NUMERICAL SIMULATION OF CELLULAR BLOOD FLOW

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The Academic Faculty

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NUMERICAL SIMULATION OF CELLULAR BLOOD FLOW

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xv
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<td>BDI</td>
<td>Blood Damage Index</td>
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<tr>
<td>BGK</td>
<td>Bhatnagar–Gross–Krook</td>
</tr>
<tr>
<td>BGP</td>
<td>IBM BlueGene/P supercomputer</td>
</tr>
<tr>
<td>CPU</td>
<td>Central processing unit</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>EBF</td>
<td>External boundary force</td>
</tr>
<tr>
<td>FE</td>
<td>Finite element</td>
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<td>FLOP</td>
<td>Floating point operation</td>
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<td>GB</td>
<td>Gigabyte</td>
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<td>GFLOPS</td>
<td>$10^9$ Floating point operations per second</td>
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<td>GPU</td>
<td>Graphics processing unit</td>
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<td>MPI</td>
<td>Message Passing Interface</td>
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<td>National Science Foundation</td>
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<tr>
<td>TACC</td>
<td>Texas Advanced Computing Center</td>
</tr>
<tr>
<td>TAU</td>
<td>Tuning Analysis Utilities</td>
</tr>
<tr>
<td>WLC</td>
<td>Worm-like chain</td>
</tr>
</tbody>
</table>
\( a \)  
\( a_p \)  
\( A_c \)  
\( A_{\text{total}} \)  
\( A_{\text{desired total}} \)  
\( A_\alpha \)  
\( A_\alpha^0 \)  
\( B \)  
\( c \)  
\( c_s \)  
\( C \)  
\( C_{aG} \)  
\( C_{aG,\text{eff}} \)  
\( D_A \)  
\( D_T \)  
\( df \)  
\( df_{\text{adhesion}} \)  
\( df_{\text{contact}} \)  
\( df_{\text{lub}} \)  
\( e_i \)  
\( E_{\text{area}} \)  
\( E_{\text{bending}} \)  
\( E_{\text{in-plane}} \)  
\( E_{\text{volume}} \)  
\( E_y \)  
\( E \)  
\( f_i \)  

Particle/RBC/Platelet radius  
Total rigid particle acceleration  
Contact scaling constant  
Total RBC surface area  
Total desired RBC surface area  
Area of triangle \( \alpha \) of RBC membrane tessellation  
Initial area of triangle \( \alpha \) of RBC membrane tessellation  
Exponent for velocity blunting estimates  
Lattice-Boltzmann spacing  
Lattice-Boltzmann pseudo sound speed  
Hydrostatic elastic energy  
Capillary number  
Effective capillary number  
Axial diameter of stretched RBC  
Traverse diameter of stretched RBC  
Link-wise lubrication force proposed by Ding & Aidun (2003)  
Link-wise adhesion force  
Link-wise contact force  
Link-wise correction to lubrication force  
Lattice-Boltzmann discrete velocity vectors  
Area controller contribution to Helmholtz free energy  
Bending contribution to Helmholtz free energy  
In-plane contribution to Helmholtz free energy  
Volume controller contribution to Helmholtz free energy  
Young’s modulus  
Rate of strain tensor  
Lattice-Boltzmann fluid distribution function
$f^{(eq)}_i$  Equilibrium lattice-Boltzmann fluid distribution function

$f_{WLC}$  Worm-like chain force-length relationship

$f_{lub}$  Lubrication force from two approaching spheres (Cox, 1974)

