechanisms to arise. That they are limited to being observational in nature partly speaks to the fact that these details are not yet well understood. In reality, these
mechanisms are really just a first step in understanding how certain partitioning behaviors can arise. The next step would then be to understand their nature to the degree that their occurrence can be predicted. What is understood though is that these subtle details are, to a large extent, stochastic in nature. This was discussed Section 3.4. Related to the analysis in this chapter, the temporary patterns form as the result of a very complex sequence of interactions. These eventually culminate in the collective RBC behavior which forms the basis for the identified mechanisms. At present then, while it can be identified when these mechanisms have occurred, as mentioned, this is not yet something predictive.

(a) Prevalence of individual cellular-scale mechanisms

To aid in analyzing the significance of each of the identified cellular scale mechanisms as they arise in a complex network, the prevalence of each is quantified for all bifurcations by the total fraction of time each mechanism is active. Data is provided in Table 4.2 below for bifurcations in each of the three networks. Each row corresponds to a bifurcation in a network, for one of the boundary condition cases that were run. Results for each bifurcation for other boundary condition cases were observed to be similar. Each bifurcation is identified by a letter corresponding to the network geometry, and a number corresponding to the bifurcation index. For example, Bifurcation B-7 is bifurcation number 7 in network B. Also given is the bifurcation type, which is listed as “Capillary” if it is the terminal bifurcation on the arterial side of the network, or simply as “Arterial” if it is upstream of this. Bifurcation indices for each network are identified in Figure 4.6.

An automated detection algorithm was developed to post-process the simulation data and determine the fraction of time each mechanism was active at each bifurcation. The basic idea behind this algorithm is to monitor time-dependent patterns in the RBC positions throughout the network in conjunction with the time signals for $Q^*(t)$ and $N^*(t)$ at each bifurcation. The salient details are as follows.

Mechanisms 1-3 are the predominant cellular-scale mechanisms that are observed to give rise to reverse partitioning behavior in the simulations. As such, they only are active during times of this reverse partitioning behavior. This is used as a criterion when determining which mechanism is active. If this is met, Mechanisms 1 or 2 are determined to be active
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Table 4.2: Fraction of total time each partitioning component is active
Figure 4.6: Bifurcation identification for each network geometry

based on the relative location of the instantaneous high flow branch to the local RBC patterns observed at the upstream bifurcation. If neither is active, Mechanism 3 is tested to be active based on RBC patterns in the present bifurcation and $Q^*(t)$ and $N^*(t)$ signals.
The time dependent hydrodynamic resistance in daughter vessels is also used as a trigger to aid in the detection. Mechanism 4, as mentioned, is a temporary flow balancing mechanism, and is active when the flow distributions temporarily come into balance with one another. As such, it is determined to be active based on the $Q^*(t)$ signal for the bifurcation and instantaneous RBC patterns observed. Similar to Mechanism 3, the daughter vessel resistance is used as well. Outside of these mechanisms, the partitioning behavior is either of the classical disproportionate type, or else it falls into a category not captured by the present classification scheme.

4.2.4 Influence of vessel diameter

The quantity $|N^* - Q^*|$ can be thought as a measure of the degree of disproportionality in cell partitioning. Of interest is the dependence of $|N^* - Q^*|$ on the feeding vessel diameter which is shown in Figure 4.7. It is observed that on average $|N^* - Q^*|$ is diameter dependent, and its value increases with decreasing diameter. What this means is that as the vessel diameter becomes smaller, cells on average are partitioned even more disproportionately. This result underscores the influence of the finite size of the RBCs. However, as is evident from Figure 4.7, the range of values of $|N^* - Q^*|$ also increases with decreasing diameter. This means that very different types of partitioning can occur at bifurcations with smaller diameters vessels from a highly disproportionate partitioning corresponding to a large value of $|N^* - Q^*|$ to a nearly proportional partitioning corresponding to $|N^* - Q^*| \to 0$. It also tends to explain why some capillary vessels in vivo have high hematocrit while others may be nearly devoid of cells [115, 71, 153]. One possible mechanism by which a large disproportionality can occur is the reverse type partitioning described previously in Figure 4.4. With this mechanism, one daughter vessel at a bifurcation can become congested with RBCs while the flow is significantly reduced, resulting in a large value of $|N^* - Q^*|$. Other possible mechanisms are those described in Figure 4.3 and could be associated with either the classical or reverse partitioning. Under these mechanisms, cells in the feeding vessel are predominantly shifted to one side, which leads to a large positive or negative value of $|N^* - Q^*|$. In contrast, a small value of $|N^* - Q^*|$ may occur when the cells in the feeding
vessel are uniformly distributed and thus leads to a more proportional partitioning to the flow.

Figure 4.7: Influence of the feeding vessel diameter on the degree of disproportionality in cell partitioning defined as $|N^* - Q^*|$. Symbols are DNS results, and the line is a fit through the data.

It may be noted that previous studies have shown the importance of the ratio of daughter vessel diameters. For example, in the empirical correlation developed by [151], there is an asymmetry parameter that is dependent on the diameter ratio. The effect of this ratio becomes most pronounced when $N^*$ can be plotted over a large range of $Q^*$ for one bifurcation to develop an $N^*$ vs. $Q^*$ curve. This can be obtained, for example, by gradually occluding a daughter vessel, as was done in this previous work (see also Section 4.2.1). The present simulations, however, do not permit modeling such vessel occlusion. As such, it is difficult to draw any conclusions as to the effects of the diameter ratio on the distribution behavior based on the DNS results. Such a dependence on the diameter ratio was in fact examined; however, this did not offer anything conclusive with regard to distribution asymmetry or other features.

4.2.5 Influence of hematocrit skewness

In Section 4.2.3, the mechanisms associated with cell partitioning were discussed. The general picture that arises from the two underlying mechanisms presented in Figure 4.3 is that an upstream bifurcation causes a skewed distribution of RBCs in a vessel, leading
to the instantaneous reverse partitioning at a downstream bifurcation. The skewness in the cell distribution may alter from one side of the feeding vessel to another due to the cell dynamics at the upstream bifurcation, also causing the downstream cell partitioning to switch between the classical and reverse types. These instantaneous events ultimately comprise the time-averaged partitioning. Therefore, one way to investigate the influence of upstream bifurcations on cell partitioning is to consider the time-averaged hematocrit and velocity profiles in the feeding vessels.

Figure 4.8: The mismatch between hematocrit and velocity skewness in the feeding vessel leading to the reverse type partitioning. (A) A selected bifurcation is shown. Color contours represent hematocrit distributions (darker representing higher values). Also shown is the separation surface (dashed line), and hematocrit (red line) and velocity (blue line) profiles at one location ahead of the bifurcation. The cross-sectional distributions of velocity and hematocrit at this location are shown in (B) and (C), respectively. The dashed line in (B) and (C) represents the separation surface.

For this analysis, the separation surface appears as a relevant quantity, which has been used in prior works studying cell distributions (e.g. [163, 35, 151]). This surface represents the boundary in the feeding vessel separating regions of the flow that go into each daughter vessel. For each bifurcation, it is obtained a posteriori from the simulation data by considering a dense collection of streamlines determined from the time averaged velocity field, moving through the bifurcation. Starting at a cross section at the bifurcation inlet, the streamlines distribute into either of the two daughter vessels, thus forming two separate groups. The separation surface is given by the interface dividing these two groups. This surface for a selected bifurcation is shown in Figure 4.8. It may be noted that the separation surface, in general, is not a flat surface but rather a curved one as evident from this figure.

First, reverse partitioning is presented in Figure 4.8, where a part of a simulated network is shown that includes the selected bifurcation of interest, the feeding vessel, and the
upstream bifurcation. The time-averaged hematocrit distribution throughout the network segment is shown in Figure 4.8(A). Also shown are the hematocrit and velocity profiles at one location in the feeding vessel, and the separation surface. The velocity and hematocrit distributions over the cross section of the feeding vessel at this specific location are also shown in Figures 4.8(B,C) along with the separation surface. Because of the way cells are partitioned at the upstream bifurcation, the hematocrit profile in the feeding vessel is skewed to the left of the separation surface. The cells, however, lag behind the flow, resulting in the whole blood velocity profile skewed to the right of the separation surface. The mismatch between the velocity and hematocrit distributions with respect to the separation surface is also evident in Figures 4.8(B,C). As a result of the mismatch, daughter branch A receives a higher fraction of the cells but a lower fraction of the flow, leading to the reverse type partitioning. A connection between the feeding vessel concentration profiles and reverse partitioning behavior was also observed in [169]. As previously mentioned, they explained this reverse behavior to occur as the result of a specific profile in the feeding vessel leading to the low flow branch recruiting less plasma than the high flow branch.

Figure 4.9: The classical partitioning occurs when the hematocrit and velocity profiles in the feeding vessel are skewed to the same side of the separation surface. Contours and line symbols are the same as those in Figure 4.8.

For the classical partitioning, a representative example is shown in Figure 4.9. Here the velocity and hematocrit profiles are both skewed to the right side of the separation surface in the feeding vessel. Hence, daughter branch B gets the higher fraction of the blood flow as well as the higher fraction of the RBC flux, resulting in the classical partitioning. To further quantify the cell partitioning in terms of the flow and hematocrit profile mismatch, the skewness in the hematocrit profile is computed at a location in the feeding vessel ahead
of the bifurcation following [170],

\[
S_h = \text{sign} \left\{ \frac{\int_{S_1/2} U(r, \theta) dA}{Q_0} - 0.5 \right\} \left| \frac{\int_0^r \int_{\theta_1}^{\theta_1+\pi} H_t(r, \theta) dA}{\int_0^r \int_{\theta_1}^{\theta_1+2\pi} H_t(r, \theta) dA} - 0.5 \right| \quad (4.3)
\]

where \( U \) and \( H_t \) are the time-averaged blood velocity and hematocrit over the vessel cross-section at the chosen location, \( S_{1/2} \) is the cross-sectional area on one side of the separation surface, and \( \theta_1 \) to \( \theta_1 + \pi \) is the part of the circumference that lies on the same side. With the skewness defined in this manner, the value gives the fraction of the profile residing on one side of the vessel centerline, while the sign specifies which side. The skewness is positive if the hematocrit profile is skewed towards the daughter vessel that gets more flow, and vice versa. Figure 4.10 shows \( N^* - Q^* \) versus \( S_h \) for all bifurcations. It is seen here that for most bifurcations, \( N^* - Q^* > 0 \) if \( S_h > 0 \), and vice versa. Thus, on average a positive skewness in the hematocrit of the feeding vessel is associated with the classical partitioning, while a negative skewness is associated with the reverse one.

Figure 4.10: \( N^* - Q^* \) versus skewness \( S_h \). Black circles represent the classical partitioning, and red triangles represent the reverse type.

This analysis further demonstrates how the sequential nature of bifurcations in a vascular network is a key component causing the diverse types of cell partitioning. It has been observed \textit{in vivo} [25, 27] that the length between successive bifurcations is typically not sufficient to discount the influence of upstream bifurcations. That such features may affect the partitioning behavior has been noted by a number of \textit{in vivo} and \textit{in vitro} studies.
Here it is shown, through the *in silico* models, how in physiological-type geometries there is a definitive and quantitative connection between cellular events at upstream bifurcations and the partitioning behavior downstream.

### 4.2.6 Plasma skimming and cell screening

To further elucidate the underlying hydrodynamics of disproportionate partitioning, the focus next is on the two classical components, namely, plasma skimming and cell screening, as defined in such studies as [200, 51]. As previously mentioned, plasma skimming is based on the advection of a hematocrit concentration by the fluid velocity field and thus assumes that the cells are volume-less point particles, while cell screening accounts for the finite-size of the cells. Furthermore, plasma skimming is a steady-state phenomenon, while cell screening is affected by the time-dependent cell behavior in bifurcations. In Sections 4.2.6a and 4.2.6b, quantitative results on each component as obtained from the simulations are presented.

#### (a) Plasma skimming

To isolate the plasma skimming component, the advection of a hematocrit profile through the modeled networks is considered. The hematocrit profile is specified at the inlet to a network and advected by the fluid as a scalar field as

\[
\frac{\partial H_t}{\partial t} + \textbf{U} \cdot \nabla H_t = 0
\]  

where \textbf{U} is the time-averaged velocity field obtained from the full DNS results (i.e. simulations with the RBCs). The inlet hematocrit profile is taken to be the time-averaged hematocrit profile at that location obtained from the DNS. The advection equation is numerically solved until a steady hematocrit distribution is established. The convective derivative in Equation 4.4 is numerically evaluated using a 2nd order upwinding scheme, the direction of which is chosen based on the direction of the velocity vector at each Eulerian grid point. Time integration is performed using an explicit 2nd order Adams-Bashforth scheme. Following this, the ratio \( N^* \) for each bifurcation is computed as the ratio of the hematocrit flux \( \int H_t \textbf{U} \cdot d\textbf{A} \) in a daughter branch to that in the feeding vessel.
Figure 4.11: (a) Simulation of pure plasma skimming in the network shown in Figure 3.1(A). Color contours represent Ht distribution at steady-state. (B) $N^*$ versus $Q^*$ plot showing the results of the plasma skimming simulations (open black circles). Also shown are the data from the full DNS simulations (i.e. with the RBCs) (closed black circles). Only a few data points are shown to avoid clutter.

The steady-state hematocrit distribution from the pure plasma skimming simulation for one network is provided in Figure 4.11(A). The resulting $N^*$ values, denoted as $N^*_{PS}$, are presented in Figure 4.11(B) for a few representative bifurcations. As evident here, the simulations predict phase separation by the plasma skimming mechanism alone. The phase separation due to plasma skimming alone occurs due to a non-uniform hematocrit profile. If the hematocrit distribution at the inlet to a bifurcation was uniform over the entire cross section, it would be partitioned proportionately to the flow, and the phase separation would not occur. In the plasma skimming simulations, the hematocrit profile at the inlet to the vascular networks is non-uniform. As the profile is advected, the hematocrit distribution naturally develops in the network, and the resulting hematocrit profiles ahead of each bifurcation, in general, are also non-uniform.

Also shown in Figure 4.11(B) are the results from the full DNS simulations. Two important observations are made here. First, the plasma skimming component alone cannot account for the full extent of disproportionate partitioning. Rather, it under-predicts the amount of disproportionality. That is, the data points representing the pure plasma skimming component are closer to the $N^* = Q^*$ line, while the actual DNS data are further away. In almost 80% of the bifurcations, plasma skimming is observed to under-predict the
disproportionate cell partitioning. To provide a more general picture of this trend, data for all bifurcations are plotted in Figure 4.12.

![Figure 4.12: $N^*$ vs. $Q^*$ data for the DNS results (black closed circles) as well as those for pure plasma skimming (open red circles). Plasma skimming under-predicts the disproportionality in nearly 80% of the bifurcations.](image)

Second, both the classical partitioning and reverse partitioning are present in the results of the pure plasma skimming simulation. This result directly follows from Section 4.2.5, where it was observed that the skewness in the hematocrit profile on average dictates the partitioning behavior at each bifurcation. Since the Ht distribution in the plasma skimming simulations is allowed to naturally develop through each sequential bifurcation, the profiles at some bifurcations could be either positively or negatively skewed with respect to the fluid velocity, resulting in the classical or reverse partitioning. The conclusions that the plasma skimming component under-predicts the total cell partitioning, and that it can yield the reverse type partitioning, are robust. Additional simulations have been performed of plasma skimming by isolating each individual bifurcation in the networks. In such simulations, a “local” hematocrit profile that is obtained from the time-averaged DNS data is specified at the inlet to the bifurcation. The profile is advected through the selected bifurcation, and the value of $N^*$ is obtained. Plasma skimming based on such local profiles also resulted in an under-prediction of the total cell partitioning, as well as the reverse partitioning. Furthermore, if the advecting fluid velocity $U$ is taken to be the velocity of pure plasma
without any RBCs flowing through the network, the same conclusions about the plasma skimming mechanism are drawn.

The plasma skimming contribution to the overall disproportionality in cell partitioning can be quantified as \( N_{PS}^* - Q^* \). The magnitude of \( N_{PS}^* - Q^* \) is plotted in Figure 4.13(A) as a function of feeding vessel diameter. The figure shows that the plasma skimming contribution increases with decreasing diameter. At first glance, this is a surprising result because plasma skimming is based on the assumption of point particles following the fluid streamlines. This diameter dependency arises from the bluntness in the hematocrit profile. To investigate this, the bluntness index \( B_H \) of the hematocrit profile as obtained from the pure plasma skimming simulations is computed. Mathematically, \( B_H \) is written as

\[
B_H = 2 \cdot \left( 1 - \frac{\int_0^{2\pi} \int_0^{\sqrt{0.05} R} H_t r \, dr \, d\theta}{\int_0^{2\pi} \int_0^{R} H_t r \, dr \, d\theta} \right) \tag{4.5}
\]

following [170]. Thus, \( B_H \) provides a measure of how focused the hematocrit profile is toward the vessel centerline: \( B_H = 1 \) if the Ht profile is uniform over the cross section and \( B_H = 0 \) if the profile is focused. As can be seen in Figure 4.13(B), \( B_H \) on average decreases with decreasing \( D \). This observation is in agreement with the plasma skimming
calculations performed by [151] based on their in vivo data. It means that, on average, the hematocrit profile is more focused in vessels with smaller diameters. A focused profile can lead to an increased disproportionality in cell partitioning. This is schematically illustrated in Figures 4.13(C,D). For the Ht distribution that is more focused (Figure 4.13(D)), there is a greater imbalance of hematocrit between each side of the separation surface compared with the distribution that is more blunt (Figure 4.13(C)).

Figure 4.13(A) also suggests that there is a wider variability of the plasma skimming contribution at the vessels with smallest diameters. This trend also follows from the bluntness of the hematocrit profile and can be illustrated by Figures 4.13(C,D). For the focused distribution in Figure 4.13(D), a small change in the location and shape of the separation surface can result in a relatively large change in $N_{PS}$. In contrast, for a distribution that is more uniform as in Figure 4.13(C), $N_{PS}$ is less sensitive to such small changes. Thus, a focused hematocrit profile, which on average is more frequently observed in smaller diameter vessels, leads to a wider range of disproportionality.

(b) Cell screening

The difference between the DNS result and the plasma skimming result is the overall cell screening effect. In Section 4.2.6, it was shown that at most bifurcations plasma skimming under-predicts the phase separation. This leaves cell screening to make up the difference. This relationship was apparent in Figure 4.11(B). Quantitatively, the cell screening contribution can be computed as $N_{CS} = N_{DNS} - N_{PS}$ for a given $Q^*$, where the subscript $CS$ refers to cell screening. The magnitude of $N_{CS}$ is presented in Figure 4.14 as a function of feeding vessel diameter. This figure, together with Figures 4.11(B) and 4.13, show that both cell screening and plasma skimming are of similar magnitudes and that together they contribute to phase separation. Additionally, Figure 4.14 shows that the magnitude of cell screening increases with decreasing vessel diameter on account of the finite cell size.

Next the mechanisms giving rise to cell screening are investigated. Two primary mechanisms are observed to be the main contributors as discussed below.

The first mechanism underlying the cell screening component is primarily associated with the average cell behavior, and it is termed here as the all-or-none effect. Note that
when considering plasma skimming, a hematocrit profile is considered that is the result of the aggregate effect of many RBCs passing through the vessel over a period of time. Thus the influence of each RBC is spread over a region, figuratively resulting in a fraction of each RBC going into each of the daughter vessels at a bifurcation. In contrast, due to the finite nature of each RBC, each daughter vessel gets either “all or none” of the RBC. This increases the degree of disproportionality in cell partitioning. This mechanism is illustrated in Figure 4.15 where selected bifurcations from the simulated networks are considered. Figure 4.15(A) shows the centroid location of each RBC on a cross-sectional plane in the vessel feeding the bifurcation. Also shown is the separation surface line.

According to the “all or none” effect, every RBC whose centroid is on one side of the separation surface should enter into the daughter vessel on that side. Thus the RBCs whose centroids are on the left side of the separation surface should enter the left daughter branch, and vice versa. In contrast, under pure plasma skimming, each daughter vessel would get a “fraction” of each RBC. Thus, the “all or none” portion of the cell screening component increases the degree of disproportionality in cell partitioning over and above that predicted by pure plasma skimming. The value of $N^*$ resulting from the “all or none” effect can be obtained as the ratio of the number of RBC centroids on one side of the separation surface to that of the total number of RBCs. For example, for the bifurcation in Figure 4.15(A), the ratio of centroids on the left side to the total number of centroids would yield the value of $N^*_{LS}$. This is demonstrated in Figure 4.15(B) where the centrifugal force $(F_c)$ is plotted against the feeding vessel diameter $(D_m)$. The slope of the line in Figure 4.15(B) is used to calculate the value of $N^*$ for each bifurcation. The resulting $N^*$ values are then plotted against the feeding vessel diameter in Figure 4.15(C).
Figure 4.15: Dominant mechanisms of the cell screening component. (A) The “all-or-none” effect. Centroids of the RBCs are shown over a cross section in the feeding vessel of a selected bifurcation. The dashed line represents the separation surface. (B) Some representative data points showing the “all-or-none” effect. Open black circles represent results based on plasma skimming alone, closed black circles represent DNS results, and open black triangles represent results based on combined plasma skimming and the “all-or-none” effect. (C) “Separation surface crossover” mechanism. Data in (A) are re-plotted by identifying the RBCs that enter the left and right daughter vessels by red circles and green triangles, respectively. The contribution from this mechanism is also marked in (B).

4.15, the plasma skimming component predicts $N^*_{PS} = 0.62$ for the daughter vessel lying on the right side of the separation surface. In contrast, the “all or none” mechanism results in $N^* = 0.87$, thereby significantly enhancing the disproportionality. Additional data shown in Figure 4.15(B) also support the increased disproportionality in cell partitioning by the “all or none” mechanism.

The “all or none” effect can be thought as plasma skimming with finite-sized cells. In reality, however, cells do not follow the streamlines. To this end, the second mechanism underlying the cell screening component is the separation surface crossover. It is evident from Figure 4.15(B) that the DNS data yield, on average, lower values of $N^*$ than the combined effect of plasma skimming and the “all or none” mechanism. This can happen if the cells whose centroids are on one side of the separation surface enter the daughter vessel that is on the other side. The data of Figure 4.15(A) is re-plotted in Figure 4.15(C) by identifying the cells that have crossed the separation surface. It is found that for this bifurcation 30% of the RBCs in the feeding vessel have crossed the separation surface before entering the daughter vessels. It is evident that this component of cell screening reduces the extreme disproportionality predicted by the all-or-none component.
What causes the cells to cross the separation surface? Two primary means by which this happens are found, each associated with the time-dependent RBC dynamics. The first is the direct result of cell-cell and cell-vasculature interactions. This generally occurs when a cell straddles around a bifurcation partly blocking a daughter vessel and forcing another RBC to enter the other daughter vessel. Figure 4.16(A) provides a time sequence illustrating the process in a selected bifurcation. In this figure, an RBC can be observed to straddle around the bifurcation, partly blocking the left daughter branch. This forces the following RBC that was on the left of the separation surface to cross over and enter the right daughter branch.

![Figure 4.16: (a) An example of the “separation-surface-crossover” component of the cell screening mechanism. A time sequence of events is shown. The RBC shown in purple straddles around the bifurcation partially blocking the left daughter branch and forcing the trailing RBC (shown in green) to cross the separation surface and enter the right branch. The dashed line is the separation surface, and the solid line is the trajectory of the RBC in green. (B,C) The fraction of RBCs ($\eta_{SS}$) at the bifurcations that enter the daughter vessels by crossing the separation surface plotted as a function of feeding vessel diameter and daughter vessel diameter, respectively. Diameters are given in $\mu m$.](image)

The second means by which cells cross the separation surface is associated with the steady-state nature of the surface as opposed to the unsteady nature of cell dynamics. The
separation surface is computed in a time-averaged (or steady-state) sense, while the cell crossing is an unsteady process. If the majority of the cells at a bifurcation flow into one daughter vessel for a certain period of time, the resistance in that daughter vessel would increase. The flow would then be diverted into the other daughter vessel taking with it some of the RBCs flowing in the feeding vessel. As such, these RBCs would enter the daughter vessel by crossing the separation surface.

How important is the “separation-surface-crossover” mechanism? To answer this, the ratio is computed of the number of RBCs that enter a daughter vessel by crossing the separation surface to the total number of RBCs in the feeding vessel of a bifurcation. This ratio, denoted by \( \eta_{SS} \), is presented in Figure 4.16(B) as a function of feeding vessel diameter. As is evident, the crossover fraction \( \eta_{SS} \) increases with decreasing vessel diameter on account of the finite-size effect. More importantly, the value of \( \eta_{SS} \) is quite large and as high as 0.45 in the smallest vessel. Thus, in some bifurcations associated with the smallest capillaries, nearly 50% of the RBCs in the feeding vessels are observed to cross the separation surface. In Figure 4.16(C), \( \eta_{SS} \) is presented as a function of the daughter vessel diameter. This figure gives the fraction of cells that have entered a particular daughter vessel by crossing the separation surface. It shows that there are bifurcations where 100% of the RBCs have entered the respective daughter vessel by crossing the separation surface.

The above result is physiologically important. If the separation surface crossover did not occur, some daughter vessels would be almost devoid of cells. Therefore, the separation surface crossover acts as a balancing mechanism and mitigates extreme heterogeneity in hematocrit variation across a vascular network.

These results stem from the ability of cells to deviate from the underlying fluid streamlines. At negligible inertia, cell deformability, as well as cell-cell and cell-vasculature interactions, all contribute to this. The deviation of cell trajectories arising from cell deformation alone can be best studied by considering the motion of an isolated cell, as considered by such studies as [12, 48]. Their studies suggest that the separation-surface crossover by cell deformation alone usually only occurs for trajectories that are already close to the separation surface, and this is also observed in the present work. Additionally, it is found here that cell-cell interactions play a major role in separation surface crossover and that
such interactions are dominant within the bifurcations. In the study of [13] with two cells, they mentioned that such cell-cell interactions tend to balance the cell distribution. This is in agreement with our finding that such interactions mitigate extreme heterogeneity in hematocrit.

4.2.7 Additional discussion

In the present work, only RBCs have been considered. The co-existence of leukocytes, or WBCs, in the blood stream would likely have a considerable impact on the partitioning behavior as these cells traverse a bifurcation. The physiological basis for excluding WBCs from the model is that they are significantly outnumbered by RBCs under healthy conditions, as mentioned previously. The present work is thus representative of a period of time when WBCs are not present in the section of the microvasculature concerned. While the numerical approach can also model WBCs, as was shown Section 2.6, at present, this is a topic of future work.

As to the potential impact of the additional presence of leukocytes on the present study, a few comments can be made. In a more general sense, the time scales associate with the transit time of a WBC through a network such as those considered here would likely be orders of magnitude higher than that of the RBCs. This is mainly on account of their larger size causing an increased transit time. Thus the partitioning results, in general, would have a different temporal basis than that presented here based on RBCs alone. In a more specific sense, some of the cellular mechanisms could be impacted. Mechanism 2 could occur instead as the result of a WBC partial blockage at an upstream bifurcation in a manner similar to that achieved by the RBCs with this mechanism. This would similarly cause the RBCs to flow into the feeding vessel by moving around the obstruction. The presence of WBCs would also likely enhance the asymmetry in resistance between daughter vessels, which is similar to what occurs with mechanism 3, and would likely be more severe. With mechanism 4, the temporary flow balancing from RBCs piling up at the bifurcation could also occur by a WBC blockage in a symmetric manner, although this would likely occur over a longer period of time.
WBCs would impact the hematocrit profiles in that RBCs would either re-route around these cells, or in the case of capillaries where they block the entire vessel, the RBCs would build up behind the WBC. As the WBC then passed through the bifurcation and entered a daughter branch, during this period the RBC flow would likely increase into the other daughter branch significantly. WBC presence would also add an additional feature to the cell screening component, where the finite-size effects would significantly alter the partitioning behavior. In the extreme case of the capillaries where a WBC could completely block one daughter vessel, the entire partitioning would be due to the cell screening component.

4.3 Conclusions

To the best of our knowledge, this chapter presents the first DNS study to consider the partitioning of RBC suspensions in simulated microvascular networks with in vivo-like features, such as the presence of a large number of sequential bifurcations, as well as and winding vessels. The model resolves the extreme deformation of individual RBCs, cell-cell and cell-vasculature interactions in a flowing suspension, and the highly complex geometry of the microvasculature. Using the DNS results, a detailed analysis is presented on the partitioning behavior as it develops naturally in successive bifurcations. The major findings from this analysis are as follows:

(i) It is found that while the time-averaged partitioning at a bifurcation could be either the classical or reverse type, the time-dependent partitioning may cycle between these two types over time. The time-averaged partitioning then depends on the duration and frequency of these cycles. Therefore, such time-dependency has influence on the ultimate distribution of the RBCs which is known to be heterogeneous in a microvascular network.

(ii) Four different cellular-scale mechanisms underlying the time-dependent partitioning are identified. This specific analysis was centered on the reverse partitioning. The first two mechanisms are due to an asymmetry in the RBC distribution in the feeding vessel caused by cell partitioning at the bifurcation upstream. The first mechanism occurs when cells in the feeding vessel flow along the side that is closer to the upstream bifurcation. The second mechanism occurs when the cells flow along the other side of the feeding vessel
due to an accumulation (or piling-up) of cells at the upstream bifurcation. The third and fourth mechanisms occur in capillary bifurcations, and they arise due to cell-cell and cell-vasculature interactions. In the third mechanism, a sudden increase in RBC flux in one daughter vessel leads to an increased flow resistance, thereby diverting more plasma to the other daughter vessel and giving rise to the reverse partitioning. The fourth mechanism is a flow-balancing mechanism, and it provides a means of transition between classical partitioning and reverse partitioning. It occurs when the flow is simultaneously reduced in both daughter vessels due to cells piling up at the bifurcation.

(iii) Using the DNS data, it is shown that, on average, a positive skewness in the hematocrit profile in the feeding vessel is associated with the classical partitioning, while a negative skewness is associated with the reverse partitioning.

(iv) Following this, detailed analysis and insight into two components of disproportionate partitioning, namely, plasma skimming and cell screening, are presented. To our knowledge, this is the first work to dissect these two components for a cell suspension flowing through complex networks. Plasma skimming is simulated by considering the advection of a hematocrit profile through the networks. It is shown that both the classical partitioning and reverse partitioning are present in the plasma skimming component. More importantly, however, it is shown that the plasma skimming component under-predicts the overall cell partitioning, leaving the cell screening component to make up for the difference. The plasma skimming contribution is found to be dependent on the vessel diameter, which is explained using trends in the hematocrit bluntness. It is further observed that both plasma skimming and cell screening are of similar magnitudes.

(v) The two primary mechanisms giving rise to the cell screening component are then identified and analyzed. The first mechanism, which has been termed here as the “all-or-none” effect, can be thought of as plasma skimming with finite-sized cells, and is observed to over-predict the disproportionality. This is countered by the second mechanism which represents cells crossing over the separation surface. Two primary means by which cells cross the separation surface are identified, each of which is associated with the time-dependent RBC dynamics near a bifurcation.
(vi) The separation surface crossover is quantified in terms of the vessel diameter and is shown to be a dominant and physiologically important mechanism. In some bifurcations, nearly half of the RBCs in the feeding vessels are observed to cross the separation surface. Furthermore, for some daughter vessels, nearly all RBCs are observed to enter by crossing the separation surface. Without the presence of this mechanism, these daughter vessels would not receive any RBCs. Thus, the separation surface crossover is a mechanism which mitigates extreme heterogeneity in RBC distribution across a microvascular network.
Chapter 5

The cell free layer in simulated microvascular networks

5.1 Overview

In the microcirculation, a plasma layer forms near the vessel walls that is free of RBCs. This region, often termed as the cell-free layer (CFL), plays important hemorheological and biophysical roles, and has been the subject of extensive research. From a hydrodynamic perspective, the extreme deformability of RBCs in the blood is the primary driver in the formation of the CFL. It results in a tendency of the cells to migrate away from vessel walls, and in the direction of decreasing velocity gradient. This is countered by the tendency of cell-cell interactions to disperse cells over the vessel cross-section. While other factors can affect the formation of the CFL, it generally forms as the net result of these two competing effects. Many previous studies have considered the CFL development in single, isolated vessels that are straight tubes or channels, as well as in isolated bifurcations and mergers. In the body, blood vessels are typically tortuous and sequentially bifurcate into smaller vessels or merge to form larger vessels. Because of this geometric complexity, the CFL in vivo is 3D and asymmetric, unlike in fully developed flow in straight tubes. The three-dimensionality of the CFL as it develops in a vascular network, and the underlying hydrodynamic mechanisms, are not well understood.

This chapter presents a detailed study on the fully three-dimensional nature of the CFL as it arises in the complex microvascular network simulations described in Chapter 3. As mentioned earlier in Section 1.4.3, the existing knowledge of the CFL in vivo, has been based on characterizing it as a 2D projection onto the image plane. To understand the 3D nature of the CFL, however, a different approach must be taken. As such, first described in this chapter is a method to obtain the 3D CFL from the simulation data in a consistent way for different vessels under diverse hemodynamic conditions. Using this,
the three-dimensionality of the CFL is studied. To this end the 3D asymmetry in the CFL is quantified, and the underlying hydrodynamic mechanisms are identified that cause such asymmetry in various facets of the vascular networks, namely, vessel segments, bifurcations, and mergers. It is shown that vessel tortuosity can result in an asymmetric CFL because of the presence of a curvature-induced migration of the RBCs. It is further shown that the vascular bifurcations can increase the asymmetry in the CFL, and a hydrodynamic basis for the discrepancy in the CFL in the daughter vessels downstream of the bifurcations is established. Similarly, it is shown that the CFL asymmetry increases over the vascular mergers, and a geometric focusing effect is identified as a dominant underlying mechanism. To our knowledge, this work provides the first simulation-based analysis of the 3D CFL structure in complex in vivo-like microvascular networks, including hydrodynamic origins of observed behavior.

5.2 CFL calculation

A fundamental component to the present analysis is the means by which the CFL is determined. The methodologies used to determine the CFL in previous experimental works have typically involved constructing some form of an RBC core used in conjunction with the location of the vessel walls. Among these works, however, different approaches have been taken. Earlier in vivo works (e.g. [20, 183, 177, 117]) and in vitro works (e.g. [22, 156]) determined the CFL thickness by visual observation and analysis of video images. More recently, in vivo works such as [96] or [132] have developed automated image analysis methods to digitally construct the RBC core and cell-free regions at individual instants in time. Specifically, the method developed in [96] constructed the core and cell-free regions as a binary image which assumed a continuous core between any plasma gaps separating individual RBCs along the length. [132] improved on this with a greyscale image-based method that provides increased accuracy in faint areas.

Somewhat similar approaches have been adopted in previous computational modeling. [54] simulated RBCs flowing in a straight tube using a dissipative particle dynamics method, and constructed an RBC core by projecting the cell outline along the vessel length onto a 2D plane in a manner similar to [96]. [206], for their 2D Lattice Boltzmann simulations,
determined the CFL as the average of the closest cell-wall distances between each side of the vessel. For the simulations in [207], the CFL thickness was determined as the boundary of the region near the wall that is occupied by 2.5% of the total RBC volume, while [205] used an occurrence frequency distribution of CFL values at locations in the modeled vessel.

Evidently, a wide variety of approaches have been used to determine the CFL in prior works. In the present work, because of the geometric complexity of the microvascular networks, and the resulting effect on the formation of the RBC core, a 2D projection of the core to determine the CFL would not be sufficient. Furthermore, the distribution of the RBCs across a network is highly heterogeneous, and constantly changes over time. As such, the CFL distribution across the network is heterogeneous and time-dependent. Due to the heterogeneity of the RBC distribution, some vessels are constantly filled with cells, while some have intermittent flows of cells. In many vessels, especially in the small capillaries, there are instances when only one or two cells are flowing through a vessel, or cells flow through a vessel in a manner in which there are plasma gaps in between the cells along the vessel length. A methodology is thus needed for the present work to accurately compute the 3D time-dependent CFL under these different flow conditions.

The procedure developed for calculation of the CFL in the present work is illustrated in Figure 5.1. For each simulation, data is stored at 0.5ms intervals, with approximately 1400 instances in total. Each dataset stored gives a 3D snapshot of the shape of all RBCs in the entire network. A number of such consecutive snapshots are first superimposed to generate an instantaneous RBC core. The RBC core is the resulting shape traced out by all the RBCs moving through a vascular segment of interest over a small window of time approximately corresponding to the RBC transit time through that segment. This time window also corresponds to the smallest time so that no plasma gap appears between the cells along the axial direction. Once the instantaneous core is traced out, the space between the core and the vessel wall gives the instantaneous CFL. Physically, it represents the space that is completely devoid of cells over the aforementioned time window. The thickness of the CFL, denoted by $\delta$, is the distance between the core and the vessel wall, and is measured at each vertex of the surface mesh used to discretize the vascular walls. The resulting instantaneous CFL thickness $\delta(s, \theta, t)$ is 3D, and is a function of axial position $s$ along a
vessel length, angular position $\theta$ on the vessel cross-section, and time $t$, as shown in Figure 5.1(C,D). The axial coordinate $s$ increases from vessel inlet ($s = 0$) to outlet ($s = L$), and the angular position $\theta$ is defined looking downstream along the flow direction. The time-averaged CFL thickness is determined by averaging $\delta(s, \theta, t)$ over the entire simulation time, and is denoted by $\bar{\delta}(s, \theta)$; thus, the 3D nature of the CFL is retained in the time-averaged value.

$$\bar{\delta} = \frac{1}{2\pi L} \int_0^L \int_0^{2\pi} \bar{\delta}(s, \theta) d\theta ds$$  \hspace{1cm} (5.1)$$

where $L$ gives the length of the vessel. The CFL thickness is compared for different ranges of vessel diameter as presented in Table 5.1. The smallest vessels in our networks are 6 $\mu$m in diameter, and among these the CFL thickness was calculated to range from 0.5 to 0.8 $\mu$m. This is in good agreement with that reported in the in vivo work of [183], where the CFL thicknesses in 6 $\mu$m vessels were reported to range from approximately 0.5 to 0.9 $\mu$m. For larger vessels in our networks less than 10 $\mu$m in diameter, the CFL thickness was

![Figure 5.1: Computation of 3D CFL. (A) An image of RBCs at one time instance in a bifurcation of a simulated network. (B) Superposition of RBCs at a few consecutive time instances. (C) Instantaneous RBC core as obtained by superimposing the RBCs over a small time window. (D) Cross-sectional view of the instantaneous RBC core and CFL. (E) Time-averaged RBC core.](image)
Table 5.1: Comparison between time-averaged CFL thickness $\bar{\delta}$ computed from the simulations and that determined in vivo calculated to range from 0.6 to 1.0 $\mu m$. This is in good agreement with the in vivo work of [177], where thicknesses ranging from approximately 0.7 to 1.1 $\mu m$ were reported for vessels in this diameter range. For vessels in the simulations between 10 and 24 $\mu m$ in diameter, $\bar{\delta}$ was calculated to range from 0.8 to 1.5 $\mu m$. In this diameter range, both the in vivo work of [177] and [97] reported values ranging from approximately 0.8 to 2.0 $\mu m$. This also generally agrees with that determined in [151] based on a theoretical estimation utilizing in vivo data. Comparisons against additional experimental measurements are also given in Table 5.1, which shows that the CFL thickness predicted with the present methodology is in good agreement with that observed in vivo. It is noted that hematocrit in the largest feeding arterioles for the present simulations was approximately 30%. The CFL thickness values reported from other works are based on the same hematocrit, with the exception of the data of [20] and [39] where the hematocrit values were not reported, and [97] where the hematocrit was approximately 40%.

<table>
<thead>
<tr>
<th>Vessel Diameter, $\mu m$</th>
<th>Present $\bar{\delta}$, $\mu m$</th>
<th>in vivo $\bar{\delta}$, $\mu m$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-6</td>
<td>0.5 - 0.8</td>
<td>0.8 - 1.2 [20] 0.5 - 0.9 [183]</td>
</tr>
<tr>
<td>7-10</td>
<td>0.6 - 1.0</td>
<td>0.9 - 1.5 [20] 0.7 - 1.1 [177]</td>
</tr>
<tr>
<td>11-24</td>
<td>0.8 - 1.5</td>
<td>1.3 - 4.5 [20] 0.6 - 3.5 [39] 0.9 - 1.8 [177] 0.8 - 2.0 [97]</td>
</tr>
</tbody>
</table>
5.3 Results and discussion

5.3.1 Three-dimensionality of the CFL

First, the general 3D nature of the CFL as predicted in the simulated networks is described. The analysis of the underlying mechanisms is presented in the subsequent sections.

The three-dimensionality is first described using a representative vessel as shown in Figure 5.2(A). The time-dependent profiles of the RBC core over the vessel cross-sections are shown in Figure 5.2(B) at four different locations along the vessel length, along with the time-averaged profiles superimposed. As this figure suggests, the time-dependent profiles at any cross-section are highly non-circular, significantly distinct at each instance, and significantly deviate from the time-averaged profiles. Also, at any time instance the cross-sectional profiles are different at different locations. To further demonstrate the 3D and non-circular nature of the CFL, its variation along the vessel length is considered but at two diametrically opposite sides, L and R, as shown in (A). The CFL thicknesses along these sides are denoted as $\delta_L(s,t)$ and $\delta_R(s,t)$, respectively, and both time-dependent and time-average results are presented in (C) and (D). While these quantities themselves give the thickness as in a 2D projection approach, when taken in conjunction with the crosssectional profiles these collectively paint a 3D picture of the CFL. These figures show that both the time-dependent and time-averaged CFL vary significantly along the vessel length. The differences between $\delta_L$ and $\delta_R$ are significant, both for the time-dependent and time-averaged results, serving as evidence of the asymmetric nature of the CFL. While both time-averaged $\delta_L$ and $\delta_R$ vary along the length, $\overline{\delta_L}$ shows a greater variation than $\overline{\delta_R}$. Furthermore, $\overline{\delta_L}$ generally increases along the vessel length while $\overline{\delta_R}$ does not have a net change between the vessel entrance and exit. The RMS of the temporal fluctuations of $\delta_L$ and $\delta_R$ scaled by the time-averaged thickness at each location along the length are shown in Figure 5.2(E). Interestingly, temporal fluctuations in $\delta_L$ generally increase along the vessel length, while those in $\delta_R$ decrease.

Figure 5.2 generally shows that not only is the time-dependent CFL highly 3D and asymmetric, but the time-averaged CFL is as well. In contrast, for a fully-developed flow in straight tubes of circular cross-section, though the time-dependent CFL is generally
Figure 5.2: (A) An instance of RBCs flowing in an example vessel in one of the simulated networks. R and L denote the right and left sides in the plane of the figure, respectively. (B) The time-averaged (thick line) and instantaneous (thin lines; several instances are shown) RBC core over the vessel cross-section at four different axial locations are shown. (C,D) Time averaged (thick line) and instantaneous (thin lines) CFL thickness along L and R, respectively. (E) RMS of temporal fluctuations in the CFL thickness along L and R.

3D, the time-averaged CFL is axisymmetric. Thus in the present work the primary focus
is on studying the three-dimensionality in the time-averaged CFL as it arises in complex networks.