$f^{(b)}$  Bounce-back force

$f^{\text{link}}$  Force on a given boundary link

$f^{(c)}$  Force associated with node (un)covering

$f^{\text{contact}}$  Contact force between two particles

$f^{\text{total}}$  Summed force on particle

$f_n$  Total spectrin-link force on each membrane vertex

$g$  Gap between particles for a surface element

$g'$  Gap along a lattice link

$g_c$  Cut-off gap for contact force

$g_j$  Weighting for force interpolation

$G$  RBC membrane shear modulus

$H$  Height of domain

$I$  Moment of inertia for rigid particles

$k_B$  Boltzmann’s constant

$k_{\text{in-plane}}$  In-plane spectrin-link model constant

$k_{\text{bend}}$  Bending spectrin-link model constant

$k_{\text{area}}^{\text{global}}$  Global area spectrin-link model constant

$k_{\text{area}}^{\text{local}}$  Local area spectrin-link model constant

$k_{\text{volume}}$  Volume spectrin-link model constant

$L_i$  Length of spectrin link $i$

$L_0$  Average spectrin link length

$L_{\text{max}}$  Maximum spectrin link length

$M$  Mass

$Ma$  Lattice-Boltzmann Mach number
\( N \)  Number of vertices used to triangulate the spectrin-link membrane
\( N_1 \)  First normal stress difference
\( N_2 \)  Second normal stress difference
\( n \)  Surface normal
\( n_{\text{avg}} \)  Average surface normal
\( n_\alpha \)  Normal vector of triangle \( \alpha \)
\( n_\beta \)  Normal vector of triangle \( \beta \)
\( p \)  Persistence length
\( P_f \)  Fluid pressure
\( \bar{q} \)  Lubrication weighting coefficient
\( Q \)  Volumetric flow rate
\( r \)  radial coordinate
\( R \)  Vessel radius
\( Re \)  Reynolds number
\( r \)  Vector from particle center to node on surface
\( s \)  Vector connecting finite element surfaces
\( S \)  Total number of spectrin-links for each RBC membrane
\( S \)  Particle stresslet
\( t \)  Time
\( T \)  Temperature
\( T_p \)  Torque on rigid particle
\( T_{\text{surf}} \)  Surface tangent vector
\( T \)  Lattice-Boltzmann time steps per second
\( u_\alpha \)  Macroscopic velocity from lattice-Boltzmann method
\( u_b \)  Boundary velocity
\( u_x \)  Axial velocity in Hagen–Poiseuille flow
\( u_\perp \)  Wall-normal velocity
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>( u )</td>
<td>Macroscopic velocity of lattice-Boltzmann fluid</td>
</tr>
<tr>
<td>( U_{\text{app}} )</td>
<td>Approach velocity</td>
</tr>
<tr>
<td>( U )</td>
<td>Velocity scale</td>
</tr>
<tr>
<td>( V )</td>
<td>Domain volume</td>
</tr>
<tr>
<td>( V_{\text{WLC}} )</td>
<td>Worm-like chain potential</td>
</tr>
<tr>
<td>( v_n )</td>
<td>Velocity of each spectrin-link vertex</td>
</tr>
<tr>
<td>( v_p )</td>
<td>Total velocity of rigid particle</td>
</tr>
<tr>
<td>( W_0 )</td>
<td>Womersley number</td>
</tr>
<tr>
<td>( w_i )</td>
<td>Lattice-Boltzmann direction weights</td>
</tr>
<tr>
<td>( w )</td>
<td>Bin widths for platelet averaging</td>
</tr>
<tr>
<td>( x_0 )</td>
<td>Average normalized spectrin-link length</td>
</tr>
<tr>
<td>( x_i )</td>
<td>Normalized spectrin-link length</td>
</tr>
<tr>
<td>( x )</td>
<td>Cartesian coordinate used in lattice-Boltzmann stencil</td>
</tr>
<tr>
<td>( x_\alpha )</td>
<td>Center of triangle ( \alpha )</td>
</tr>
<tr>
<td>( x_n )</td>
<td>Points used to triangulate RBC surface</td>
</tr>
<tr>
<td>( x_p )</td>
<td>Center of rigid particle</td>
</tr>
<tr>
<td>( \alpha )</td>
<td>Asphericity</td>
</tr>
<tr>
<td>( \gamma )</td>
<td>Moment of inertia multiplication factor</td>
</tr>
<tr>
<td>( \dot{\gamma} )</td>
<td>Shear rate</td>
</tr>
<tr>
<td>( \dot{\gamma}_w )</td>
<td>Wall shear rate in Hagen–Poiseuille flow</td>
</tr>
<tr>
<td>( \Gamma )</td>
<td>Deformation index for parachuting RBC</td>
</tr>
<tr>
<td>( \delta )</td>
<td>Cell-depleted layer thickness</td>
</tr>
<tr>
<td>( \Delta L )</td>
<td>Length difference</td>
</tr>
<tr>
<td>( \Delta p )</td>
<td>Pressure difference</td>
</tr>
<tr>
<td>( \Delta t )</td>
<td>Time discretization for numerical simulation</td>
</tr>
<tr>
<td>( \varepsilon )</td>
<td>Cutoff distance for force interpolation</td>
</tr>
<tr>
<td>( \epsilon )</td>
<td>Curvature parameter</td>
</tr>
</tbody>
</table>
\( \zeta \) Eigenvalue of tensor of gyration
\( \eta_{\text{membrane}} \) Membrane viscosity
\( \theta \) Orientation angle between particle and flow direction
\( \theta_{\alpha\beta} \) Angle between adjacent triangles \( \alpha \) and \( \beta \)
\( \theta_0 \) Instantaneous angle between adjacent triangle pairs
\( \kappa_b \) Bending energy
\( \lambda \) Viscosity ratio
\( \mu \) Suspending fluid dynamic viscosity
\( \mu_{\text{eff}} \) or \( \mu_a \) Effective or apparent dynamic viscosity
\( \mu_r \) Relative viscosity
\( \nu \) Kinematic viscosity
\( \nu_p \) Poisson ratio
\( \xi \) BDI correction factor
\( \Pi_p \) Particle pressure
\( \Pi \) Number of triangles used in spectrin-link membrane
\( \rho \) Density
\( \rho_s \) Solid density
\( \sigma_c \) Scaling for contact force
\( \sigma_{ij} \) Local stress tensor
\( \Sigma \) Stress in the suspension
\( \Sigma^f \) Stress in the fluid phase
\( \Sigma^p \) Stress in the particle phase
\( \tau \) Lattice-Boltzmann relaxation time
\( \phi \) Volume fraction or hematocrit
\( \phi_m \) Maximum packing fraction
\( \chi \) Bending to in-plane energy ratio (bending ratio)
\( \psi \) Electrostatic potential
\( \omega \) \hspace{1em} \text{Oscillating flow frequency} \\
\( \Omega_{\text{total}} \) \hspace{1em} \text{Total volume of RBC} \\
\( \Omega_{\text{desired total}} \) \hspace{1em} \text{Total desired RBC volume}
SUMMARY