To quantify the 3D and asymmetric nature of the time-averaged CFL, an asymmetry parameter is first considered, defined as:

$$\varepsilon(s) = \frac{\delta_{max}(s)}{\delta_{min}(s)}$$  \hspace{1cm} (5.2)

where $\delta_{max}(s)$ and $\delta_{min}(s)$ are the maximum and minimum values, respectively, of the time-averaged CFL thickness over the vessel cross-section ($0 \leq \theta < 2\pi$) at any location $s$ along the vessel length. This gives a value of 1 for a symmetric profile, and values greater than 1 for increasing asymmetry. $\varepsilon(s)$ is plotted in Figure 5.3(A) for a few representative vessels with length-to-diameter ratio in the range of 10-15. Several important observations are made here. First, this shows that even for relatively long vessels, the time-averaged CFL does not become axisymmetric over the length. While for some vessels the profile becomes more symmetric near the end, for others it becomes more asymmetric. Second, while there may be a net increase or decrease in $\varepsilon$ between the inlet and exit of a vessel, there is a significant fluctuation along the vessel length. This often results in the extremum of $\varepsilon$ occurring at locations in the middle of the vessels rather than at the inlet and exit. In vessels where the extremum of $\varepsilon$ do occur at the inlet and outlet, $\varepsilon$ does not typically change monotonically along the length but rather fluctuates significantly as well. Even when $\varepsilon$ is nearly the same at the inlet and outlet, in between fluctuations of large magnitudes are observed. These results are in contrast to what would happen in a straight tube, where any CFL asymmetry at the inlet would monotonically decrease over the vessel length.

To quantify the CFL asymmetry $\varepsilon$ for all vessels in the networks, the difference between $\varepsilon$ at the beginning and end of each vessel is computed, i.e. $\varepsilon|_{s=L} - \varepsilon|_{s=0}$, and plotted with respect to the cumulative change in $\varepsilon$ over the length defined as $\Delta \varepsilon = \Sigma_i |d\varepsilon(s_i)|$. Here, $\Delta \varepsilon$ is evaluated by dividing each vessel into $N$ finite segments, each given by the index $i$. The relationship between these quantities is presented in Figure 5.3(B). If $\varepsilon$ were to change monotonically over the length, then $\Delta \varepsilon$ would equal the magnitude of $\varepsilon|_{s=L} - \varepsilon|_{s=0}$. This relationship is given by two straight lines in this figure: the line $\Delta \varepsilon = -(\varepsilon|_{s=L} - \varepsilon|_{s=0})$ corresponds to a straight tube, where an asymmetric CFL profile at the vessel entrance
Figure 5.3: (A) The CFL asymmetry parameter $\varepsilon$ along the length for several representative vessels in the networks. (B) The change in asymmetry, $\varepsilon|_{s=L} - \varepsilon|_{s=0}$, between vessel inlet and outlet versus the cumulative change $\Delta \varepsilon$ over the entire length, for all vessels (data points). The straight lines correspond to a monotonic change in $\varepsilon$ over the length.

monotonically shifts towards a symmetric one with increasing axial distance. In contrast, the line $\Delta \varepsilon = +(\varepsilon|_{s=L} - \varepsilon|_{s=0})$ means the asymmetry at the inlet monotonically increases along the length. As this figure shows, most data points from the simulations lie above the lines, i.e. $\Delta \varepsilon > |(\varepsilon|_{s=L} - \varepsilon|_{s=0})|$, meaning that the CFL does not change monotonically along the vessel length. As noted above, this is in contrast to what happens in straight tubes. Even for vessels in which $\varepsilon|_{s=L} - \varepsilon|_{s=0} \approx 0$, $\Delta \varepsilon$ may have large values. Furthermore, of the points that do nearly fall on the lines, some of them are on the $\Delta \varepsilon = +(\varepsilon|_{s=L} - \varepsilon|_{s=0})$ line, which means the asymmetry at the inlet monotonically increases with length. Overall,
Figure 5.3(B) suggests that while there may be a net increase or decrease in $\varepsilon$ between the inlet and outlet, the evolution of $\varepsilon$ over the length is much more complex, and, in most vessels, the time-averaged CFL profile significantly and non-monotonically varies along the vessel length.

Figure 5.4: Axial variation of the angular locations on the vessel cross section where the maximum and minimum time-averaged CFL thicknesses occur, denoted by the angles $\theta_{\delta=\delta_{\text{max}}}$ and $\theta_{\delta=\delta_{\text{min}}}$, respectively. Results are shown for the same six vessels as in Figure 5.3(A).

Additional quantification of the 3D, non-symmetric nature of the time-averaged CFL is made by considering the angular locations on the vessel cross-section where the maximum and minimum thickness values occur, denoted by the angles $\theta_{\delta=\delta_{\text{max}}}$ and $\theta_{\delta=\delta_{\text{min}}}$, respectively. As noted before, $\theta$ is defined using the vessel centerline as the origin and looking downstream in the flow direction. Here, $\theta = 0$ is located on the plane passing through the vessel centerline at the location on the perimeter closest to the upstream bifurcation (see Figure 5.1). Figure 5.4 presents the variations in $\theta_{\delta=\delta_{\text{max}}}$ and $\theta_{\delta=\delta_{\text{min}}}$ over the length of the same representative vessels as considered in Figure 5.3(A). When plotting these values along the vessel length, the sign of $\theta$ was chosen so as to result in a smooth curve without discontinuities. This figure shows that there are significant variations in $\theta_{\delta=\delta_{\text{max}}}$ and $\theta_{\delta=\delta_{\text{min}}}$ along the vessel length. Another interesting observation in Figure 5.4 is that $\theta_{\delta=\delta_{\text{min}}} \approx 0$ at
vessel entrances, meaning that the location of the minimum CFL thickness occurs on the side of the vessel that is closest to the upstream bifurcation. In contrast, \( \theta_{\delta=\delta_{\text{max}}} \) at vessel entrances is such that the maximum thickness is observed to occur at any location over the perimeter. Additional analysis of \( \theta_{\delta=\delta_{\text{max}}} \) and \( \theta_{\delta=\delta_{\text{min}}} \) and the underlying cellular-scale mechanisms will be considered in later sections. It is noted that while these examples utilize vessels on the arterial side, similar fluctuations and variations with vessel length were observed in post-capillary venules as well.

Together, Figures 5.2-5.4 demonstrate the highly complex, 3D and asymmetric nature of the time-averaged CFL in the vessels comprising the networks. Next, the mechanisms that give rise to such complexity are identified and analyzed. These mechanisms are discussed as they arise in three different facets of the networks, namely, along the vessel lengths, and over the bifurcations and the mergers.

### 5.3.2 Mechanism causing CFL variations along vessel length

In this section, a primary mechanism is identified causing the axial variations in the time-averaged CFL. In general, the CFL at the entrance to a vessel in the networks is asymmetric due to the presence of the upstream bifurcation or merger. If the vessel were straight, the asymmetric CFL at the entrance would gradually shift towards a symmetric profile with increasing axial distance. This has been shown \textit{in vivo} in such works as \cite{131}, and \textit{in silico} in \cite{90}, among others. Most vessels in the networks are, however, tortuous. We find that vessel tortuosity results in the increased asymmetry of the CFL along the length, as discussed below.

To quantify the effect of vessel tortuosity, the curvature of the vessel centerline is considered, defined as \( \kappa(s) = R/r(s) \), where \( r(s) \) is the radius of curvature of the vessel centerline at an axial location \( s \), and \( R \) is the vessel radius. As a measure of tortuosity, the mean absolute curvature is defined as

\[
\kappa = \frac{\sum_{i=1}^{N} |\kappa(s_i)|}{N}
\]  

which is computed by dividing each vessel into \( N \) finite segments, as previously described. In addition, as a measure of the axial variation of the CFL, the mean absolute change in
the asymmetry parameter $\varepsilon$ is defined as

$$\Delta \varepsilon = \frac{\Sigma_{i=1}^{N}|d\varepsilon(s_i)|}{N}$$  \hspace{1cm} (5.4)

In Figure 5.5, $\Delta \varepsilon$ is plotted as a function of $\kappa$ for all vessels. This figure shows that $\Delta \varepsilon$ generally increases with increasing $\kappa$, which implies that the CFL asymmetry is higher in tortuous vessels. The plot, however, also shows a noticeable scatter, which will be discussed later.

![Figure 5.5: Effect of vessel tortuosity. The mean absolute change in asymmetry, $\Delta \varepsilon$, is presented as a function of the mean absolute curvature, $\kappa$, for every vessel.](image)

Having established that the CFL asymmetry generally increases with increasing vessel tortuosity, now considered is how the CFL profile at an axial location is affected by the centerline curvature at that location. This is illustrated in Figure 5.6 using a representative vessel from one network. The time-averaged RBC core along the vessel length is shown, along with the cross-sectional profiles at four different axial locations. The centerline curvature, and the ratio $\overline{\delta_L}/\overline{\delta_R}$, which is the ratio of the time-averaged CFL thickness on diametrically opposite sides of the vessel in the plane of the figure, are plotted in Figure 5.6(B). In the present orientation, a negative curvature occurs when a vessel bends to the left looking downstream in the flow direction, and vice versa. At location (i), which is near the entrance, the profile is asymmetric ($\overline{\delta_L} > \overline{\delta_R}$) due to the influence of the upstream bifurcation. As the flow naturally develops along the axial direction, the CFL becomes
symmetric at location (ii). This symmetric profile however becomes asymmetric again at location (iii) where $\delta_L > \delta_R$. Beyond location (iii), the RBC core gradually shifts towards the left side of the vessel, and at location (iv), $\delta_L \lesssim \delta_R$. Hence, when the vessel bends to the right, the RBC core also shifts to the right, resulting in a thinner CFL on the right side but a thicker CFL on the left. Conversely, when the vessel bends to the left, the RBC core shifts to the left, resulting in a thinner CFL on the left side of the vessel and a thicker CFL on the right.

What these results imply is the presence of a \textit{curvature-induced migration} of the RBCs. To further illustrate this phenomenon, we simulate the flow of an isolated RBC in a semi-circular tube as shown in Figure 5.7. The flow is driven by a pressure difference between the inlet and outlet, and the cell is initially placed symmetrically on the centerline of the tube. If the tube were straight, the cell would flow along the centerline. However, for the curved tube, the predicted trajectory shows the cell deviates from the centerline and migrates towards the side of the vessel that has higher curvature. The hydrodynamic origin of such migration is as follows. In absence of inertia, as is the case for the present work, no secondary flow exists in a bending vessel of constant curvature. The pressure is then constant over each subsequent cross-section, and varies only along the axial direction. As such, the axial pressure gradient is larger for a streamline that is closer to the side of the vessel with shorter length than the one that is closer to the other side. This causes the maximum velocity to be shifted towards the side of the vessel with smaller arc length, as predicted in Figure 5.7. This shift in the velocity profile in the absence of inertia has been noted in a number of previous works (e.g. [126, 30, 193, 189]). Since a deformable cell tends to migrate in the direction of decreasing velocity gradient, the shifted velocity profile causes the cell to migrate away from the vessel centerline and towards the side of the vessel with the shorter arc length.

When considering the effect of the curvature-induced migration on the CFL profile in a curved vessel, this indicates that the local CFL thickness would be smaller on the side of the vessel with a higher curvature, and vice versa. Hence, the vessel curvature causes increased asymmetry of the CFL. If the vessel bends more often, the cross-sectional CFL profile would shift from one side to the other along the length.
Figure 5.6: Effect of vessel centerline curvature on the time-averaged CFL profile. (A) A representative vessel showing the time-averaged RBC core and the cross-sectional profiles at four axial locations marked as (i)(iv). $\delta_L(s)$ and $\delta_R(s)$ are the CFL thicknesses along the left and right sides of the vessel, respectively, in the plane of the figure looking in the flow direction (arrow). (B) $\delta_L/\delta_R$ (dashed line, left axis) and centerline curvature $\kappa$ (solid line, right axis) are plotted along the vessel length.

In addition to the curvature itself, the rate of change in curvature also locally enhances the CFL asymmetry. In Figure 5.7(B) it can be seen that $\kappa$ drops abruptly near profile (ii) and increases abruptly near profile (iii), which corresponds to the locations where $\delta_L/\delta_R$ most abruptly decreases and increases, respectively. Since the fluid velocity would be more skewed with increasing curvature, when the curvature changes over a small length it can induce an additional shift in the RBC core and enhance the asymmetry in the CFL. Such
Figure 5.7: Curvature-induced migration of a red blood cell. Motion of a red blood cell in a semi-circular tube is simulated in absence of inertia. The flow is driven by constant pressures over the cross-sections at the inlet and outlet. The vessel centerline is given by the dashed line, and the trajectory of the RBC center-of-mass is given by the continuous line. The cell trajectory deviates from the centerline and towards the side of the vessel with the shorter arc length. The contour on the right shows the velocity magnitude in cross-section A-B looking in the flow direction. The maximum velocity is shifted towards A.

behavior is in fact observed in the simple example in Figure 5.7, where the most abrupt changes to the RBC trajectory occur at the two locations where the vessel curvature changes (i.e. at the location where the vessel changes from straight to curved, and then back from curved to straight).

To quantify the effect of curvature change, a mean absolute change in vessel curvature is defined as

$$\Delta \kappa = \frac{\sum_{i=1}^{N} |d\kappa(s_i)|}{N}$$

(5.5)

where $\Delta \kappa(s_i)$ is the change in curvature in segment $i$ along the length. The mean absolute change in the CFL asymmetry, $\overline{\Delta \varepsilon}$, is plotted against $\overline{\Delta \kappa}$ in Figure 5.8. The general trend in the data suggests that $\overline{\Delta \varepsilon}$ increases with increasing $\overline{\Delta \kappa}$, and implies that changes in vessel curvature result in an increased and locally enhanced CFL asymmetry.
Figure 5.8: Influence of change in curvature on the CFL asymmetry. Plotted here is the cumulative change in centerline curvature versus the cumulative change in $\varepsilon$ for each vessel in the networks.

With regard to the data scatter in Figures 5.5 and 5.8, it should be noted that in a microvascular network the hemodynamic quantities such as flow rate and hematocrit are highly heterogeneous. As such, the CFL and its characteristics, such as the asymmetry, are also widely varying between different vessels, resulting in the data scatter. Additionally, the mean absolute change in asymmetry can be relatively small for some vessels with larger mean absolute curvature. This occurs in vessels where the RBC core at the entrance is skewed towards the side with higher curvature. Since the profile is already shifted towards the side favored by curvature, the average change in the CFL profile over the vessel length would be small. Changes to the CFL due to changes in curvature, however, are less affected by this, as is evident from the higher average slope of the data in Figure 5.8 than in Figure 5.5. It may be noted that $\Delta \kappa$ can also be considered as a measure of the vessel tortuosity, further bolstering the connection between vessel tortuosity and CFL asymmetry.

5.3.3 Development of the CFL over bifurcations

On the arterial side of the network, vessels continually bifurcate until the terminal capillaries are reached. The time-averaged CFL profiles are observed to change over the bifurcations. This is illustrated in Figure 5.9 using polar plots, with the radial coordinate representing
\( \delta_{\text{min}} \) or \( \delta_{\text{max}} \), and the angular coordinate representing \( \theta_{\delta=\delta_{\text{max}}} \) or \( \theta_{\delta=\delta_{\text{min}}} \). Data are shown at locations immediately upstream of bifurcations, and at locations immediately downstream of bifurcations (as marked in Figure 5.9(A)). In the discussion and analysis within this section, the \( \delta_{\text{min}} \) and \( \delta_{\text{max}} \) values are computed at \( s = L \) in vessels feeding a bifurcation (i.e. locations immediately upstream of the bifurcation), and at \( s = 0 \) in the daughter vessels (i.e. locations immediately downstream). A clear pattern is noted in the data for the downstream locations: \( \delta_{\text{min}} \) is predominantly localized near \( \theta = 0 \), which is the side of the daughter vessel closest to the bifurcation, and \( \delta_{\text{max}} \) predominantly occurs in the range \( \pi/2 < \theta < 3\pi/2 \), that is, near the side farther away from the bifurcation. In contrast, \( \delta_{\text{min}} \) and \( \delta_{\text{max}} \) in the upstream location feeding the bifurcation are not localized, but rather occur all over \( \theta \). Thus for most bifurcations, the CFL downstream narrows on the side of the daughter vessel that is closer to the bifurcation, and widens away from this side.

Figure 5.9: (A) Schematic of a bifurcation showing the feeding vessel (F), and daughter vessels (D1 and D2). Arrows indicate flow directions, and dashed lines indicate upstream and downstream locations where CFL properties are extracted. (B,C) Polar plots showing how a bifurcation affects the CFL asymmetry. The radial coordinate gives \( \delta_{\text{max}} \) (filled, black circles) and \( \delta_{\text{min}} \) (open, red circles) in \( \mu \text{m} \), while the angular coordinate gives their angular positions (\( \delta_{\text{min}} \) and \( \delta_{\text{max}} \)). As shown in (A), for the feeding vessel \( \theta = 0 \) corresponds to the right most side of the vessel. For the daughter vessels, \( \theta = 0 \) corresponds to the side that is nearest to the bifurcation. \( \theta = 0, \pi \) is the plane of bifurcation.

The predominant mechanisms by which the above changes in the CFL over a bifurcation occur are shown in Figure 5.10. The RBC core in the feeding vessel splits as it traverses a bifurcation, and the resulting cores in the downstream daughter vessels are typically shifted towards the inside edge of the bifurcation (\( \theta = 0 \)). This happens because the RBCs from
the central region of the feeding vessel directly flow into the daughter vessels via the inside edge of the bifurcation. As a result, the thickness of the CFL is smallest near this edge, but increases towards the opposite side. Additional discussions about Figure 5.10 are provided later.

Figure 5.10: Change in the CFL profiles over bifurcations. Cross-sectional profiles are shown upstream (feeding vessel) and downstream (daughter vessels) for four bifurcations. Profiles are looking downstream the flow direction. (A) A nearly symmetric profile in the feeding vessel becomes asymmetric in the daughter vessels as mirror images of one another. (B) A nearly symmetric profile upstream becomes more asymmetric in one daughter vessel ($D_1$) than in the other ($D_2$). (C) An asymmetric profile upstream becomes more asymmetric in one daughter vessel ($D_1$), but less asymmetric in the other ($D_2$). (D) An asymmetric profile upstream becomes more symmetric in both daughter vessels.

This change in the CFL characteristics causes a change in the CFL asymmetry between the upstream and downstream locations of a bifurcation. The change in the CFL asymmetry over all bifurcations in the simulated networks is presented in Figure 5.11(A) where the asymmetry parameter downstream ($\varepsilon_{D_1}$ and $\varepsilon_{D_2}$) is plotted against the upstream asymmetry $\varepsilon_F$. In this figure, the straight line gives $\varepsilon_{D_1} = \varepsilon_{D_2} = \varepsilon_F$, and the closed and open black circles are data points above and below this line, respectively. Here, 70% of the data points lie above this line, which shows that in the majority of the bifurcations the asymmetry downstream has increased relative to upstream. The remaining points which lie below the line however show that for these bifurcations the asymmetry decreases in one or both daughter vessels. This will be discussed later.

The change in the CFL asymmetry can be explained by looking at how the RBC core upstream splits into the daughter vessels as it flows through a bifurcation. This is shown in
Figure 5.11: (A) CFL asymmetry upstream ($\varepsilon_F$) and downstream ($\varepsilon_{D1}$ and $\varepsilon_{D2}$) of bifurcations. The straight line gives $\varepsilon_{D1} = \varepsilon_{D2} = \varepsilon_F$, and the closed and open black circles are data points above and below this line, respectively. (B) $\varepsilon_{D1}/\varepsilon_F$ versus $\varepsilon_{D2}/\varepsilon_F$. The regions marked as (I)-(IV) correspond to the behaviors (A-D), respectively, as described in Figure 5.10.

Figure 5.10. As seen for (A), a nearly symmetric CFL profile upstream becomes asymmetric downstream such that the profiles are essentially mirror images of one another. Similar asymmetries in the cross-sectional profiles downstream of a bifurcation have been predicted in theoretical analyses (e.g. [51]). In (B), the asymmetry increases in both daughter vessels, but this increase is more pronounced in one than the other. Here the CFL profile is nearly symmetric upstream, but the hematocrit profile upstream is skewed towards one daughter vessel. As such, this daughter vessel is on average more filled with RBCs resulting in reduced $\delta_{\max}$, while the other daughter vessel receives fewer RBCs resulting in an increased $\delta_{\max}$. In (C), the asymmetry increases in one daughter vessel but decreases in the other. This happens when the CFL profile upstream is already asymmetric. For example, if the upstream profile is shifted to the right, then the asymmetry would decrease in the right daughter vessel since the RBC core is more directly fed into this vessel. For the opposite reason, the asymmetry increases in the left daughter vessel. Such a discrepancy in the CFL between the daughter vessels is also observed when they have different diameters, with the larger asymmetry typically occurring in the smaller vessel. Lastly, in case (D) an
asymmetric CFL in the feeding vessel splits into less asymmetric profiles in both daughter vessels. Such behavior is observed in bifurcations with feeding vessels that are relatively shorter in length, where the effects of the upstream bifurcation come into play, or when one daughter vessel emanates as a small side branch from the feeding vessel. As such, this behavior is dictated by the geometry. This happens, however, in only a few bifurcations in the networks.

The behaviors described in Figure 5.10 are identified in a phase plot in Figure 5.11(B) which presents $\varepsilon_{D1}/\varepsilon_F$ versus $\varepsilon_{D2}/\varepsilon_F$. The line marked as (I) represents $\varepsilon_{D1} = \varepsilon_{D2}$ and, hence, the behavior shown by Figure 5.10(A). The regions (II), (III) and (IV) represent the behaviors shown by Figures 5.10(B), (C), and (D), respectively.

An important conclusion that is readily derived from Figure 5.11(B) is that for many bifurcations, $\varepsilon_{D1} \neq \varepsilon_{D2}$. What this means is that a discrepancy between the CFL asymmetry in the two daughter vessels is commonly observed. This can also be seen in the examples shown in Figures 5.10(B) and (C). This discrepancy arises primarily due to the discrepancy in $\bar{\delta}_{max}$ in the daughter vessels. As noted previously in Figure 5.9, the values of $\bar{\delta}_{max}$ at the downstream locations of the bifurcations have a much wider range, while the values of $\bar{\delta}_{min}$ have a very narrow range. It appears, as discussed below, $\bar{\delta}_{max}$ is dependent on specific hemodynamic conditions which are generally different in the daughter vessels.

Previous studies have shown that the CFL thickness is affected by both the volumetric flow rate and the hematocrit in a vessel [98]. For a given hematocrit, the thickness increases with increasing flow rate. Alternatively, for a given flow rate the CFL thickness decreases with increasing hematocrit. The interest here is in the CFL discrepancy between the two daughter vessels in a bifurcation. As such, the difference of $\bar{\delta}_{max}$ between the two daughter vessels is considered, namely $\bar{\delta}_{max,D1} - \bar{\delta}_{max,D2}$, as a measure of the discrepancy of the CFL. To relate this discrepancy to the hemodynamic quantities, one needs to consider not the flow rate or hematocrit, but rather the discrepancy in the flow rates and the RBC fluxes between the two daughter vessels. Note that the flow rate $Q$ and RBC flux $N$ are conserved over a bifurcation, that is, $Q_F = Q_{D1} + Q_{D2}$ and $N_F = N_{D1} + N_{D2}$. The relevant dimensionless quantities are the volume flow ratio ($Q^*$) and the RBC flow ratio ($N^*$) between a daughter
branch and feeding vessel, defined as

\begin{align}
Q_{D1}^* &= \frac{Q_{D1}}{Q_F} \quad (5.6) \\
N_{D1}^* &= \frac{N_{D1}}{N_F} \quad (5.7)
\end{align}

for daughter vessel \( D1 \), and similarly for \( D2 \). The computation of these quantities from the simulation data has been described in Section 4.2.1. As discussed, the quantities \( Q^* \) and \( N^* \) represent how the flow rate and RBCs in the feeding vessel are distributed to the daughter vessels. If \( Q^* = N^* \), the RBCs distribute in proportion to the flow rate, and the distribution is called proportionate. In general though, the distributioning is disproportionate at bifurcations, or \( Q^* \neq N^* \). This was shown in Chapter 4, as well as other previous studies, as discussed therein. Hence, if \( Q_{D1}^* > N_{D1}^* \), then \( Q_{D2}^* < N_{D2}^* \), and vice versa. This means that if the flow rate is higher than the RBC flux in one daughter vessel, the opposite is the case in the other daughter vessel. Therefore, when considering the comparative CFL behavior between the two daughter vessels, in one the flow rate effect will be more pronounced than the hematocrit effect, while in the other it will be reversed. For vessels where \( Q^* \) exceeds \( N^* \), the cells will tend to focus more towards the vessel center, and thus \( \bar{\delta}_{\text{max}} \) will tend to be greater than in the other daughter vessel where \( Q^* \) is less than \( N^* \). Therefore, if \( Q_1^* - N_1^* > 0 \), then \( \delta_{\text{max},D1} - \bar{\delta}_{\text{max},D2} > 0 \), and vice versa. This analysis, therefore, suggests a hydrodynamic basis for the CFL discrepancy between the daughter vessels in a bifurcation.

In Figure 5.12 \( Q_1^* - N_1^* \) is plotted versus \( \delta_{\text{max},D1} - \bar{\delta}_{\text{max},D2} \). Considered here are those bifurcations that follow the examples shown in Figures 5.10(A-C). The ones that exhibit the behavior given by Figure 5.10(D) are not considered. This is because, as noted previously, the CFL behavior given by Figure 5.10(D) is dictated by the geometry, while those given by Figures 5.10(A-C) are dictated by flow conditions. As seen in Figure 5.12, for nearly 80% of the data points, \( \delta_{\text{max},D1} - \delta_{\text{max},D2} > 0 \) if \( Q_1^* - N_1^* > 0 \), and vice versa, supporting the above analysis that the CFL discrepancy between the daughter vessels has a hydrodynamic origin.
Figure 5.12: A hydrodynamic basis of CFL discrepancy between two daughter vessels downstream of a bifurcation. Plotted here is flow rate and RBC flux discrepancy $Q_1^* - N_1^*$ for one daughter vessel versus the difference in the maximum CFL thickness between the daughter vessels, $\delta_{\text{max},D1} - \delta_{\text{max},D2}$.

5.3.4 Development of the CFL over mergers

On the venous side of a network, starting with the terminal capillaries, vessels continually merge to form larger venules. The CFL profiles are observed to change over the mergers. This is illustrated in Figure 5.13 using polar plots, with the radial coordinate representing $\bar{\delta}_{\text{min}}$ or $\bar{\delta}_{\text{max}}$, and the angular coordinate representing $\theta_{\delta=\delta_{\text{min}}}$ or $\theta_{\delta=\delta_{\text{max}}}$. Data is shown at locations immediately upstream and downstream of the mergers. Note that $\theta = 0, \pi$ is the plane of merger, and that for this section the $\bar{\delta}_{\text{min}}$ and $\bar{\delta}_{\text{max}}$ values are computed at $s = L$ in vessels feeding a merger (i.e. locations immediately upstream), and at $s = 0$ in the merged vessel (i.e. immediately downstream). At the downstream locations, $\bar{\delta}_{\text{min}}$ is predominantly localized near $\theta = 0$ and $\pi$, while $\bar{\delta}_{\text{max}}$ mostly occurs offset from these regions and around $\theta = \pm \pi/2$. In contrast, upstream $\bar{\delta}_{\text{min}}$ and $\bar{\delta}_{\text{max}}$ are not localized. This implies that for most mergers, the CFL downstream narrows in the plane of the merger, but widens away from this plane.

The mechanisms by which the change in the CFL occurs over the mergers are identified in Figure 5.14 using two example mergers selected from the simulated networks. For the example in (A), the RBC core downstream is flattened at the top and bottom ($\theta \approx \pi/2, 3\pi/2$).
Figure 5.13: (A) Schematic of a merger showing the feeding vessels \((F1 \text{ and } F2)\), and the merged vessel \((M)\). For the feeding vessels, \(\theta = 0\) corresponds to the side of the vessels nearest to the merger and in the plane of merger. For the merged vessel, \(\theta = 0\) corresponds to the right side (looking downstream the flow direction) of the vessel in the plane of merger. (B,C) Polar plots showing how CFL changes over the mergers. The radial coordinate gives \(\bar{\delta}_{\text{max}}\) (filled, black circles) and \(\bar{\delta}_{\text{min}}\) (open, red circles) in \(\mu m\), while the angular coordinate gives their angular positions \((\theta_{\delta=\delta_{\text{min}}} \text{ and } \theta_{\delta=\delta_{\text{max}}})\).

As such, the CFL widens near these locations. This behavior is reminiscent of the so-called geometric focusing that is observed in vessels with a rapid expansion in diameter (e.g. [52]). An important distinction should be noted when considering geometric focusing in a single vessel as opposed to two merging vessels. For a single vessel with uniformly expanding diameter, the focusing is uniform over the cross-section. However, as the present results show, for the mergers the focusing occurs at the top and bottom regions of the merged vessels. This is due to the two merging streams of RBCs which cause the focusing to occur away from the merger plane.

The second mechanism is concerned with the angles at which two feeding vessels merge. As can be seen in Figure 5.14(A), in the plane of the merger the CFL downstream is not the same on the right and left sides; it is smaller on the right side than on the left. This happens because the feeding vessel \(F2\) is nearly perpendicular to the merged vessel, while vessel \(F1\) is mostly aligned. The CFL on the right-most side of \(F2\) decreases as it enters the merged vessel due to the abrupt change in flow direction, or more specifically the abrupt change in curvature on that side of the vessel. The CFL on the left-most side of \(F1\) mostly stays the same due to the alignment with the merged vessel (see Figure 5.14(B)). Together this leads to the unequal narrowing of the profile on either side in the merger plane.
Figure 5.14: Mechanisms of change in CFL profiles over the mergers. Cross-sectional profiles of RBC cores are shown looking downstream in the flow direction. Dashed line is the plane of the merger, and R and L mean right and left sides of a vessel in this plane, respectively. (A) Geometric focusing effect results in an increase in the CFL thickness near the top and bottom ($\theta \approx \pi/2, 3\pi/2$) regions of the merged vessel. (B) The angle effect. The RBC core in the merged vessel (solid, red line) and those in the feeding vessels (dashed, red lines) are plotted together to show that the CFL changes more on the right side in the plane of merger than on the left side. (C) Discrepancy in flow rates and RBC fluxes in the two feeding vessels can cause nearly symmetric upstream CFL profiles to become asymmetric in the merged vessel.

The angle effect can be most easily identified when the flow rates and RBC fluxes from the two feeding vessels are equally balanced, for example, for the merger given in Figure 5.14(A,B). When the flow rates and RBC fluxes in the feeding vessels are different, their discrepancy contributes to the downstream CFL profile. Another example merger is shown in Figure 5.14(C). Here the merged vessel receives approximately 75% of both the flow and cells from $F1$, and 25% from $F2$. Accordingly, the focusing observed is more enhanced on
the right side of the merged vessel, which is the side nearest $F2$. It is noted that for this example the angle made by each feeding vessel is much smaller than that of the previous example, and thus the narrowing of the profile that occurs in the plane of the merger is nearly equal between the left and right sides. Furthermore, while the contribution fraction from each feeding vessel is different for this example, the distribution is proportionate, or $Q^* \approx N^*$ for both $F1$ and $F2$. An unequal narrowing between the sides was in fact observed in mergers with relatively small angles, but this occurred for cases where $Q^* \neq N^*$ for each feeding vessel. This is analogous to what was observed in bifurcations for $Q^* - N^*$ dependence. Here, the CFL thickness was observed to be larger on the side of the merged vessel closer to the feeding vessel with $Q^* - N^* > 0$. Such unequal narrowing was also observed downstream of a merger in vivo [129].

![Figure 5.15: The focusing effect on the change in the CFL over the mergers. Plotted here is the focusing parameter $f_p$ versus $\bar{\delta}_{\pm\pi/2,M}/\bar{\delta}_{\pm\pi/2,F1}$ and $\bar{\delta}_{\pm\pi/2,M}/\bar{\delta}_{\pm\pi/2,F2}$](image)

The focusing effect is observed to be more dominant in the simulated networks than the angle effect. It can be isolated by considering the CFL thickness at the top and bottom, $\theta = \pm\pi/2$. Then, the change in the CFL due to focusing alone is quantified by the ratio of the CFL thickness downstream of a merger to that upstream, both evaluated at $\theta = \pm\pi/2$, that is, $\bar{\delta}_{\pm\pi/2,M}/\bar{\delta}_{\pm\pi/2,F1}$ and $\bar{\delta}_{\pm\pi/2,M}/\bar{\delta}_{\pm\pi/2,F2}$. In terms of geometry alone, the focusing effect will depend on the increase in vessel diameter over the merger segment. A focusing
parameter \( f_p \) is introduced, defined as:

\[
f_p = \frac{r_m - r_f}{l_s}
\]  

(5.8)

where \( r_m \) and \( r_f \) are the radii of the merged and feeding vessels, respectively, and \( l_s \) is the axial distance between them through the merger. Then, \( f_p \) quantifies the rate of increase in vessel size over the merger. The focusing effect is expected to increase with increasing rate of diameter change, and would be the maximum for an abrupt change in diameter. In Figure 5.15, \( f_p \) is plotted versus \( \bar{\delta}_{\pm \pi/2,M} / \bar{\delta}_{\pm \pi/2,F1} \) and \( \bar{\delta}_{\pm \pi/2,M} / \bar{\delta}_{\pm \pi/2,F2} \) for all mergers. As evident, for most mergers the ratio is greater than one, and it increases with increasing \( f_p \).

Figure 5.16: Change in CFL asymmetry over the mergers. Plotted is the CFL asymmetry upstream of the mergers (in the feeding vessels), \( \varepsilon_{F1} \) and \( \varepsilon_{F2} \), versus that downstream (in the merged vessel), \( \varepsilon_M \). The straight line represents \( \varepsilon_{F1, F2} = \varepsilon_M \). Filled and open circles represent increase and decrease, respectively, in CFL asymmetry.

Finally, the change in CFL over the mergers is quantified by considering the CFL asymmetry upstream in the feeding vessels, \( \varepsilon_{F1} \) and \( \varepsilon_{F2} \), and downstream in the merged vessel, \( \varepsilon_M \). Figure 5.16 shows \( \varepsilon_{F1} \) and \( \varepsilon_{F2} \) versus \( \varepsilon_M \). For more than 70% of the feeding vessels, the asymmetry increases over the mergers. The increase in asymmetry is primarily caused by the focusing and angle effects as noted before, in conjunction with cell-flow discrepancies. For some mergers, the asymmetry decreases in the merged vessel relative to the feeding vessel. This occurs in feeding vessels with proportionate cell-flow distributions that have
small values of $f_p$ so that the focusing effect is small, or vessels that are aligned with the merged vessel so that the angle effect is small. Furthermore, if the asymmetry in the feeding vessel is such that $\bar{\delta}_{\text{max}}$ occurs near $\theta = 0$, and $\bar{\delta}_{\text{min}}$ occurs near $\theta = \pi$, then the CFL profile in the merged vessel is generally more symmetric.

5.4 Conclusions

A detailed quantitative analysis has been presented on the near-wall RBC-free layer. Unlike previous studies which primarily focused on the CFL development in single, isolated vessels, or isolated bifurcations or mergers, the present work studies the CFL as it develops naturally in a complex network. Furthermore, unlike in fully developed flows in straight tubes where the CFL is axisymmetric, the geometric complexity and the heterogeneity in hemodynamic quantities in the vascular networks make the CFL highly 3D and non-axisymmetric. The 3D asymmetric nature of the CFL is fully quantified, and the mechanisms are identified that lead to such complexities in different facets of the networks, namely, along the vessel lengths, and over the bifurcations and mergers. The new findings from this study presented in this chapter are summarized below.

It was shown that the CFL is distinctly three-dimensional and asymmetric, and significantly varies over all aspects of the networks. Such complexity occurs in both space and time, while the primary focus here has been on the time-averaged CFL. Its highly asymmetric nature has been quantified by means of an asymmetry parameter, which was observed to vary significantly along the vessel length. Such variations were predominantly non-monotonic, which indicated that CFL profiles did not simply become more symmetric over the length as they would in straight vessels, but rather continuously fluctuated in their degree of asymmetry. Furthermore, the shape of the CFL profile associated with the changing asymmetry was quantified by the angular locations of the maximum and minimum thicknesses. These angular locations were also shown to significantly fluctuate over the length, thus providing further quantitative insight into the highly 3D and asymmetric nature of the CFL in the networks.
It was shown that vessel tortuosity causes the CFL to significantly vary along the length. A curvature-induced migration of the RBCs was specifically identified, which causes the CFL to be smaller on the side of the vessel with smaller local arc length. Furthermore, it was shown that the changes in vessel curvature can locally enhance the CFL.

The vascular bifurcations are observed to change the CFL profile, and in the majority of them the CFL asymmetry increases. This is generally observed to occur such that the CFL downstream narrows on the side of the vessel nearest the upstream bifurcation, and widens on the other side. While such behavior has been observed previously, the present study elucidates the 3D nature. Specifically, four different behaviors are identified which characterize the means by which the CFL changes over the bifurcations. For many bifurcations, a discrepancy exists between the CFL asymmetry in the daughter vessels. A hydrodynamic basis underlying the discrepancy is presented that arises from a disproportionate partitioning of the flow rate and RBC flux in the daughter vessels.

Similar to the bifurcations, the mergers also change the CFL profile, and in the majority of them the asymmetry increases. For most mergers the downstream CFL narrows in the plane of the merger, but widens away from this plane. The mechanisms by which such changes occur are identified as a geometric focusing of two merging streams, and an angle effect associated with the relative orientation of each merging stream. The former causes an enhanced CFL out of the plane of the merger, while the latter causes an unequal narrowing of the CFL on either side in the merger plane. While collectively these contribute to the changing CFL, the focusing effect is observed to be dominant.

These findings have important hemorheological and other biophysical implications. The highly varying and asymmetric CFL profiles suggest a highly varying and asymmetric viscosity field near the vessel walls, which would eventually affect the apparent viscosity of blood, both at the level of individual vessels as well as at the whole network level. This, and, in particular, the finding of the curvature-induced migration, could motivate theoretical works for low-dimensional models of blood viscosity in curved vessels. In terms of biophysical implications, the results suggest that the margination of platelets, leukocytes, and other elements such as drug particulates may be impacted, especially in regions of enhanced CFL due to curvature-induced migration. Because these cells and particles are more rigid than
RBCs, they would be less affected by this geometry-induced migration and could marginate faster in the regions of locally enhanced CFL. The highly varying and asymmetric nature of the CFL also suggests that such local variations in wall shear stress may occur. This would likely cause a heterogeneity in the endothelial cell response over individual vessels. The present findings also suggest that certain regions in microvascular networks may be more susceptible to nitric oxide (NO) scavenging than others, as the CFL provides a barrier inhibiting this. For example, the consistent narrowing of the CFL observed on one side of vessels downstream of the bifurcations may represent a local region of increased NO scavenging, as would the sides of vessels with a relatively small radius of curvature. The present work could motivate investigation of these subtle but important issues.
Chapter 6

Wall shear stress in simulated microvascular networks

6.1 Overview

The wall shear stress in vessels comprising the microcirculation plays an important role in physiology, as discussed in Section 1.4.4. Because the size of the vessels is generally on the same order as that of the RBCs, both the geometry of the vasculature and the cellular-scale particulate nature of blood will affect the wall shear stress patterns throughout the networks. Experimental works that have studied this within complex geometries have provided insight into the variations in a two-dimensional sense. On the other hand, previous studies that have considered the 3D cellular scale details of blood have been limited to simplified geometries such as straight tubes.

This chapter bridges this gap by presenting a detailed study on the fully three-dimensional nature of spatial variations in the wall shear stress as they arise in the complex microvascular network simulations described in Chapter 3. After comparing values calculated from the simulations to both experimental and idealized values, some general features of the three-dimensional nature are presented. The magnitude of the variations in wall shear stress is shown to span an order of magnitude within even a small section of one network. The 3D asymmetry is quantified, and is shown to significantly vary over all vessels in the networks as well. Next, the effects of vessel curvature on these variations is quantified, and the vessel tortuosity is directly connected to such significant changes. Different patterns in wall shear stress variations over vessel length are also identified based on the nature of the curving vessels. Following this, the cellular influence on the wall shear stress is studied. Due to the complex geometry, the wall shear stress will spatially vary even in the absence of cells. What is not known, however, is the specific cellular contribution to such variations. To this end, the cellular influence is isolated by comparing the wall shear stress patterns from the
full DNS results with cells to that determined from separate simulations performed based on pure plasma flowing through the networks. From this, different locations in the networks are identified where the cellular influence is especially enhanced.

6.2 Calculation of wall shear stress

Different approaches have been taken to determine the wall shear stress in prior works. For example, the in vivo work of [130] determined this as $\tau_w = \mu V_{\text{edge}}/W$, where $\mu$ is the viscosity the plasma, $V_{\text{edge}}$ is the velocity of the edge of the RBC core, and $W$ is the width of the cell-free layer. With this, the quantity $V_{\text{edge}}/W$ is an approximation to the wall shear rate, which assumes a linear velocity profile through the CFL, and $V_{\text{edge}}$ was determined based on the observed motion of RBCs. [115] determined the wall shear stress in vessels in vivo based on the measured pressure drop between the inlet and outlet of each vessel, and the diameter and length of the vessel, as $\tau_w = \Delta P D/4L$ (i.e. force balance on a cylindrical control volume). A similar approach was taken in [152] in their mathematical modeling based on in vivo data. Other in vivo works (e.g. [104, 61]) have calculated the wall shear rate based on a Poiseuille flow as $\gamma_w = 8V_{\text{avg}}/D$, and determined the wall shear stress as the product of this and some measure of blood viscosity, $\mu_{\text{blood}}$. The average velocity $V_{\text{avg}}$ is typically determined from observed RBC velocities, and $\mu_{\text{blood}}$ is typically determined based on an empirical correlation in terms of vessel diameter and hematocrit (e.g. [154]). [95] improved on this by determining the shear rate as the slope of the velocity profile within the RBC core adjacent to the CFL.

Somewhat similar approaches have been adopted in previous computational modeling. [83, 84] determined the wall shear stress based on idealized Poiseuille flow in their 1D modeling of blood flow in constructed vascular trees. [66] performed 3D cellular-scale simulations of RBCs in a straight tube using a boundary integral-based approach, and determined the wall shear stress by computing the traction vector at the vessel wall. [206], in their 2D Lattice Boltzmann simulations of cellular scale flow in a straight vessel, determined it based on plasma viscosity and the velocity gradient at the wall. A similar approach was taken in [205], who also performed 2D Lattice Boltzmann simulations.
The method used in the present work is similar to that of [66] in that the wall shear stress is studied by determining the traction at each vertex of the mesh defining the vessel walls. As mentioned in Section 2.4.3, the traction ($\mathbf{t}$) is a vector giving the force per area at the surface, and is related to the stress tensor $\mathbf{\sigma}$ by $\mathbf{t} = \mathbf{n} \cdot \mathbf{\sigma}$, where $\mathbf{n}$ is the unit normal vector at the surface. In the present work a cylindrical coordinate system local to each mesh vertex is used. This is defined such that the radial component ($\mathbf{e}_r$) points inward from the vessel wall, the axial component ($\mathbf{e}_a$) points in the direction of the mean flow, and the angular component is defined as $\mathbf{e}_\theta = \mathbf{e}_a \times \mathbf{e}_r$. The radial basis vector in this coordinate system is the unit normal vector at the surface, i.e. $\mathbf{n} = \mathbf{e}_r$, and thus the traction vector is written as:

$$\mathbf{t} = \sigma_{rr} \mathbf{e}_r + \sigma_{r\theta} \mathbf{e}_\theta + \sigma_{ra} \mathbf{e}_a$$  \hspace{1cm} (6.1)

This convention is illustrated in Figure 6.1.

Figure 6.1: Schematic illustrating the local cylindrical coordinate system used at each vertex of the mesh defining the vessel walls. Components of the traction vector are shown, with the radial component pointing inward normal to the vessel wall, the axial component pointing in the direction of the time-averaged velocity field ($\mathbf{v}$) a short distance from the wall, and the angular component pointing in the direction given by their cross-product.