In order to simulate cellular blood, a coarse-grained (Pivkin & Karniadakis, 2008) spectrin-link (SL) red blood cell (RBC) membrane model (Li et al., 2005; Dao et al., 2006) is coupled with a lattice-Boltzmann (LB) based suspension solver (MacMeccan et al., 2009). The LB method resolves the hydrodynamics governed by the Navier–Stokes equations while the SL method accurately models the deformation of RBCs under numerous configurations. This method has been parallelized using Message Passing Interface (MPI) protocols for the simulation of dense suspensions of RBCs characteristic of whole blood on world-class computing resources.

Simulations were performed to study rheological effects in unbounded shear using the Lees–Edwards boundary condition (Lees & Edwards, 1972) with good agreement with rotational viscometer results from literature. The particle-phase normal-stress tensor was analyzed and demonstrated a change in sign of the particle-phase pressure from low to high shear rates due to RBCs transitioning from a compressive state to a tensile state in the flow direction. Non-Newtonian effects such as viscosity shear thinning were observed for shear rates ranging from 14-440 sec$^{-1}$ as well as the strong dependence on hematocrit at low shear rates. An increase in membrane bending energy was shown to be an important factor for determining the average orientation of RBCs, which ultimately affects the suspension viscosity. The shear stress on platelets was observed to be higher than the average shear stress in blood, which emphasized the importance of modeling platelets as finite particles.

Hagen–Poiseuille flow simulations were performed in rigid vessels for investigating the change in cell-depleted layer thickness with shear rate, the Fåhraeus–Linqvist
effect, and the process of platelet margination. The process of platelet margination was shown to be sensitive to platelet shape. Specifically, it is shown that lower aspect ratio particles migrate more rapidly than thin disks. Margination rate is shown to increase with hematocrit, due to the larger number of RBC-platelet interactions, and with the increase in suspending fluid viscosity.
CHAPTER I

INTRODUCTION

1.1 Background

Coronary thrombosis and cardiovascular disease are among the leading causes of death among Americans. The mortality rate associated with cardiovascular disease has declined from 1997 to 2007, but still accounts for more than one third of all deaths at a rate of 2,200 per day (Roger et al., 2011). The formation of thrombi is a driving factor in these mortality rates and can manifest itself in the form of atherosclerosis, coronary artery calcification, or via venous thromboembolisms from deep vein thrombosis among many other causes. The deposition of platelets leading to the formation of thrombi is of interest to the research community that study vascular implants (artificial hearts and heart valves), vascular grafts, and those who study formation due to plaque rupture or disfunctioning endothelium. The knowledge of the mechanisms that cause platelet deposition and diffusion can be enriched using numerical methods that account for the cellular nature of blood and the shear stress environment experienced by platelets.