To calculate $\mathbf{t}$ at each mesh vertex, $\mathbf{e}_r$ is first determined simply from the local geometry of the vessel surface. $\mathbf{e}_a$ is determined numerically by interpolating from the time-averaged velocity field a short distance inward from the wall. Specifically, the velocity vector $\mathbf{v}$ as denoted in Figure 6.1 is determined from the time-averaged velocity field of the full DNS solution, and this is used to define the direction of $\mathbf{e}_a$. This is based on the general idea
that the mean flow moves in the axial direction. Mathematically speaking $e_a$ needs to be perpendicular to $e_r$, and to ensure this it is defined by projecting $v$ onto the plane defined by $e_r$:

$$e_a = \frac{v - (v \cdot e_r) e_r}{\| v - (v \cdot e_r) e_r \|}$$  \hspace{1cm} (6.2)$$

The stress components in the cylindrical coordinate system are given by [136]:

$$\sigma_{rr} = -p + 2\mu \frac{\partial u_r}{\partial r}$$
$$\sigma_{r\Theta} = \mu \left( \frac{1}{r} \frac{\partial u_r}{\partial \Theta} + \frac{\partial u_\Theta}{\partial r} - \frac{u_\Theta}{r} \right)$$
$$\sigma_{ra} = \mu \left( \frac{\partial u_r}{\partial a} + \frac{\partial u_a}{\partial r} \right)$$  \hspace{1cm} (6.3)$$

where $\mu$ is taken as the viscosity of the plasma. At the surface $u_r = u_a = u_\Theta = 0$, and thus the components of the traction vector are:

$$t_r = -p + 2\mu \frac{\partial u_r}{\partial r}$$
$$t_\Theta = \mu \frac{\partial u_\Theta}{\partial r}$$
$$t_a = \mu \frac{\partial u_a}{\partial r}$$  \hspace{1cm} (6.4)$$

The derivatives are evaluated numerically at each mesh vertex using second-order differencing inwards from the surface. The velocity components at each location in the stencil are first interpolated from the DNS velocity field, and then converted to the local cylindrical coordinate system at the vertex. The wall shear stress in the following sections is specifically the axial component of the traction vector, and is denoted by $\tau_a$ for consistency with the commonly used symbol for shear stress.

In general $\tau_a$ is a function of both space and time, and is represented as $\tau_a(s, \theta, t)$. Here, $s$ gives the axial position along a vessel length and $\theta$ gives the angular location, as shown in Figure 6.2. The focus of this chapter is on studying the time-averaged wall shear stress, or $\bar{\tau}_a(s, \theta)$, which is determined by averaging $\tau_a(s, \theta, t)$ over the entire simulation time. Any mention of or discussion involving the term wall shear stress in this chapter thus refers to the time-averaged quantity. The time-dependent nature of the wall shear stress is left for future work, as are the other directional components, namely those given by $t_r$ and $t_\Theta$ in Eq. 6.4.
To validate the present approach for determining the wall shear stress, comparisons are made with values reported in previous in vivo works. The average wall shear stress for each vessel is determined from the DNS data as:

\[
\overline{\tau}_a = \frac{1}{2\pi L} \int_0^L \int_0^{2\pi} \tau_a(s, \theta) d\theta ds
\]  

(6.5)

where, \(L\) gives the length of the vessel. With values reported in previous works, distinction is typically made with regard to both vessel diameter as well as the location of the vessels within the microvascular network hierarchy (i.e. arterial, capillary, or venous). To reiterate for clarity, vessels on the arterial side continually bifurcate into smaller vessels until the capillaries are reached, after which vessels are on the venous side as they continually merge to form larger venules. Table 6.1 presents a comparison between \(\overline{\tau}_a\) as computed in the simulations and that reported in prior in vivo works by giving the range of wall shear stress within the reported range of vessel diameters, broken down by location in the network.
<table>
<thead>
<tr>
<th>Work</th>
<th>Vessel Diameter $\mu$m</th>
<th>Location in Network</th>
<th>$\bar{\tau}_a$ dyne/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>8-24</td>
<td>Arterial</td>
<td>6-50</td>
</tr>
<tr>
<td>[115]</td>
<td>8-26</td>
<td>Arterial</td>
<td>5-100</td>
</tr>
<tr>
<td>[162]</td>
<td>13-30</td>
<td>Arterial</td>
<td>5-30</td>
</tr>
<tr>
<td>[130]</td>
<td>30-67</td>
<td>Arterial</td>
<td>20-50</td>
</tr>
<tr>
<td>[104]</td>
<td>6-12</td>
<td>Arterial</td>
<td>10-150</td>
</tr>
<tr>
<td>Present</td>
<td>6-7</td>
<td>Capillary</td>
<td>4-65</td>
</tr>
<tr>
<td>[115]</td>
<td>~7</td>
<td>Capillary</td>
<td>10-50</td>
</tr>
<tr>
<td>[105]</td>
<td>4-7</td>
<td>Capillary</td>
<td>20-100</td>
</tr>
<tr>
<td>Present</td>
<td>6-20</td>
<td>Venous</td>
<td>3-40</td>
</tr>
<tr>
<td>[115]</td>
<td>7-26</td>
<td>Venous</td>
<td>20-30</td>
</tr>
<tr>
<td>[95]</td>
<td>12-39</td>
<td>Venous</td>
<td>2-5</td>
</tr>
<tr>
<td>[105]</td>
<td>8-24</td>
<td>Venous</td>
<td>5-40</td>
</tr>
</tbody>
</table>

Table 6.1: Comparison between simulation data for $\bar{\tau}_a$ and that of previous in vivo works. Data for vessels on the arterial and venous sides are separately listed, as is data for capillary vessels.

It is generally observed that $\bar{\tau}_a$ as computed in the simulations agrees well for the range of diameters associated with each network location. Wall shear stresses in vivo are typically higher on the arterial side than the venous side, and this is reflected in the data here. It is also noted that, in general, a wide range of wall shear stress values can be observed in this table. In some of these prior works, values are given in terms of vessel diameter, while in others only a range of diameters is given. The magnitude of the wall shear stress will depend on the vessel diameter, and this will contribute to this somewhat wide range of $\bar{\tau}_a$. Additionally, the hematocrit associated with values reported varied among the different works, which will also contribute to this. For the present simulations the hematocrit in the largest feeding arterioles was approximately 30%, as previously mentioned. In the other works listed this varied from approximately 20% to 45%. In terms of vessel diameter, a more detailed comparison is presented in Figure 6.3. Here, $\bar{\tau}_a$ is compared with the in vivo data of [105], who determined the wall shear stress in capillaries and post-capillary venules in the human eye. As is evident, a good agreement between the two is observed over the range of diameters considered.
6.2.1 Comparison with idealized values

To further validate the approach for calculating the wall shear stress, comparisons are made with idealized values for each vessel. A theoretical estimate for the wall shear stress can be formulated based on the force balance on a cylindrical control volume, resulting in the classical expression for wall shear stress:

\[ \tau_w = \frac{\Delta P \cdot D}{4L} \]  

as mentioned previously. This value is computed for each vessel based on the time-averaged DNS data using the pressure difference \( \Delta P \) between the inlet and outlet, in conjunction with the vessel diameter \( D \) and length \( L \). As this is a time-averaged value, it is referred to here as \( \bar{\tau}_w \). Figure 6.4 provides a plot of \( \bar{\tau}_w \) versus \( \bar{\tau}_a \) as computed using the above approach.

Figure 6.4(A) provides a scatter plot of the data for all vessels. As can be seen, in many of them there is a 1:1 correspondence between the two values, as is evident from the clustering of the data points about the straight black line which represents \( \bar{\tau}_a = \bar{\tau}_w \). It is also observed that in some vessels \( \bar{\tau}_w \) is much greater than \( \bar{\tau}_a \). Figure 6.4(B) shows data
6.3 Results and discussion

6.3.1 3D spatial variation of the wall shear stress

First described is the general nature of the spatial variations of the wall shear stress that occur in the simulated networks. As a representative example of such variations, Figure 6.5 provides a view of a small section of one network. Figure 6.5(A) gives contours of $\bar{\tau}_a$ on the vessel walls in a plan-view perspective, with lighting adjusted so as to remove any depth effect in the plane of view and better highlight the variations. Values on the contour scale...
box are in units of dyne/cm$^2$, and as can be seen, even in this small section the values span an order of magnitude. Four separate cross-sections are identified on an example vessel in this figure, identified as (i)-(iv), respectively. The angular coordinate $\theta$ is defined as shown in the inset for (i), where $\theta = 0$ corresponds to the side of the cross-section nearest the upstream bifurcation. This same convention is used for (ii)-(iv) as well.

Figure 6.5: Spatial variation of the wall shear stress in a small section of one network. (A) Contours of $\bar{\tau}_a$ on the vessel walls in a plan-view perspective, with lighting adjusted so as to remove any depth effect in the plane of view and better highlight the variations. The red arrows give the flow direction. (B) The angular variation of the wall shear stress at cross-section(i)-(iv) as identified in (A). The angular coordinate $\theta$ is defined as shown in the inset for (A,i), and the same convention is used for cross-sections (ii)-(iv). Units for $\bar{\tau}_a$ are in dyne/cm$^2$. 
Figure 6.5(B) provides the angular variation of the wall shear stress around the vessel wall for each of these cross-sections, as identified. At the inlet to the vessel, Figure 6.5(B,i) shows that the maximum wall shear stress occurs at the edge nearest the upstream bifurcation (i.e. $\theta \approx 0$), the minimum occurs at $\theta \approx \pi \pm \pi/3$, and in between varies as shown. Downstream at cross-section (ii), the wall shear stress values span an even wider range over the cross section, with the extremum occurring on similarly opposite sides of the vessel. At cross-section (iii) the locations of the minimum and maximum each shift by roughly $\pi$ radians compared with (ii), although the axial distance between them is less than two vessel diameters. At cross-section (iv) the extremum of $\tau_a$ are located at the same angular positions as in (iii), although the range spanned by them has doubled.

The variation of the wall shear stress over each of these cross-sections is significant, and the patterns formed are all highly asymmetric. The contours shown on other vessels throughout this figure also indicate a similar high degree of heterogeneity in $\tau_a$. Similar to what was done with the CFL in Chapter 5, the highly varying and asymmetric nature of the wall shear stress is quantified by first considering an asymmetry parameter defined as:

$$\epsilon(s) = \frac{\tau_{a,\text{max}}(s)}{\tau_{a,\text{min}}(s)}$$

(6.7)

where $\tau_{a,\text{max}}(s)$ and $\tau_{a,\text{min}}(s)$ are the maximum and minimum values, respectively, of the wall shear stress over the cross section ($0 \leq \theta < 2\pi$) at any location $s$ along the vessel length. This gives a value of 1 for a symmetric profile, and values greater than one for increasing asymmetry. $\epsilon(s)$ is plotted in Figure 5.3(A) for a few representative vessels with length-to-diameter ratio in the range of 10-15. The observations made from this on the nature of the wall shear stress are very similar to those made regarding the nature of the CFL as discussed in Section 5.3.1. In the majority of vessels, even those that have a relatively long length, $\tau_a$ does not simply tend towards an axisymmetric profile as it would in a straight tube. While in some vessels $\epsilon$ is lower at the outlet than at the inlet, there are significant fluctuations along the length, often resulting in the extremum occurring at locations along the length away from the inlet or outlet. In other vessels, similar fluctuations are observed, and the profile either has a higher $\epsilon$ value at the outlet than it does at the inlet, or it is roughly the same at the inlet and outlet. All of these behaviors occur due to the complexity of the
networks and tortuous nature of the vessels, because in a straight tube any $\tau_0$ asymmetry at the inlet would monotonically decrease over the length.

![Figure 6.6](image)

**Figure 6.6:** (A) The wall shear stress asymmetry parameter $\epsilon$ along the length for several representative vessels in the networks. (B) The change in asymmetry, $\epsilon|_{s=L} - \epsilon|_{s=0}$, between vessel inlet and outlet versus the cumulative change $\Delta \epsilon$ over the entire length, for all vessels (data points). The straight lines correspond to a monotonic change in $\epsilon$ over the length.

Next, a quantitative measure is provided over all vessels in the networks of the degree of asymmetry in the wall shear stress. Specifically, Figure 6.6(B) provides a plot of the change in asymmetry between vessel inlet and outlet, i.e. $\epsilon|_{s=L} - \epsilon|_{s=0}$, versus the cumulative change in asymmetry over the vessel length, $\Delta \epsilon$. Here $\Delta \epsilon$ is computed for each vessel in the same way as was done for the CFL in Section 5.3.1. The two straight lines in this figure correspond to $\epsilon$ monotonically changing along the vessel length. A monotonically decreasing asymmetry in the wall shear stress, as would occur in a straight tube, is given
by the line $\Delta \epsilon = -(\epsilon|_{s=L} - \epsilon|_{s=0})$, while a monotonically increasing asymmetry is given by the line $\Delta \epsilon = +(\epsilon|_{s=L} - \epsilon|_{s=0})$. This figure definitively shows that for the vast majority of the vessels, $\epsilon$ does not change monotonically over the length, and fluctuates significantly. A wide variety of changing wall shear stress behaviors within vessels is suggested by the data shown in Figure 6.6.

Overall, Figure 6.6(B) suggests that while there may be a net increase or decrease in $\epsilon$ between the inlet and outlet, the evolution of $\epsilon$ over the length is much more complex, and, in most vessels, the time-averaged $\bar{\tau}_a$ profile significantly and non-monotonically varies along the vessel length.

Figure 6.7: Axial variation of the ‘aspect ratio’ of the wall shear stress profile for the same representative vessels as in Figure 6.6(A). Here the subscripts $L$ and $R$ refer to the left and right-most sides of the vessel cross-section, looking downstream in the direction of the flow, and $TB$ refers to top and bottom.

Additional quantification of the 3D spatial variations and non-symmetric nature of the wall shear stress is made by considering the relationship between $\bar{\tau}_a$ at different locations
on each cross-section, and how it changes along the length. If one considers a vessel cross-section from the perspective of looking downstream in the direction of the flow, the locations considered here are the left- and right-most sides of the vessel, and top and bottom of the vessel. For the example vessel in Figure 6.5(A), the $\theta = 0$ location is the left-most side, $\theta = \pi$ is the right-most side, and the top and bottom are offset from these by $\pi/2$ radians. Figure 6.7(A) plots the ratio $\bar{\tau}_{a,L}/\bar{\tau}_{a,TB}$ along the length of the same representative vessels as in Figure 6.6(A), and Figure 6.7(B) plots $\bar{\tau}_{a,R}/\bar{\tau}_{a,TB}$. Here the subscripts L and R refer to the left- and right-most sides of the vessel. Due to the planar nature of the networks, the wall shear stress at the top and bottom are approximately the same, and are thus referred to by the subscript TB. In general this ratio provides a geometric parameter analogous to an ‘aspect ratio’ of the wall shear stress profile at individual vessel cross-sections along the length. As can be seen in Figure 6.7, both of these quantities vary significantly over the length. In each plot the ratio constantly changes over the length between values less than 1 and greater than 1, indicating that at certain points along the vessel length the wall shear stress is greater on the sides, and in others it is greater at the top and bottom. Together these paint an additional picture quantifying the means by which the wall shear stress varies in 3D space throughout the networks.

Collectively Figures 6.5-6.7 illustrate the highly complex three-dimensional spatial variations of the wall shear stress, as well as its asymmetric nature, as it arises in complex networks. Next, the mechanisms that give rise to such complexity over vessel lengths are identified and analyzed.

6.3.2 Mechanism causing wall shear stress variations along vessel length

As was discussed in Section 5.3.2, in curved vessels the velocity profile is shifted more towards the side of the vessel with the smaller radius of curvature. It follows from this that the wall shear stress would be higher on this side of the vessel owing to the relatively larger velocity gradient near the wall, compared with the other side of the vessel with the larger radius of curvature. This is based on idealized conditions, and such behavior was in fact shown analytically by modeling the flow of a two-phase fluid in the absence of inertia through a circular tube of constant curvature [193].
In the complex networks here, the vessels are tortuous with curvatures that widely vary. The effect of vessel tortuosity was quantified in Section 5.3.2 by the mean absolute curvature per vessel, \( \bar{\kappa} \) (Eq. 5.3). As measure of the axial variation of the wall shear stress, the mean absolute change in the asymmetry parameter \( \epsilon \) is defined similarly to Eq. 5.4

\[
\Delta \epsilon = \frac{\sum_{i=1}^{N} |d\epsilon(s_i)|}{N}
\]

(6.8)

In Figure 6.8, \( \Delta \epsilon \) is plotted as a function of \( \bar{\kappa} \) for all vessels. This figure shows that \( \Delta \epsilon \) generally increases with increasing \( \bar{\kappa} \), which implies that the wall shear stress asymmetry is generally higher in more tortuous vessels.

![Figure 6.8: Effect of vessel tortuosity. The mean absolute change in asymmetry, \( \Delta \epsilon \), is presented as a function of the mean absolute curvature, \( \bar{\kappa} \), for every vessel.](image)

Having established that the wall shear stress asymmetry generally increases with increasing vessel tortuosity, now considered is how the wall shear stress profile at an axial location is affected by the centerline curvature at that location. This is illustrated in Figure 6.9 using a representative vessel from one network. Contours of the wall shear stress are given on the surface of the vessel in Figure 6.9(A), in a manner similar to Figure 6.5(A). Four cross-sections along the length of the vessel are identified as (i)-(iv), and the black arrow gives the flow direction. Figure 6.9(B) provides plots of \( \bar{\tau}_a \) as a function of angular position at cross-sections (i)-(iv) as identified. The convention used to define \( \theta \) is given in
the inset to cross-section (i) in Figure (A). Figure 6.9(C) plots the vessel centerline curvature as well as the ratio $\bar{\tau}_{a,L}/\bar{\tau}_{a,R}$ over the length of the vessel. $\bar{\tau}_{a,L}$ and $\bar{\tau}_{a,R}$ are the wall shear stress on the left and right sides of the vessel, respectively, as indicated in this figure and as previously described.

From the contours in Figure 6.9(A) it can be seen that the changes in vessel curvature at cross-section (i)-(iii) directly correspond to sharp changes in the wall shear stress contours. Here the maximum and minimum values of the wall shear stress occur on diametrically opposite sides of the vessel, and switch back and forth between the left and right sides at these locations. The profiles in Figure 6.9(B) and Figure 6.9(C) quantitatively show this dynamic behavior.

Figure 6.9(B) shows that at location (i), which is near the entrance, the profile is asymmetric such that the maximum occurs near $\theta = 0$ and the minimum occurs near $\theta = \pi$. These correspond to to that given by the $\bar{\tau}_{a,R}$ and $\bar{\tau}_{a,L}$ quantities at this axial location, respectively. At location (ii), the profile shifts such that the angular locations of the extremum are reversed. At location (iii) the profile shifts back again to a similar profile as observed at (i), but the range spanned by the values is larger. Lastly, at location (iv) the profile is closer to symmetric, although the maximum occurs at $\theta = \pi$ and the minimum occurs at $\theta = 0$. Figure 6.9(C) shows how these changes to the wall shear stress profile directly correspond to the centerline curvature. In the present orientation, a negative curvature occurs when a vessel bends to the left looking downstream in the flow direction, and vice versa. At location (i), $\kappa$ is positive and $\bar{\tau}_{a,L} < \bar{\tau}_{a,R}$. At location (ii), $\kappa$ is negative and $\bar{\tau}_{a,L} > \bar{\tau}_{a,R}$. Then again at location (iii), $\kappa$ is positive and $\bar{\tau}_{a,L} < \bar{\tau}_{a,R}$. In between these regions the the same relationship holds, namely $\kappa > 0$ for $\bar{\tau}_{a,L} < \bar{\tau}_{a,R}$ and $\kappa < 0$ for $\bar{\tau}_{a,L} > \bar{\tau}_{a,R}$. At location (iv) the profile is closer to symmetric, and the curvature of the vessel between (iii) and (iv) is close to zero.

Collectively Figures 6.9(A-C) show how the wall shear stress profile changes with the vessel curvature. This behavior is caused by the effects of the curvature on the flow field, and by extension, the curvature-induced migration of the RBCs described in Section 5.3.2. If the vessel bends more often, the cross-sectional wall shear stress profile would shift from one side to the other along the length. Figure 6.10 below provides a visualization of such a...
Figure 6.9: Effect of vessel centerline curvature on the wall shear stress profile. (A) A representative vessel showing contours of the wall shear stress. Units are in dyne/cm². (B) Cross-sectional profiles at four axial locations marked as (i)-(iv) in (A) giving $\overline{\tau_a}$ as a function of angular position at the respective location along the length. (C) $\overline{\tau_{a,L}}/\overline{\tau_{a,R}}$ (dashed line, left axis) and centerline curvature $\kappa$ (solid line, right axis) are plotted along the vessel length. As identified in (A), $\overline{\tau_{a,L}}(s)$ and $\overline{\tau_{a,R}}(s)$ are the wall shear stress values along the left and right sides of the vessel, respectively, in the plane of the figure looking in the flow direction (black arrow).
process as occurs in two representative vessels. Figure 6.10(A) is for a vessel that bends back and forth over the length, while Figure 6.10(B) is for a vessel that bends in one direction over the length. The individual curves in each figure give the $\bar{\tau}_a$ versus $\theta$ relationship at an individual axial location along the length, and all axial locations are provided. For the vessel that bends back and forth, the shifting of the wall shear stress profile manifests in the bimodal-type shape formed by the curves in Figure 6.10(A). For the vessel that bends in one direction over the length, the profile stays shifted to one side of the vessel, and the curves form the composite shape shown in Figure 6.10(B). Note that here the angular coordinate $\theta$ is shifted to better visualize this behavior such the the left and right sides of the vessels occur at $\theta = \pi/2, 3\pi/2$. Together, the curves in each figure illustrate the 3D variation in the wall shear stress over the respective vessels.

Figure 6.10: Angular variations of wall shear stress along the length of two representative vessels. The individual curves in each figure give the $\bar{\tau}_a$ versus $\theta$ relationship at an individual axial location along the length, and all axial locations are provided. (A) Vessel that bends back and forth over the length. (B) Vessel that bends in one direction over the length.

In addition to the curvature itself, the rate of change in curvature also locally enhances the wall shear stress asymmetry. This is evident from the trends in Figure 6.9. As discussed in Section 5.3.2, since the fluid velocity would be more skewed with increasing curvature, when the curvature changes over a small length the change to the velocity gradient will also occur more abruptly. Furthermore, it will cause the RBCs to flow closer to the vessel walls in these local regions, as shown previously, also enhancing the wall shear stress.
Using Eq. 5.5, the effect of curvature change on the change in wall shear stress asymmetry is quantified in Figure 6.11 by plotting $\Delta\epsilon$ versus $\Delta\kappa$. The general trend in the data suggests that $\Delta\epsilon$ increases with increasing $\Delta\kappa$, and implies that changes in vessel curvature result in an increased and locally enhanced wall shear stress asymmetry.

![Figure 6.11: Influence of change in curvature on the wall shear stress asymmetry. Plotted here is the cumulative change in centerline curvature ($\Delta\kappa$) versus the cumulative change in asymmetry ($\Delta\epsilon$) for each vessel in the networks.](image)

Per the discussion at the end of Section 5.3.2, it is noted that the data scatter in both this figure and Figure 6.8 arise because in a microvascular network the hemodynamic quantities such as flow rate and hematocrit are highly heterogeneous. As such, the wall shear stress and its characteristics, such as the asymmetry, are also widely varying between different vessels, resulting in the data scatter. Additionally, the mean absolute change in asymmetry can be relatively small for some vessels with larger mean absolute curvature. This occurs in vessels where the wall shear stress profile at the inlet to the vessel is already shifted to the side favored by the curvature. It is noted that generally speaking the magnitude of the wall shear stress is inversely related to the thickness of the CFL [130]. That is, for a smaller CFL thickness (i.e. RBC core is closer to the vessel walls) the wall shear stress will tend to be higher owing to the greater near-wall presence of the RBCs. Thus in vessels where the RBC core at the entrance is skewed towards the side with higher curvature, the wall shear stress profile can also also be such that it is maximum on this side. Since the profile is
already shifted towards the side favored by curvature, the average change in the wall shear stress profile over the vessel length would be small.

6.3.3 Isolating the cellular influence on wall shear stress

In this section the influence of the RBCs on the wall shear stress is isolated by comparing the results based on the DNS data with cells to that computed for pure plasma. To do this, the simulations are run to a steady state without cells, and $\overline{\tau}_{a,\text{plasma}}$ is computed as described in Section 6.2. At each vertex of the mesh defining the vessel walls for each network, the ratio $\overline{\tau}_a/\overline{\tau}_{a,\text{plasma}}$ is then computed. Figure 6.12 gives the contours of this value for each of the three networks for the fixed inlet flow rate boundary condition cases.

(a) Arterial vs. venous sides of the networks

First, it can be qualitatively observed in Figure 6.12 that in each of the networks the impact of the RBCs on the wall shear stress is more pronounced in vessels on the venous side than on the arterial side. That is, the contours of $\overline{\tau}_a/\overline{\tau}_{a,\text{plasma}}$ are generally higher in vessels downstream of the capillaries (i.e. greener shade in these figures) and lower in vessels upstream (i.e. bluer shade in these figures). This is interesting because it is generally known that the wall shear stress itself is higher on the arterial side, which was also observed for the present work as shown in Section 6.2. In spite of this, these results show that when considering the influence of the RBCs on the wall shear stress, this is more pronounced on the venous side.

This behavior can be explained in terms of the hydrodynamics associated with microvascular network blood flow. Generally speaking, the same volume of fluid that flows through the vessels on the arterial side will also flow through the vessels on the venous side. Since on the venous side the vessel diameters are, in general, larger, the difference in near-wall velocity profiles between blood and pure plasma that can arise under such circumstances can be more pronounced in the larger vessel. This then results in the wall shear stress ratio between blood and pure plasma being greater on the venous side. This can be readily observed in networks such as that of Figure 6.12(C), where vessels on the arterial side directly correspond to vessels on the venous side. This direct correspondence is illustrated in Figure
Figure 6.12: Contours of the ratio of wall shear stress as computed from the full DNS results with cells to that of pure plasma, $\bar{\tau}_a / \bar{\tau}_{a,\text{plasma}}$. (A-C) Results for each of the three simulated microvascular networks for the fixed inlet flow rate boundary condition cases.

6.13(A) for this particular network. The vessel order in the Strahler ordering scheme as discussed in Section 3.2 is also shown. The data points giving the average $\bar{\tau}_a / \bar{\tau}_{a,\text{plasma}}$ per
Figure 6.13: The influence of the RBCs on the wall shear stress is more pronounced in vessels on the venous side than on the arterial side. (A) Contours of $\bar{\tau}_a/\bar{\tau}_{a,\text{plasma}}$ from Figure 6.12(C). Vessel orders are denoted, as well as the arterial and venous sides of the network. (B) Plot of $\bar{\tau}_a/\bar{\tau}_{a,\text{plasma}}$ vs. vessel diameter, distinguished by network location. Also given is the order number, which shows how vessels on the venous side have a larger diameter than those of the same order on the arterial side. This ultimately leads to $\bar{\tau}_a/\bar{\tau}_{a,\text{plasma}}$ being higher on the venous side than in vessels of the same order on the arterial side, as discussed in the text.

vessel are given in Figure 6.13(B) as a function of vessel diameter, with the order associated with each group of vessels also denoted, as identified in Figure 6.13(A).

As shown here, $\bar{\tau}_a/\bar{\tau}_{a,\text{plasma}}$ for vessels on the venous side are higher than the corresponding vessels of the same order on the arterial side. Because of the structure of this network, vessels on the arterial side will generally have the same volume flow as their counterparts on the venous side, although the vessel diameters on the venous side are larger than those of the same order on the arterial side. This results in the wall shear stress ratio being higher in the vessels on the venous side. This behavior can be conceptually explained by
considering the idealized flow of a two-phase fluid, as blood flow is often modeled analytically, with the same flow rate flowing through two separate vessels of different diameter. The velocity profile of a two-phase fluid flowing through a tube, where each phase has the same density but is of a different viscosity, can be derived as \[ u_I = \frac{A a^2}{4 \mu_I} \left[ B - \left( \frac{r}{a} \right)^2 \right] \]
\[ u_{II} = \frac{A a^2}{4 \mu_{II}} \left[ 1 - \left( \frac{r}{a} \right)^2 \right] \]
for radial position \( r \) in a tube of radius \( a \). Region \( I \) denotes the near-wall plasma region of viscosity \( \mu_I \) and specified thickness \( t \), and region \( II \) denotes the central RBC core region of viscosity \( \mu_{II} \). The constant \( A \) gives the driving pressure gradient, and the constant \( B \) is defined as:
\[ B = \left( 1 - \frac{t}{a} \right)^2 - \frac{\mu_I}{\mu_{II}} \left[ \left( 1 - \frac{t}{a} \right)^2 - 1 \right] \]

Using this, velocity profiles are calculated through tubes of radius \( a = 8 \mu m \) and \( a = 11 \mu m \), with \( t = 1 \mu m \) and \( \mu_I/\mu_{II} = 0.2 \), which are representative of that from the simulations. The driving pressure gradient \( A \) used for each case is such that the same flow rate is achieved. The velocity profiles are given in Figure 6.14 over the radius of each vessel (red curves), and also given is the profile for that of pure plasma (blue curves). The difference between the wall shear stress for blood and pure plasma is given by \( \alpha \), which is the difference between the slope of the two profiles near the wall. For this example, \( \alpha \) for the larger diameter vessel in (A) is roughly 20% greater than \( \alpha \) for the smaller vessel in (B). This shows how \( \tau_a/\tau_{a,\text{plasma}} \) can be higher in a larger diameter vessel compared with that in a smaller diameter vessel that has the same flow rate.

(b) Inlet to capillary vessels

Another general location in the networks where the impact of the RBCs on the wall shear stress is more pronounced is at the inlet to capillaries just downstream of a bifurcation. This can be qualitatively seen in Figure 6.12 at the outlet of most bifurcations by the yellow-redish contours observed, which represent local regions of enhanced \( \tau_a/\tau_{a,\text{plasma}} \). An example from the network in Figure 6.12(B) is provided in Figure 6.15.
Figure 6.14: Velocity profiles of idealized single-phase (i.e. plasma) and two-phase (i.e. blood) fluids through tubes of different diameter but the same volume flow rate. (A) is for a tube of radius 11µm, and (B) is for a tube of radius 8µm. The red curves give the blood velocity profile and the blue curves give the pure plasma velocity profile. For each diameter, the difference between the wall shear stress for blood and pure plasma is given by α, which is the difference between the slope of the two profiles near the wall. For this example, α for the larger diameter vessel in (A) is roughly 20% greater than α for the smaller vessel in (B).

Figure 6.15: Contours of $\tau_a/\tau_{a,\text{plasma}}$ over an example bifurcation from Figure 6.12(B), showing regions at the inlet to daughter vessels where the impact of the RBCs on the wall shear stress is more pronounced.

One reason why this occurs is that with pure plasma, the wall shear stress profile at the capillary inlets has a relatively large variation compared to that which occurs with both plasma and RBCs. The RBCs tend to spread out the profile more evenly around the vessel circumference, thus resulting in less variation. This mechanism is quantitatively shown in
Figure 6.16 below for a representative capillary. This figure gives contours of $\bar{\tau}_a$ at angular locations around the cross-section as a fraction of the maximum value over the cross-section. Results are shown for both pure plasma and the full DNS with RBCs, and cross-sections are provided at the vessel inlet, as well as an axial location downstream. Here the terms

![Figure 6.16: Mechanism causing the impact of RBCs on $\bar{\tau}_a$ to be more pronounced at the inlet to capillaries. Shown are contours of $\bar{\tau}_a$ at angular positions around the cross-section at specific axial locations along the length of a representative vessel. Contours give the wall shear stress divided by the maximum value over the cross-section, and range from 0.5-1.0, as shown. The orientation is that of standing on the vessel centerline and looking downstream in the direction of the flow. (A,B) are for cross-sections at the vessel inlet, and correspond to profiles for pure plasma and the full DNS with RBCs, respectively. (C,D) are for cross-sections at a downstream location, and also respectively correspond to pure plasma and the full DNS with RBCs.](image)

left, right, top, and bottom are used to describe locations on vessel cross-sections. These are based on an orientation of standing on the vessel centerline and looking downstream in the direction of the flow. At the inlet for pure plasma, as shown in Figure 6.16(A), the maximum wall shear stress occurs on the right-most side, while the minimum occurs on the left-most side, and here the minimum is 50% of the maximum. At the inlet for plasma and RBCs, as shown in Figure 6.16(B), the wall shear stress extremum also occur on the right- and left-most sides, but here the minimum is $\sim$75% of the maximum. This shows that with
cells, there is less variation in the wall shear stress over the cross-section compared with pure plasma. Downstream of the inlet, the variation in wall shear stress over the cross-section is smaller than that observed at the inlet. Figure 6.16(C) gives the contours for pure plasma over the cross-section at a downstream location. Here the variation in the wall shear stress over the cross-section is such that the minimum is \( \sim 80\% \) of the maximum. Similarly, Figure 6.16(D) gives the contours for plasma and cells at the same downstream location as in (C), and the wall shear stress variation is such that the minimum is \( \sim 85\% \) of the maximum.

At the inlet to a capillary (i.e. outlet of a bifurcation), there is a large variation in the velocity gradients over the cross-section due to the geometry of the bifurcation. Figure 6.16 shows how the presence of the cells tends to reduce this variation compared with pure plasma. For the plasma, downstream of the inlet the flow becomes more developed and thus the variation in the wall shear stress over the cross-section reduces.

Another reason why the impact of the RBCs on the wall shear stress is more pronounced at the inlet to the capillaries is that in some vessels, the inlet \( \bar{\tau}_a \) profile is such that the maximum values occur near the top and bottom of the cross-section. In contrast, with pure plasma the maximum always occurs at the left- or right-most sides. An example illustrating this mechanism is provided in Figure 6.17. At the inlet, the profile with pure plasma in Figure 6.17(A) shows that the maximum occurs on the left-most side of the vessel, which is the side nearest the upstream bifurcation. The profile with plasma and cells in Figure 6.17(B) shows that the maximum occurs near the top and bottom regions. This behavior with cells can occur at the inlet to daughter vessels of bifurcations where RBC lingering at the bifurcation more significantly effects the flow into the daughter vessel. When such persistent lingering occurs, the cells often flow through the bifurcation by moving slowly around the inside edge and into the vessel. This results in a larger region around the inlet to these vessels where the time-averaged velocity field is very small, and thus the velocity gradient is also very small. When this happens, the minimum wall shear stress actually occurs at the location on the cross-section where the maximum occurred for pure plasma (i.e. the side of the vessel closest to the upstream bifurcation edge). Away from the inlet, the wall shear stress profile looks similar to that of pure plasma, as evident from Figures 6.17(C,D).
Figure 6.17: Another mechanism causing the impact of RBCs on $\tau_a$ to be more pronounced at the inlet to capillaries. Similar to Figure 6.16, shown are contours of $\tau_a$ at angular positions around the cross-section at specific axial locations along the length of another representative vessel. Contours give the wall shear stress divided by the maximum value over the cross-section, and range from 0.6-1.0, as shown. The orientation is that of standing on the vessel centerline and looking downstream in the direction of the flow. (A,B) are for cross-sections at the vessel inlet, and correspond to profiles for pure plasma and the full DNS with RBCs, respectively. (C,D) are for cross-sections at a downstream location, and also respectively correspond to pure plasma and the full DNS with RBCs.

(c) Along vessel length

Along the length of vessels, the cellular influence on the fluctuations in time-averaged wall shear stress is significant. Figure 6.18 first gives results for a representative vessel considering pure plasma. The simulations performed for each of the three network geometries considered four different boundary condition cases, as discussed in Chapter 3.2. For the example vessel considered here, values of the wall shear stress vs. length are given in Figure 6.18(A) for each of these cases, identified in the figure as Cases 1-4. Specifically shown is the maximum, mean, and minimum $\tau_{a,\text{plasma}}$ at each cross-section along the length of the vessel. The dashed line gives the maximum value, the solid line gives the mean value, and the dotted line gives the minimum value. This shows that while the mean value for pure plasma does not significantly vary over the length, the maximum and minimum values (i.e. the
Figure 6.18: Plot of wall shear stress versus length for pure plasma, for a representative vessel. (A) Results for this vessel from each of the four boundary condition cases, labeled as Cases 1-4. For each case, the dashed line gives the maximum wall shear stress at each cross-section along the length, the solid line gives the mean wall shear stress, and the dotted line gives the minimum. (B) Results from (A) scaled by the pressure difference between vessel inlet and outlet, $\Delta P$. Due to the linearity of the flow without cells, the curves in (A) collapse to one curve each for the maximum, mean, and minimum values along the length.

Asymmetry) does. In Figure 6.18(B), the maximum, mean, and minimum values of $\tau_{a,\text{plasma}}$ scaled by the pressure difference between vessel inlet and outlet ($\Delta P$) are plotted versus length for each of the four cases as well. As can be seen, the curves for each case in Figure (A) collapse to one curve each for the maximum, mean, and minimum values along the length due to the linear nature of the flow in absence of the RBCs.

Considering now the presence of the RBCs, plotted in Figure 6.19(A) is $\tau_a$ scaled by the vessel $\Delta P$ along the length of the same vessel in Figure 6.18. Results are included for each of the four cases, with the maximum values given by the dashed lines, the mean values given by the solid lines, and the minimum values given by the dotted lines. As can be seen, the curves for each case do not collapse to one curve for each of the quantities, which demonstrates how the presence of the deformable RBCs break the linearity of the flow. It also shows that the fluctuation of each of these quantities varies more significantly along the length than does that for pure plasma. Comparisons are made in Figure 6.19(B-D) to directly show this, where the results for pure plasma are given by the black curves, and that
Figure 6.19: Plot of wall shear stress versus length for the full DNS results with cells, for the same representative vessel as in Figure 6.18. (A) Results from each of the four boundary condition cases for $\bar{\tau}_a$ scaled by the vessel $\Delta P$. The dashed lines gives the maximum wall shear stress at each cross-section along the length, the solid lines give the mean wall shear stress, and the dotted lines gives the minimum. The RBCs break the linearity of the flow, and thus the curves for each quantity do not collapse to one. (B-D) Direct comparison between the results for pure plasma vs. the full DNS with cells over the length of the vessel. The results for pure plasma are given by the black curves, and that for plasma with RBCs are given by the red curves. (B) gives results for the maximum wall shear stress, (C) gives results for the mean, and (D) gives results for the minimum. Collectively these show how the influence of the RBCs on the wall shear stress significantly varies along the length of a vessel, as does the non-linear contribution of the deformable cells to the flow.

The cellular influence on the degree of variation of the wall shear stress is quantified over all vessels in the networks in Figure 6.20. This is done by computing the standard deviation of the plot of mean wall shear stress versus length, for all vessels in the networks. This is denoted by $SD_{\text{plasma}}$ for that associated with the pure plasma simulations, and $SD_{\text{DNS}}$ for the full DNS with RBCs. Specifically plotted is the ratio $SD_{\text{DNS}} / SD_{\text{plasma}}$ versus vessel diameter, which quantifies the contribution of the RBCs to the fluctuations.
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Figure 6.20: Quantifying the cellular influence on the fluctuations in wall shear stress over vessel length, for all vessels. The standard deviation ($SD$) of the mean wall shear stress over the lengths of all vessels is computed, and plotted here is the ratio of that for the full DNS with cells to that of pure plasma, or $SD_{DNS} / SD_{plasma}$, as a function of vessel diameter.

in wall shear stress over vessel length. As can be seen, the cellular influence increases with decreasing vessel diameter, and in the smallest vessels the fluctuations with cells reach as high as nearly 40 times that observed with pure plasma. Furthermore, in more that 90% of the vessels $SD_{DNS}$ is greater $SD_{plasma}$, and the average value of $SD_{DNS} / SD_{plasma}$ for all data points approximately 5. On the whole, this quantitatively shows that the cellular influence on the fluctuations in wall shear stress over vessel length is significant.

6.4 Conclusions

This chapter has presented a detailed study on the three-dimensional spatial variations of the wall shear stress in complex microvascular networks. Previous studies have either considered blood flowing through complex geometries in vivo or in vitro, and considered at most the spatial variations in a 2D sense, or have studied 3D aspects of it in silico for cellular-scale flows, but only considered simple geometries such as a straight tube. While all of these prior works have provided invaluable insight into the fundamental nature of the wall shear stress, the present work bridges this gap and considers both the full three-dimensionality as well as the complex in vivo-like geometries of the microvasculature. The
present work has focused on the time-averaged wall shear stress, and any discussion on the three-dimensional spatial variations is with respect to this quantity. A summary of the findings as discussed and presented in this chapter are subsequently presented.

First, it was shown that the variations in the wall shear stress throughout the networks were distinctly three-dimensional and asymmetric. An example of a small section was given where such variations spanned an order of magnitude. Its highly asymmetric nature has been quantified by means of an asymmetry parameter which was observed to vary significantly along the vessel length. Such variations were predominantly non-monotonic, which indicated that the wall shear stress profiles did not simply become more symmetric over the length as they would in straight vessels, but rather continuously fluctuated in their degree of asymmetry. The character of the wall shear stress profile around each cross-section was additionally described with a quantity analogous to an aspect ratio, and this was shown to be highly varying along the length of vessels as well.

It has been known in the literature that asymmetry in the wall shear stress can occur in curved vessels, and it was shown here how this manifests in 3D in complex vascular networks. This was quantified for all vessels by directly connecting measures for the vessel tortuosity to such significant changes. It was specifically observed that with increasing vessel tortuosity the variations in the 3D asymmetry increased along vessel length.

Following this, a detailed analysis isolating the cellular influence on the wall shear stress was presented. On account of the complex 3D geometries, significant spatial variations in the wall shear stress occur even in the absence of cells. What was not known, however, was the specific contribution of the RBCs to such variations. This cellular influence was isolated by first computing the wall shear stress for simulations of pure plasma flowing through the networks (i.e. without RBCs), and this was compared to that calculated from the full DNS results with cells. Three areas of the networks were identified where the cellular influence was most enhanced. First, the cellular influence was generally greater in vessels on the venous sides than those on the arterial side. This is especially interesting because the wall shear stress itself is actually greater in vessels on the arterial side, which is commonly known. The cause of this trend was identified as being due to differences in near wall velocity profiles between blood and pure plasma for different diameter vessels with the
same volume flow. This was also conceptually explained by means of an analytical two-
phase flow model. Second, regions of enhanced cellular influence on the wall shear stress
were identified at the inlet to capillary vessels. This was generally caused by the cell-cell
and cell-vascular interactions and their effects on the distribution of shear stress around the
vessel circumference just downstream of a bifurcation. Lastly, along the length of vessels it
was shown that fluctuations in the time-averaged shear stress were significantly enhanced
by the presence of the RBCs. This was quantified over all vessels, and it was shown that
in some the variation along the length can be upwards of 40 times greater with cells than
with pure plasma.

To our knowledge, this work provides the first analysis of the 3D spatial variations in the
wall shear stress in complex in vivo-like microvascular networks, including isolating regions
where the cellular influence is enhanced.
Chapter 7

Conclusions of Thesis

This final chapter summarizes the main conclusions presented in this thesis, and the overall contributions to this field of science.

First, a numerical method has been developed to model 3D cellular-scale blood flow within highly complex large-scale geometries. This was presented in Chapter 2. An approach is detailed to simultaneously model a wide variety of interfaces within one computational framework, and this has been shown to be efficient, accurate, and robust. Rigorous validations were presented to assess the accuracy by comparing results with analytical solutions, experimental data, and previous numerical results. The capabilities and overall robustness of the method were also demonstrated by simulating cellular-scale flows in complex microvascular networks, as well as geometrically intricate microfluidic devices with sharp-edged obstructions.