Artificial implants are susceptible to causing health problems and are currently major topics in computational and experimental research. The effects of stent implantation can be postponed as many as eight months (Camenzind et al., 2007) due to phenomena such as vascular wall remodeling (Intengan & Schifflin, 2001). Remodeling has shown to cause visible aneurysms that can lead to death. The effect of these aneurysms is vessel widening and, as a result, slower flow velocities due to the increase in cross-sectional area which ultimately cause thrombogenesis. The development of safe artificial implants for children (Baldwing et al., 2006) is important because many
times these devices are replaced multiple times during early stages of development. Artificial drug delivery systems (Balakrishnan et al., 2005) that use artificial implants (or drug-eluting stints) are also challenging problems where detailed understandings can be enhanced using data-rich numerical simulations. In many instances, these delivery systems can cause “pools” due to disruption of the flow. Therefore, the use of computational tools that are robust enough to capture the flow physics of non-Newtonian blood flow within complicated geometries can further assist the understanding of after-effects of such implant devices and can lead to a more thorough understanding for developing future implants.

In small vessels, the cellular nature of blood is of utmost importance and precise experimental measurements can be cumbersome due to its opaque nature. Due to extensive research in the experimental community, many phenomena have been discovered that are influenced by the constituents in blood. The two most important factors that influence blood viscosity have been determined to be hematocrit and shear rate. Using direct numerical simulation, many flow properties that cannot be measured experimentally or those that may be difficult to measure with non-intrusive methods, can be monitored. Examples include orientation and stresses on particles, diffusion of particles, and individual particle trajectories.

The flow through arteries and veins can be characterized as low Reynolds number, incompressible, and internal. In larger vessels, such as the aorta, the flow of blood is also unsteady due to its proximity to the heart and is influenced by the oscillating pressure gradients of the cardiovascular cycle. Complicated geometries associated with the accumulation of plaque or the formation of thrombi in vessels can cause the flow to separate or become turbulent. However, in this work, the primary focus is on laminar flows at low Reynolds numbers. Inertial effects are captured by using the lattice-Boltzmann method which resolves the flow governed by the incompressible Navier–Stokes equations (Chen & Doolen, 1998; Aidun & Clausen, 2010). In most
cardiovascular flow simulations, the common assumption is that blood behaves as a single-phase Newtonian fluid which is valid for the high shear rate flow conditions in large vessels. In flows where the cellular nature of blood is not critical, non-Newtonian viscosity models have also been used to investigate flow features near prosthetic valves (Ellis et al., 2000) in addition to studying turbulence and coherent structures present downstream from bileaflet valves (Dasi et al., 2007). In this work, blood is modeled as a suspension of deformable RBCs and rigid platelets at realistic hematocrit values that inherently captures non-Newtonian effects.

1.2 Objective

The purpose of this research is to investigate the rheological properties of blood at moderate shear rates and to study the flow of blood in small vessels in more detail. To attain these goals, a RBC membrane model suitable of capturing large deformations and multiple dynamical regimes in multiple flow configurations must be implemented. The fluid phase is solved using the lattice-Boltzmann (LB) method on a fixed Cartesian grid of fluid points. The LB method is an accurate and efficient method for the analysis of particle-laden flows. Deformable RBCs are allowed to travel freely through the underlying LB stencil as Lagrangian particles. The no-slip condition on the RBC membrane surface is enforced with the standard bounce-back boundary condition. As an improvement to the previously developed hybrid lattice-Boltzmann finite-element (FE) method for simulating blood flow at low shear rates, a spectrin-link (SL) based membrane model is implemented.