The approach developed uses immersed boundary methods in the context of a finite volume/spectral flow solver. Fluid flow is considered here in the absence of inertia, although generally speaking finite inertia can be considered as well. The Stokes equations are solved for a constant density, variable viscosity, incompressible fluid, with immersed boundary methods used to model the wide variety of complex interfaces. These include deformable interfaces, moving rigid interfaces, and stationary interfaces of complex shape. The deformable interfaces are those of red blood cells, white blood cells, and circulating tumor cells, while the moving rigid interfaces include inactivated platelets and drug particles. Other types of deformable cells can be considered as well, and are by no means limited to that listed here. Additionally, while the moving rigid body shapes considered here have been spheres and spheroids, generally speaking moving rigid bodies of arbitrary shape can be modeled as well. Stationary interfaces of complex shape include microvascular networks,
microfluidic devices, constricted tubes, arrays of obstacles, etc. A novel technique was presented to ensure fluid leakage remains negligible with increasingly complex rigid interfaces. Overall, the method detailed here provides a viable means of taking cellular-scale *in silico* modeling to the next level, by being able to consider large-scale highly complex physiological geometries in 3D. The method has the potential to scale up to very large microvascular networks at organ-levels.

The second part of thesis has involved applying this computational method to understand new physics associated with the cellular-scale nature of blood flow in physiological geometries. Specifically considered was the simulation of red blood cells flowing through complex *in vivo*-like microvascular networks. The content of Chapters 3-6 focused on different topics, that were studied and analyzed using the data from these simulations.

Three different microvascular networks were designed based on *in vivo* images and data, and the simulation details were provided in Chapter 3. These simulations represent, to our knowledge, the first direct numerical simulation of 3D cellular-scale blood flow in physiologically realistic microvascular networks. Also presented in Chapter 3 is a detailed analysis of some general hemo- and hydro-dynamics observed in the simulations. This analysis revealed, to our knowledge, several novel and unexpected phenomena. It was shown that heterogeneity in hemodynamic quantities, which is a hallmark of microvascular blood flow, appears both in space and time, and that the temporal heterogeneity is more severe than its spatial counterpart. The cells are observed to frequently jam at vascular bifurcations, resulting in reductions in hematocrit and flow rate in the daughter and mother vessels. It was found that red blood cell jamming at vascular bifurcations (also referred to in this work as RBC lingering) results in several orders-of-magnitude increase in hemodynamic resistance, and thus provides an additional mechanism of increased *in vivo* blood viscosity as compared to that determined *in vitro*. A striking result from the simulations was negative pressure-flow correlations observed in several vessels, implying a significant deviation from Poiseuille’s law. Furthermore, negative correlations between vascular resistance and hematocrit were observed in various vessels, also defying a major principle of particulate suspension flow. These novel findings are absent in blood flow in straight tubes, and they underscore the
importance of considering realistic physiological geometry and resolved cellular interactions in modeling microvascular hemodynamics.

In Chapter 4 a detailed study on RBC partitioning at the network bifurcations was presented, based on data from the simulations. When considering the flow of RBCs through a vessel that bifurcates, it is well known that RBCs usually do not distribute to the daughter vessels with the same proportion as the blood flow. Such disproportionality occurs whereby the cell distribution fractions are either higher or lower than the flow fractions, and have been referred to as classical partitioning and reverse partitioning, respectively. The focus of Chapter 4 was on the detailed analysis of the RBC partitioning in the networks as it developed naturally in successive bifurcations, and the underlying mechanisms. It was found that while the time-averaged partitioning at a bifurcation manifests in one of two ways, namely, the classical or reverse partitioning, the time-dependent behavior could cycle between these two types. Four different cellular-scale mechanisms underlying the time-dependent partitioning were identified and analyzed. These mechanisms arose, in general, either due to an asymmetry in the RBC distribution in the feeding vessels caused by the events at an upstream bifurcation or due to a temporary increase in cell concentration near capillary bifurcations. Using the DNS results, it was shown that a positive skewness in the hematocrit profile in the feeding vessel is associated with the classical partitioning, while a negative skewness is associated with the reverse one. Following this, a detailed analysis was presented of the two classical components of disproportionate partitioning as identified in prior studies, namely, plasma skimming and cell screening. The plasma skimming component was shown to under-predict the disproportionality, leaving the cell screening component to make up for the difference. The crossing of the separation surface by the cells was observed to be a dominant mechanism underlying the cell screening, which was shown to mitigate extreme heterogeneity in RBC distribution across the networks. This represents, to our knowledge, the first 3D simulation-based analysis of RBC partitioning through modeled in vivo-like microvascular networks that are comprised of multiple bifurcations in sequence. Also to our knowledge, this is the first work to simultaneously dissect the plasma skimming and cell screening components for a cell suspension flowing through complex networks.
In Chapter 5 the three-dimensionality of the cell free layer (CFL) was studied as it arose in the microvascular network simulations. The CFL is a well known feature of the microcirculation, and is a near-wall plasma layer that forms in vessels that is completely devoid of RBCs. It is very physiologically important, for reasons discussed in the chapter as well as in Chapter 1.4.3. The existing knowledge of the CFL as it arises in vivo has been based on characterizing it as a 2D projection onto the image plane. In this sense it has been defined by two thickness values, with each one on diametrically opposite sides of the vessel. The three-dimensionality of the CFL as it develops in a vascular network, and the underlying hydrodynamic mechanisms, are not well understood. This chapter thus presented a detailed analysis of the fully 3D and asymmetric nature of the CFL in such networks. It was shown that the CFL significantly varies over different aspects of the networks. Along the vessel lengths, such variations were predominantly non-monotonic, which indicated that the CFL profiles did not simply become more symmetric over the length as they would in straight vessels. It was shown that vessel tortuosity causes the CFL to become more asymmetric along the length. A curvature-induced migration of the RBCs was specifically identified as the underlying mechanism of increased asymmetry in curved vessels. The vascular bifurcations and mergers were also observed to change the CFL profiles, and in the majority of them the CFL became more asymmetric. For most bifurcations, it was generally observed to occur such that the CFL downstream narrowed on the side of the vessel nearest the upstream bifurcation, and widened on the other side. 3D aspects of such behavior were elucidated. For many bifurcations, a discrepancy existed between the CFL in the daughter vessels that arose from a disproportionate partitioning between the flow rate and RBC flux. For most mergers, the downstream CFL narrowed in the plane of the merger, but widened away from this plane. The dominant mechanism by which such changes occurred was identified as the geometric focusing of the two merging streams. To our knowledge, this work provided the first simulation-based analysis of the 3D CFL structure in complex in vivo-like microvascular networks, including hydrodynamic origins of the observed behavior.

Lastly, in Chapter 6 a detailed study was presented on the three-dimensional spatial variations of the wall shear stress that arose in the complex microvascular networks. To
date, 3D aspects of the wall shear stress have been studied in simple geometries such as straight tubes, while the nature of it as it arises in complex geometries \textit{in vivo} has been, at best, two-dimensional. The analysis presented on its 3D nature as it arose in the microvascular networks is the first to bridge this gap, to our knowledge. As with the CFL, it was shown that the variations in the wall shear stress throughout the networks were distinctly three-dimensional and asymmetric. Its highly asymmetric nature was quantified with an asymmetry parameter, and it was revealed that for the vast majority of vessels such variations were significant and non-monotonic over their lengths. Additional descriptions of its varying nature over vessel lengths were quantified by fluctuations in the profile aspect ratio at each cross-section along the length. A quantitative connection between vessel tortuosity and changes in the 3D wall shear stress profile asymmetry along the vessel length were made as well.

Following this, a detailed analysis isolating the cellular influence on the wall shear stress was presented. Spatial variations in the wall shear stress will occur even for a single phase fluid flowing through a geometry as complex as the microvascular networks considered here, due to the geometry itself. The presence of the RBCs will change the character of these fluctuations, although it was unclear how. To understand this, the cellular influence was isolated by performing simulations for each of the network geometries involving pure plasma without any RBCs, and the resulting wall shear stress throughout the networks was compared with that determined from the full DNS results with cells. From this, it was shown that there were three areas of the networks where the cellular influence was most enhanced. First, it was observed that the wall shear stress in vessels on the venous side was generally more influenced by the cells than in vessels on the arterial side. Considering the fact that the wall shear stress itself is generally smaller in vessels on the venous side, this is especially interesting. The cause of this trend was identified as being due to differences in near wall velocity profiles between blood and pure plasma for different diameter vessels with the same volume flow. This was also conceptually explained by means of an analytical two-phase flow model. Second, regions of enhanced cellular influence on the wall shear stress were identified at the inlet to capillary vessels. This was generally caused by the cell-cell and cell-vascular interactions and their effects on the distribution of shear stress.
around the vessel circumference just downstream of a bifurcation. Lastly, along the length of vessels it was shown that fluctuations in the time-averaged shear stress were significantly enhanced by the presence of the RBCs. This was quantified over all vessels, and it was shown that in some the variation along the length could be upwards of 40 times greater with cells than with pure plasma. These findings underscore the importance of considering the cellular-scale particulate nature of blood to most accurately capture the full nature of the wall shear stress.

To our knowledge, this work has provided the first analysis of the 3D spatial variations in the wall shear stress in complex \textit{in vivo}-like microvascular networks, including isolating regions where the cellular influence is enhanced.
Appendix A

Force Computations in Spheroidal Coordinate Systems for Moving Rigid Bodies

Computations involving the stress tensor ($\sigma$) used in the procedure developed for moving rigid objects are most efficient and accurate if the coordinate system used aligns with the object surface. The shapes of rigid objects considered in the present work are spheres and spheroids. While the components of the stress tensor in spherical coordinates are commonly given in the literature and textbooks, this was not found to be the case for the components in spheroidal coordinate systems. As such, for completeness this tensor is derived here for the oblate and prolate spheroidal coordinate systems, along with other relevant quantities and general considerations for accurately computing forces on a moving rigid object. Derivations utilize concepts presented in [46].

Considering

$$\sigma = -P\delta_{ij} + 2\eta S,$$  \hspace{1cm} (A.1)

where $P$ is the pressure, $\delta$ is the Kronecker delta, $\eta$ is the viscosity, and $S$ is the rate of strain tensor given by

$$S = \frac{1}{2} \left[ (\nabla u) + (\nabla u)^T \right],$$  \hspace{1cm} (A.2)

this task essentially amounts to deriving the velocity gradient tensor ($\nabla u$) in the desired coordinate system.
A.1 Oblate Spheroidal Coordinates

The coordinate transformation used to define the oblate spheroidal coordinate system \((\mu, \nu, \phi)\) is:

\[
\begin{align*}
x &= a \cosh \mu \cos \nu \cos \phi \\
y &= a \cosh \mu \cos \nu \sin \phi \\
z &= a \sinh \mu \sin \nu
\end{align*}
\]  

(A.3)

for Cartesian coordinates \((x, y, z)\). When defined in this manner, surfaces of constant \(\mu\) represent ellipses in the \(x - z\) plane rotated about the \(z\)-axis. The focal points of the ellipses are located on the \(x\)-axis at locations \(x = \pm a\), and thus the spheroids formed are oblate. For a given rigid object that is an oblate spheroid with specified semi-minor axis \(b_1\) and semi-major axis \(b_2\), these are related to the parameter \(a\) and the coordinate \(\mu_0\) corresponding to the object surface by:

\[
\begin{align*}
b_1 &= a \sinh \mu_0 \\
b_2 &= a \cosh \mu_0
\end{align*}
\]  

(A.4)

For calculations involving rigid oblate spheroids, the origin of the coordinate system is placed at the centroid, and the \(a\) and \(\mu_0\) values corresponding to the object surface are determined from:

\[
\begin{align*}
\mu_0 &= \text{atanh} \left( \frac{b_1}{b_2} \right) \\
a &= \frac{b_1}{\sinh \mu_0}
\end{align*}
\]  

(A.5)

With these parameters now set for a particular object, the surface is covered by varying the \(\nu\) and \(\phi\) coordinates, which in general span the ranges \(-\pi/2 \leq \nu \leq \pi/2\) and \(-\pi \leq \phi \leq \pi\).

In evaluating discrete derivatives in this coordinate system, the direction outward from the surface is given by increasing \(\mu\), while varying \(\nu\) and \(\phi\) to locate the desired point in space.

The gradient operator for this coordinate system is written as:

\[
\nabla = e_\mu \frac{1}{h_1} \frac{\partial}{\partial \mu} + e_\nu \frac{1}{h_2} \frac{\partial}{\partial \nu} + e_\phi \frac{1}{h_3} \frac{\partial}{\partial \phi}
\]  

(A.6)

where \(h_i\) are the scale factors. In general these factors provide a measure of the relative spatial change between the two coordinate systems. This can be seen for \(h_1\), which is
calculated as:

\[ h_1 = \sqrt{\left( \frac{\partial x}{\partial \mu} \right)^2 + \left( \frac{\partial y}{\partial \mu} \right)^2 + \left( \frac{\partial z}{\partial \mu} \right)^2} \]  

(A.7)

and corresponds to the \( \mu \) coordinate. \( h_2 \) and \( h_3 \) are calculated in a similar manner for the \( \nu \) and \( \phi \) coordinates, respectively. Thus, for the oblate spheroidal coordinate system (A.3) these are:

\[ h_1 = a \sqrt{\sinh^2 \mu + \sin^2 \nu} \]
\[ h_2 = h_1 \]
\[ h_3 = a \cosh \mu \cos \nu \]  

(A.8)

Using A.6 the velocity gradient tensor is formed for this coordinate system:

\[ \nabla \mathbf{u} = \left[ u_\mu \mathbf{e}_\mu + u_\nu \mathbf{e}_\nu + u_\phi \mathbf{e}_\phi \right] \otimes \left[ \mathbf{e}_\mu \frac{1}{h_1} \frac{\partial}{\partial \mu} + \mathbf{e}_\nu \frac{1}{h_2} \frac{\partial}{\partial \nu} + \mathbf{e}_\phi \frac{1}{h_3} \frac{\partial}{\partial \phi} \right] \]  

(A.9)

To determine the components of the resulting tensor, derivatives of the basis vectors must be evaluated. These are computed using:

\[ \frac{\partial \mathbf{e}_i}{\partial \zeta^j} = \frac{1}{h_i} \left[ \Gamma^k_{ij} h_k \mathbf{e}_k - \frac{\partial h_i}{\partial \zeta^j} \mathbf{e}_i \right] \]  

(A.10)

where \( \Gamma^k_{ij} \) are the Christoffel symbols of the 2nd kind, and provide a convenient means of evaluating these derivatives. They are defined as:

\[ \Gamma^k_{ij} = \frac{1}{2g_{km}} \left( \frac{\partial g_{jm}}{\partial \zeta^i} + \frac{\partial g_{mi}}{\partial \zeta^j} - \frac{\partial g_{ij}}{\partial \zeta^m} \right) \]  

(A.11)

where the scalars \( g_{ij} \) are the metric coefficients:

\[ [g_{ij}] = \left[ \frac{\partial x^k}{\partial \zeta^i} \right]^T \left[ \frac{\partial x^k}{\partial \zeta^j} \right] \]  

(A.12)

For the present, \( x^i \) are the Cartesian coordinates and \( \zeta^i \) are the oblate spheroidal coordinates. Using A.3 in A.12 the non-zero metric coefficients are:

\[ g_{11} = a^2 \left( \sinh^2 \mu + \sin^2 \nu \right) \]
\[ g_{22} = g_{11} \]  

(A.13)
\[ g_{33} = a^2 \cosh^2 \mu \cos^2 \nu \]
To evaluate the Christoffel symbols (A.11), the derivatives of the metric tensor components are:

\[
\frac{\partial g_{11}}{\partial \mu} = 2a^2 \sinh \mu \cosh \mu = \frac{\partial g_{22}}{\partial \mu},
\]

\[
\frac{\partial g_{11}}{\partial \nu} = 2a^2 \sin \nu \cos \nu = \frac{\partial g_{22}}{\partial \nu},
\]

\[
\frac{\partial g_{33}}{\partial \mu} = 2a^2 \sinh \mu \cosh \mu \cos^2 \nu,
\]

\[
\frac{\partial g_{33}}{\partial \nu} = -2a^2 \cosh^2 \mu \sin \nu \cos \nu
\]

which are used with A.13 in A.11:

\[
\Gamma^1_{ij} = \frac{1}{\sinh^2 \mu + \sin^2 \nu} \begin{bmatrix}
\sinh \mu \cosh \mu & \sin \nu \cos \nu & 0 \\
\sin \nu \cos \nu & -\sinh \mu \cosh \mu & 0 \\
0 & 0 & -\cos^2 \nu \sinh \mu \cosh \mu
\end{bmatrix}
\]

\[
\Gamma^2_{ij} = \frac{1}{\sinh^2 \mu + \sin^2 \nu} \begin{bmatrix}
-\sin \nu \cos \nu & \sinh \mu \cosh \mu & 0 \\
\sinh \mu \cosh \mu & \sin \nu \cos \nu & 0 \\
0 & 0 & -\cosh^2 \mu \sin \nu \cos \nu
\end{bmatrix}
\]

\[
\Gamma^3_{ij} = \frac{1}{\sinh^2 \mu + \sin^2 \nu} \begin{bmatrix}
0 & 0 & \tanh \mu \\
0 & 0 & -\tan \nu \\
\tanh \mu & -\tan \nu & 0
\end{bmatrix}
\]

Using these with

\[
\frac{\partial h_1}{\partial \mu} = \frac{\partial h_2}{\partial \mu} = \frac{a \sinh \mu \cosh \mu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}},
\]

\[
\frac{\partial h_1}{\partial \nu} = \frac{\partial h_2}{\partial \nu} = \frac{a \sin \nu \cos \nu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}},
\]

\[
\frac{\partial h_3}{\partial \mu} = a \sinh \mu \cos \nu,
\]

\[
\frac{\partial h_3}{\partial \nu} = -a \cosh \mu \sin \nu
\]
the derivatives of the basis vectors are determined from A.10:

\[
\begin{align*}
\frac{\partial e_\mu}{\partial \mu} &= -\sin \nu \cos \nu e_\nu - \frac{\sinh^2 \mu + \sin^2 \nu}{\sinh^2 \mu \sin^2 \nu} e_\nu \\
\frac{\partial e_\mu}{\partial \nu} &= \sinh \mu \cosh \mu e_\nu \\
\frac{\partial e_\mu}{\partial \phi} &= -\frac{\sinh \mu \cos \nu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} e_\phi \\
\frac{\partial e_\nu}{\partial \mu} &= \frac{\sin \nu \cos \nu}{\sinh^2 \mu + \sin^2 \nu} e_\mu \\
\frac{\partial e_\nu}{\partial \nu} &= -\frac{\sinh \mu \cosh \mu}{\sinh^2 \mu + \sin^2 \nu} e_\mu \\
\frac{\partial e_\nu}{\partial \phi} &= -\frac{\cosh \mu \sin \nu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} e_\phi \\
\frac{\partial e_\phi}{\partial \mu} &= 0 \\
\frac{\partial e_\phi}{\partial \nu} &= 0 \\
\frac{\partial e_\phi}{\partial \phi} &= \frac{1}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} (-\cos \nu \sinh \mu e_\mu + \cosh \mu \sin \nu e_\nu) 
\end{align*}
\] (A.17)
Now that we have these, the components of velocity gradient tensor can be determined.

Each of the nine components of A.9 are evaluated:

\[
\begin{align*}
\frac{1}{h_1} \frac{\partial}{\partial \mu} (u_\mu e_\mu) \otimes e_\mu &= \frac{1}{h_1} \frac{\partial u_\mu}{\partial \mu} e_\mu \otimes e_\mu + \frac{u_\mu}{h_1} \left( \frac{- \sin \nu \cos \nu}{\sinh^2 \mu + \sin^2 \nu} \right) e_\nu \otimes e_\mu \\
\frac{1}{h_2} \frac{\partial}{\partial \nu} (u_\mu e_\mu) \otimes e_\nu &= \frac{1}{h_2} \frac{\partial u_\mu}{\partial \nu} e_\mu \otimes e_\nu + \frac{u_\mu}{h_2} \left( \frac{\sinh \mu \cosh \mu}{\sinh^2 \mu + \sin^2 \nu} \right) e_\nu \otimes e_\nu \\
\frac{1}{h_3} \frac{\partial}{\partial \phi} (u_\mu e_\mu) \otimes e_\phi &= \frac{1}{h_3} \frac{\partial u_\mu}{\partial \phi} e_\mu \otimes e_\phi + \frac{u_\mu}{h_3} \left( \frac{\sinh \mu \cos \nu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} \right) e_\phi \otimes e_\phi \\
\frac{1}{h_1} \frac{\partial}{\partial \mu} (u_\nu e_\nu) \otimes e_\mu &= \frac{1}{h_1} \frac{\partial u_\nu}{\partial \mu} e_\nu \otimes e_\mu + \frac{u_\nu}{h_1} \left( \frac{\sin \nu \cos \nu}{\sinh^2 \mu + \sin^2 \nu} \right) e_\mu \otimes e_\mu \\
\frac{1}{h_2} \frac{\partial}{\partial \nu} (u_\nu e_\nu) \otimes e_\nu &= \frac{1}{h_2} \frac{\partial u_\nu}{\partial \nu} e_\nu \otimes e_\nu + \frac{u_\nu}{h_2} \left( \frac{- \sin \mu \cosh \mu}{\sinh^2 \mu + \sin^2 \nu} \right) e_\mu \otimes e_\nu \\
\frac{1}{h_3} \frac{\partial}{\partial \phi} (u_\nu e_\nu) \otimes e_\phi &= \frac{1}{h_3} \frac{\partial u_\nu}{\partial \phi} e_\nu \otimes e_\phi + \frac{u_\nu}{h_3} \left( \frac{- \cos \mu \sin \nu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} \right) e_\phi \otimes e_\phi \\
\frac{1}{h_1} \frac{\partial}{\partial \mu} (u_\phi e_\phi) \otimes e_\mu &= \frac{1}{h_1} \frac{\partial u_\phi}{\partial \mu} e_\phi \otimes e_\mu \\
\frac{1}{h_2} \frac{\partial}{\partial \nu} (u_\phi e_\phi) \otimes e_\nu &= \frac{1}{h_2} \frac{\partial u_\phi}{\partial \nu} e_\phi \otimes e_\nu \\
\frac{1}{h_3} \frac{\partial}{\partial \phi} (u_\phi e_\phi) \otimes e_\phi &= \frac{1}{h_3} \frac{\partial u_\phi}{\partial \phi} e_\phi \otimes e_\phi + \frac{u_\phi}{h_3} \left( \frac{\cosh \mu \sin \nu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} \right) e_\nu \otimes e_\phi
\end{align*}
\]

(A.18)

To give the velocity gradient tensor in the oblate spheroidal coordinate system:

\[
\nabla u = \begin{bmatrix}
\frac{1}{h_1} \left( \frac{\partial u_\mu}{\partial \mu} + u_\nu \frac{\sin \nu \cos \nu}{\sinh^2 \mu + \sin^2 \nu} \right) \\
\frac{1}{h_1} \left( \frac{\partial u_\mu}{\partial \nu} - u_\mu \frac{\sin \nu \cos \nu}{\sinh^2 \mu + \sin^2 \nu} \right) \\
\frac{1}{h_1} \left( \frac{\partial u_\phi}{\partial \phi} \right) \\
\frac{1}{h_2} \left( \frac{\partial u_\mu}{\partial \nu} - u_\nu \frac{\sin \mu \cosh \mu}{\sinh^2 \mu + \sin^2 \nu} \right) \\
\frac{1}{h_2} \left( \frac{\partial u_\mu}{\partial \phi} + u_\mu \frac{\sin \mu \cosh \mu}{\sinh^2 \mu + \sin^2 \nu} \right) \\
\frac{1}{h_2} \left( \frac{\partial u_\nu}{\partial \phi} \right) \\
\frac{1}{h_3} \left( \frac{\partial u_\mu}{\partial \phi} - u_\phi \frac{\cosh \mu \sin \nu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} \right) \\
\frac{1}{h_3} \left( \frac{\partial u_\nu}{\partial \phi} + u_\phi \frac{\cosh \mu \sin \nu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} \right) \\
\frac{1}{h_3} \left( \frac{\partial u_\phi}{\partial \phi} \right)
\end{bmatrix}
\]  

(A.19)
Finally, the stress tensor is determined from A.1. The components are:

\[
\begin{align*}
\sigma_{\mu\mu} &= -P + \frac{2\eta}{h_1} \left( \frac{\partial u_\mu}{\partial \mu} + u_\nu \frac{\sin \nu \cos \nu}{\sinh^2 \mu + \sin^2 \nu} \right) \\
\sigma_{\mu\nu} &= \tau_{\nu\mu} = \frac{\eta}{h_1} \left( \frac{\partial u_\mu}{\partial \nu} + \frac{\partial u_\nu}{\partial \mu} - \left( \frac{u_\nu \sinh \mu \cosh \mu + u_\nu \sin \nu \cos \nu}{\sinh^2 \mu + \sin^2 \nu} \right) \right) \\
\sigma_{\mu\phi} &= \tau_{\phi\mu} = \frac{\eta}{h_1} \left( \frac{\partial u_\phi}{\partial \mu} + \frac{\partial u_\phi}{\partial \phi} - \left( \frac{u_\phi \cosh \mu \sin \nu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} \right) \right) \\
\sigma_{\nu\nu} &= -P + \frac{2\eta}{h_2} \left( \frac{\partial u_\nu}{\partial \nu} + u_\mu \frac{\sinh \mu \cosh \mu}{\sinh^2 \mu + \sin^2 \nu} \right) \\
\sigma_{\nu\phi} &= \tau_{\phi\nu} = \frac{\eta}{h_2} \left( \frac{\partial u_\phi}{\partial \nu} + \frac{\partial u_\phi}{\partial \phi} + \left( \frac{u_\phi \cosh \mu \sin \nu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} \right) \right) \\
\sigma_{\phi\phi} &= -P + \frac{2\eta}{h_3} \left( \frac{\partial u_\phi}{\partial \phi} + u_\mu \frac{\sinh \mu \cosh \nu - u_\nu \cosh \mu \sin \nu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} \right)
\end{align*}
\]  

(A.20)

The force on each element discretizing a rigid object surface is computed from the traction vector, \( \mathbf{t} = \mathbf{n} \cdot \sigma \), where \( \mathbf{n} \) is the outward normal vector at the element. The traction vector gives the force per area on a surface, so the force components on the element are simply the traction components multiplied by the element area. In the oblate spheroidal coordinate system, at a point on the surface \( \mathbf{n} = \mathbf{e}_\mu \), so:

\[
\mathbf{t} = \sigma_{\mu\mu} \mathbf{e}_\mu + \sigma_{\mu\nu} \mathbf{e}_\nu + \sigma_{\mu\phi} \mathbf{e}_\phi
\]  

(A.21)

Thus, only three components of the stress tensor are needed, and are evaluated from the pressure and velocity field. However, since the fluid flow solver uses the Cartesian coordinate system the oblate spheroidal components of the velocity field must be determined from the Cartesian components. To relate these coordinate systems the oblate spheroidal basis vectors are written in terms of the Cartesian basis vectors. This is done using the covariant base vectors, defined as:

\[
g_{ij} = \frac{\partial x^i}{\partial \zeta^j} \mathbf{e}_i
\]  

(A.22)

in conjunction with the metric coefficients A.12 (no sum on \( i \)):

\[
\mathbf{e}_i = \frac{g_{ii}}{\sqrt{g_{ii}}}
\]  

(A.23)
For A.3 the covariant base vectors are:

\[ g_1 = a \sinh \mu \cos \nu \cos \phi e_x + a \sinh \mu \cos \nu \sin \phi e_y + a \cosh \mu \sin \nu e_z \]
\[ g_2 = -a \cosh \mu \sin \nu \cos \phi e_x - a \cosh \mu \sin \nu \sin \phi e_y + a \sinh \mu \cos \nu e_z \] \hspace{1cm} (A.24)
\[ g_3 = -a \cosh \mu \cos \nu \sin \phi e_x + a \cosh \mu \cos \nu \cos \phi e_y \]

which gives:

\[ e_{\mu} = \frac{1}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} \cdot (\sinh \mu \cos \nu \cos \phi e_x + \sinh \mu \cos \nu \sin \phi e_y + \cosh \mu \sin \nu e_z) \]
\[ e_{\nu} = \frac{1}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} \cdot (-\cosh \mu \sin \nu \cos \phi e_x - \cosh \mu \sin \nu \sin \phi e_y + \sinh \mu \cos \nu e_z) \]
\[ e_{\phi} = -\sin \phi e_x + \cos \phi e_y \] \hspace{1cm} (A.25)

It follows from this that the velocity components in the oblate spheroidal coordinate system written in terms of the Cartesian components are:

\[ u_{\mu} = \frac{1}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} (\sinh \mu \cos \nu \cos \phi u_x + \sinh \mu \cos \nu \sin \phi u_y + \cosh \mu \sin \nu u_z) \]
\[ u_{\nu} = \frac{1}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} (-\cosh \mu \sin \nu \cos \phi u_x - \cosh \mu \sin \nu \sin \phi u_y + \sinh \mu \cos \nu u_z) \]
\[ u_{\phi} = -\sin \phi u_x + \cos \phi u_y \] \hspace{1cm} (A.26)

Since the stress tensor is being evaluated at the object surface, velocity derivatives with respect to the coordinates \( \nu \) and \( \phi \) are evaluated analytically. Only velocity derivatives with respect to \( \mu \) must be evaluated numerically. From A.20, the surface derivatives only involve \( u_{\mu} \), and in general the velocity at the surface will have translational and rotational components. Thus \( u_{\mu} = u_{\mu,\text{trans}} + u_{\mu,\text{rot}} \). In terms of the rigid-body translational \((U_x, U_y, U_z)\) and rotational \((\omega_x, \omega_y, \omega_z)\) velocities these are:

\[ u_{\mu,\text{trans}} = \frac{1}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} (\sinh \mu \cos \nu \cos \phi U_x + \sinh \mu \cos \nu \sin \phi U_y + \cosh \mu \sin \nu U_z) \]
\[ u_{\mu,\text{rot}} = \frac{a (\omega_y \cos \phi - \omega_z \sin \phi) \sin \nu \cos \nu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} \] \hspace{1cm} (A.27)
where the latter is simply determined from $\omega \times r$, with $r$ being the position vector relative to the object centroid. The derivatives with respect to $\nu$ and $\phi$ are:

$$\frac{\partial u_{\mu,\text{trans}}}{\partial \nu} = \frac{1}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} \left[ -\sinh \mu \sin \nu (\cos \phi U_x + \sin \phi U_y) + \cosh \mu \cos \nu U_z \right]$$

$$- \frac{\sin \nu \cos \nu}{(\sinh^2 \mu + \sin^2 \nu)^{3/2}} \left[ \sinh \mu \cos \nu (\cos \phi U_x + \sin \phi U_y) + \cosh \mu \sin \nu U_z \right]$$

$$\frac{\partial u_{\mu,\text{trans}}}{\partial \phi} = \frac{\sinh \mu \cos \nu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} (-\sin \phi U_x + \cos \phi U_y)$$

$$\frac{\partial u_{\mu,\text{rot}}}{\partial \nu} = a (\omega_y \cos \phi - \omega_x \sin \phi) \left[ \frac{\cos^2 \nu - \sin^2 \nu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} - \frac{\sin^2 \nu \cos^2 \nu}{(\sinh^2 \mu + \sin^2 \nu)^{3/2}} \right]$$

$$\frac{\partial u_{\mu,\text{rot}}}{\partial \phi} = \frac{-a \sin \nu \cos \nu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} (\omega_y \sin \phi + \omega_x \cos \phi)$$

(A.28)

The derivatives with respect to $\mu$ are evaluated using 2nd order outward differencing, with one point located on the object surface and two points located in the fluid domain, as shown in Figure A.1. The choice of $\Delta \mu$ used in this computation is such that the equivalent spacing on the Cartesian grid, $\Delta r$, is equal to the uniform Eulerian grid spacing $\Delta e$. This is done to maintain consistency with the differencing scheme used for the fluid flow solver.

The relationship between $\Delta \mu$ and $\Delta r$ can be approximated from A.3 as:

$$\Delta r = \sqrt{\Delta x^2 + \Delta y^2 + \Delta z^2}$$

$$= a \sqrt{\cosh^2 \nu (\cosh \alpha - \cosh \mu)^2 + \sin^2 \nu (\sinh \alpha - \sinh \mu)^2}$$

(A.29)

where $\alpha = \mu + \Delta \mu$. From this it is evident that for a given $\Delta \mu$, $\Delta r$ will vary based on the $\mu$ and $\nu$ coordinates. Thus when evaluating $\frac{\partial}{\partial \mu}$ for the velocity components at each point on the surface, the value of $\Delta \mu$ that results in $\Delta r = \Delta e$ will be different for each point. Additionally, at each point it will also be different between $u_i$ and $\mu_{i+1}$, and $\mu_{i+1}$ and $\mu_{i+2}$.

These two spacings $\Delta \mu_1$ and $\Delta \mu_2$ are each determined by inverting A.29 with $\Delta r = \Delta e$. Since the velocity components at each point in the stencil are interpolated from the values on the Cartesian grid, this approach provides a consistent framework for evaluating these
derivatives over the entire surface. Furthermore, it ensures that the numerical error does not become biased towards a particular location on the object surface.

Figure A.1: (A) Example of a surface mesh used for the force computations on a rigid oblate spheroid. (B) Example of a finite difference stencil used to numerically evaluate derivatives with respect to $\mu$

To determine the net force exerted on a moving rigid object, the surface is discretized by triangular elements. The force on each is computed from the traction vector, which gives the force per area on each element. Using A.21 with A.25 the Cartesian components of the traction vector are:

$t_x = \frac{1}{\sqrt{\sinh^2\mu + \sin^2\nu}} (\sigma_{\mu\mu} \sinh \mu \cos \nu \cos \phi - \sigma_{\mu\nu} \cosh \mu \sin \nu \cos \phi) - \tau_{\mu\phi} \sin \phi$

$t_y = \frac{1}{\sqrt{\sinh^2\mu + \sin^2\nu}} (\sigma_{\mu\mu} \sinh \mu \cos \nu \sin \phi - \sigma_{\mu\nu} \cosh \mu \sin \nu \sin \phi) + \tau_{\mu\phi} \cos \phi$  \hspace{1cm} (A.30)

$t_z = \frac{1}{\sqrt{\sinh^2\mu + \sin^2\nu}} (\sigma_{\mu\mu} \cosh \mu \sin \nu + \sigma_{\mu\nu} \sinh \mu \cos \nu)$

The force on each element then is simply the traction multiplied by the element area, and these are summed over all elements to give the net force on the object. To determine the net torque on the object, the force vector at each element is used with the radial position of the element to determine the torque components on each element. These are then summed to give the net torque components on the object.
A.2 Prolate Spheroidal Coordinates

The coordinate transformation used to define the prolate spheroidal coordinate system \((\mu, \nu, \phi)\) is:

\[
\begin{align*}
x &= a \sinh \mu \sin \nu \cos \phi \\
y &= a \sinh \mu \sin \nu \sin \phi \\
z &= a \cosh \mu \cos \nu
\end{align*}
\]  

(A.31)

for Cartesian coordinates \((x, y, z)\). When defined in this manner, surfaces of constant \(\mu\) represent ellipses in the \(x - z\) plane rotated about the \(z\)-axis. The focal points of the ellipses are located on the \(z\)-axis at locations \(z = \pm a\), and thus the spheroids formed are prolate. For a given rigid object that is a prolate spheroid with specified semi-minor axis \(b_1\) and semi-major axis \(b_2\), these are related to the parameter \(a\) and the coordinate \(\mu_0\) corresponding to the object surface by Eq. A.5. With these parameters now set for a particular object, the surface is covered by varying the \(\nu\) and \(\phi\) coordinates, which in general span the ranges \(0 \leq \nu \leq \pi\) and \(0 \leq \phi \leq 2\pi\).

The procedure for determining the velocity gradient tensor in this coordinate system is identical to that which was done for the oblate spheroidal coordinate system, except now we use Eq. A.31 for the coordinate transformation. The velocity gradient tensor in the prolate spheroidal coordinate system is thus determined to be:

\[
\nabla \mathbf{u} = \begin{bmatrix}
\frac{1}{h_1} \left( \frac{\partial u_\mu}{\partial \mu} + u_\nu \frac{\sin \mu \cos \nu}{\sinh^2 \mu + \sin^2 \nu} \right) & \frac{1}{h_2} \left( \frac{\partial u_\mu}{\partial \nu} - u_\mu \frac{\sinh \mu \cosh \mu \sin \nu}{\sinh^2 \mu + \sin^2 \nu} \right) \\
\frac{1}{h_2} \left( \frac{\partial u_\nu}{\partial \mu} - u_\mu \frac{\sin \nu \cos \nu}{\sinh^2 \mu + \sin^2 \nu} \right) & \frac{1}{h_2} \left( \frac{\partial u_\nu}{\partial \nu} + u_\mu \frac{\sin \mu \cosh \mu \sin \nu}{\sinh^2 \mu + \sin^2 \nu} \right) \\
\frac{1}{h_3} \left( \frac{\partial u_\phi}{\partial \mu} - u_\phi \frac{\sin \nu \cosh \mu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} \right) & \frac{1}{h_3} \left( \frac{\partial u_\phi}{\partial \nu} - u_\phi \frac{\sin \nu \cosh \mu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} \right) \\
\frac{1}{h_3} \left( \frac{\partial u_\phi}{\partial \phi} + u_\mu \cos \nu + u_\nu \sin \mu \sin \nu / \sqrt{\sinh^2 \mu + \sin^2 \nu} \right)
\end{bmatrix}
\]  

(A.32)

where the scale factors are given by:

\[
\begin{align*}
h_1 &= a \sqrt{\sinh^2 \mu + \sin^2 \nu} \\
h_2 &= h_1 \\
h_3 &= a \sinh \mu \sin \nu
\end{align*}
\]  

(A.33)
The components of the stress tensor in the prolate spheroidal coordinate system are:

\[
\sigma_{\mu\mu} = -P + 2\eta \frac{\partial u_\mu}{\partial \mu} + u_\nu \frac{\sin \nu \cos \nu}{\sinh^2 \mu + \sin^2 \nu}
\]

\[
\sigma_{\mu\nu} = \tau_{\nu\mu} = \eta \left[ \frac{\partial u_\mu}{\partial \nu} + \frac{\partial u_\nu}{\partial \mu} \right] - \left( \frac{u_\nu \sinh \mu \cosh \nu + u_\nu \sin \nu \cos \nu}{\sinh^2 \mu + \sin^2 \nu} \right)
\]

\[
\sigma_{\mu\phi} = \tau_{\phi\mu} = \eta \frac{\partial u_\phi}{\partial \mu} + \eta \frac{\partial u_\phi}{\partial \phi} - u_\phi \frac{\sin \nu \cosh \mu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}}
\]

\[
\sigma_{\nu\nu} = -P + 2\eta \frac{\partial u_\nu}{\partial \nu} + \frac{\sin \nu \cosh \mu}{\sinh^2 \mu + \sin^2 \nu}
\]

\[
\sigma_{\nu\phi} = \tau_{\phi\nu} = \eta \frac{\partial u_\phi}{\partial \nu} - u_\phi \frac{\sin \nu \cosh \mu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}}
\]

\[
\sigma_{\phi\phi} = -P + 2\eta \frac{\partial u_\phi}{\partial \phi} + \frac{u_\mu \cosh \nu \cos \nu + u_\nu \sin \nu \cos \nu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}}
\]

(A.34)

The traction vector for this coordinate system is given by A.21, with unit base vectors:

\[
e_\mu = \frac{1}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} \cdot \left( \cosh \mu \sin \nu \cos \phi e_x + \cosh \mu \sin \nu \sin \phi e_y + \sinh \mu \cos \nu e_z \right)
\]

\[
e_\nu = \frac{1}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} \cdot \left( \sinh \mu \cos \nu \cos \phi e_x + \sinh \mu \cos \nu \sin \phi e_y - \cosh \mu \sin \nu e_z \right)
\]

\[
e_\phi = -\sin \phi e_x + \cos \phi e_y
\]

(A.35)

It follows from this that the velocity components in the prolate spheroidal coordinate system written in terms of the Cartesian components are:

\[
u_\mu = \frac{1}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} \left( \cosh \mu \sin \nu \cos \phi u_x + \cosh \mu \sin \nu \sin \phi u_y + \sinh \mu \cos \nu u_z \right)
\]

\[
u_\nu = \frac{1}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} \left( \sinh \mu \cos \nu \cos \phi u_x + \sinh \mu \cos \nu \sin \phi u_y - \cosh \mu \sin \nu u_z \right)
\]

\[
u_\phi = -\sin \phi u_x + \cos \phi u_y
\]

(A.36)

Similar to that done in the oblate spheroidal coordinate system, the evaluation of the required components of the stress tensor to compute the force on the object surface is done analytically for derivatives with respect to \( \nu \) and \( \phi \), and numerically with respect to \( \mu \).
Similar to A.27, here we have:

\[ u_{\mu,\text{trans}} = \frac{1}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} (\cosh \mu \sin \nu \cos \phi \, U_x + \cosh \mu \sin \nu \sin \phi \, U_y + \sinh \mu \cos \nu \, U_z) \]

\[ u_{\mu,\text{rot}} = \frac{a(\omega_y \cos \phi - \omega_x \sin \phi) \sin \nu \cos \nu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} \]

(A.37)

The derivatives with respect to \( \nu \) and \( \phi \) are:

\[ \frac{\partial u_{\mu,\text{trans}}}{\partial \nu} = \frac{1}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} [\cosh \mu \cos \nu (\cos \phi \, U_x + \sin \phi \, U_y) - \sinh \mu \sin \nu U_z] \]

\[ - \frac{\sin \nu \cos \nu}{(\sinh^2 \mu + \sin^2 \nu)^{3/2}} [\cosh \mu \sin \nu (\cos \phi \, U_x + \sin \phi \, U_y) + \sinh \mu \cos \nu U_z] \]

\[ \frac{\partial u_{\mu,\text{trans}}}{\partial \phi} = \frac{\cosh \mu \sin \nu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} (-\sin \phi \, U_x + \cos \phi \, U_y) \]

\[ \frac{\partial u_{\mu,\text{rot}}}{\partial \nu} = a(\omega_y \cos \phi - \omega_x \sin \phi) \left[ \frac{\cos^2 \nu - \sin^2 \nu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} - \frac{\sin^2 \nu \cos^2 \nu}{(\sinh^2 \mu + \sin^2 \nu)^{3/2}} \right] \]

\[ \frac{\partial u_{\mu,\text{rot}}}{\partial \phi} = -\frac{a \sin \nu \cos \nu}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} (\omega_y \sin \phi + \omega_x \cos \phi) \]

(A.38)

Similar to the oblate spheroidal coordinate system, the derivatives with respect to \( \mu \) are evaluated numerically using discrete values of \( \Delta \mu \) that correspond to the spacing used on the Cartesian grid. The relationship between \( \Delta \mu \) and \( \Delta r \) in this coordinate system is identical to that in the oblate spheroidal coordinate system, and is given by A.3. Finally, the Cartesian components of the traction vector in terms of the components of the stress tensor in the prolate spheroidal coordinate system are:

\[ t_x = \frac{1}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} (\sigma_{\mu \mu} \cosh \mu \sin \nu \cos \phi + \sigma_{\mu \nu} \sinh \mu \cos \nu \cos \phi) - \tau_{\mu \phi} \sin \phi \]

\[ t_y = \frac{1}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} (\sigma_{\mu \mu} \cosh \mu \sin \nu \sin \phi + \sigma_{\mu \nu} \sinh \mu \cos \nu \sin \phi) + \tau_{\mu \phi} \cos \phi \]  

(A.39)

\[ t_z = \frac{1}{\sqrt{\sinh^2 \mu + \sin^2 \nu}} (\sigma_{\mu \mu} \sinh \mu \cos \nu - \sigma_{\mu \nu} \cosh \mu \sin \nu) \]
which are used to compute the net force and torque on rigid prolate spheroids in the same manner as was done with the rigid oblate spheroids.
References


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