This research will address the following objectives:

- Provide a significantly improved method for the RBC membrane that can be coupled easily and effectively to the LB method while also being suitable for parallelization on distributed memory architectures and for simulating dense suspensions of RBCs at realistic hematocrit levels.
• Validate this method with comparisons of isolated RBC dynamics and deformations in multiple flow configurations.

• Demonstrate the ability to capture known continuum-level physics, for blood in shear, and to investigate parameters that have not been reported in literature including the particle-phase normal-stress tensor, the particle-phase pressure, and normal stress differences.

• Investigate the process of platelet margination in blood flow through small vessels to reveal the underlying physics and to determine the rate of margination based on platelet shape, hematocrit, and hemoglobin to suspending fluid viscosity ratio.

1.3 Relevant dimensionless parameters in cellular blood

The flow of blood through vessels shares the common dimensionless parameters associated with the flow through pipes, but the addition of particles increases the complexity. The dimensionless parameters relevant to single-phase flow through small vessels are primarily the vessel Reynolds number and Womersley number. By adding particles to the flow, the particle-based Reynolds number, volume fraction of particles, Péclet number, and relative viscosity become important dimensionless parameters. Deformable particles add even more complexity with the capillary number and bending ratio. If these deformable particles contain an internal fluid, the ratio of densities and viscosities must also be considered.

For flow in larger arteries, such as the aorta, tube diameter based Reynolds numbers can be $\mathcal{O}(10^3)$, but for small vessels they are less than unity. A small Reynolds number implies that viscous effects are more dominant than inertial effects and the flow is controlled by the balance of viscous forces and pressure-gradient forces. The tube Reynolds number based on the tube diameter, average axial velocity, and kinematic viscosity of the plasma range from 0.1-10 for the simulations in this work. The
tube Reynolds number is defined as

\[ Re_D \equiv \frac{\bar{u}D}{\nu} = \frac{\bar{Q}D}{(\frac{\pi}{4}D^2)\nu} \]  

(1)

where \( \bar{u} \) is the average velocity in the tube, \( \bar{Q} \) is the average flow rate, \( D \) is the vessel diameter, and \( \nu \) is the kinematic viscosity of the suspending fluid (plasma). For Hagen–Poiseuille flow simulations with a dense distribution of RBCs the exact value of \( Re_D \) cannot be prescribed without knowledge of the apparent viscosity, \( \mu_a \), of the fluid. Therefore, it is calculated after the flow rate is obtained by integrating the axial velocity over the vessel cross-sectional area.

It is well known that the flow of blood in many parts of the cardiovascular system is unsteady. The nature of blood flow in large arteries is characterized as pulsatile through its strong coupling with the mechanics of the heart. The periodicity is described with a dimensionless parameter known as the Womersley number (Womersley, 1955). The Womersley number is defined as

\[ Wo \equiv R \sqrt{\frac{\omega \rho}{\mu_a}}, \]  

(2)

where \( \omega \) is the frequency of the oscillating flow, \( R \) is the vessel radius, \( \rho \) is the density of the fluid, and \( \mu_a \) is the apparent (or effective) dynamic viscosity. The values of the Womersley number vary throughout the circulatory system with the highest values observed in the larger arteries, such as the aorta, and the smallest values in capillaries. For the simulations presented in this work, the Womersley number is assumed to be identically zero, i.e., the pressure-gradient force driving the flow is constant.

The red blood cell Reynolds number can be described as the ratio of inertial to viscous forces on the local level of the RBC. For the investigations presented herein, the Reynolds number is formulated based on the shear rate experienced by the RBC, \( \dot{\gamma} \), the RBC radius, \( a \), and the kinematic viscosity of the suspending fluid, \( \nu \). The RBC Reynolds number is defined as

\[ Re_{RBC} \equiv \frac{\dot{\gamma}a^2}{\nu}. \]  

(3)
The RBC Reynolds numbers in this work are small, approximately 0.1, but some of the simulations in Hagen–Poiseuille flow result in $Re_{RBC}$ values as high as 0.5 in the high shear rate regions near vessel walls.

The volume fraction of RBCs in blood is known as the hematocrit, $\phi$. This is one of the most important and difficult factors to consider when modeling blood as a suspension of deformable cells. The viscosity of suspensions, in general, show a strong dependence on the volume fraction of particles. Therefore, it is important to simulate blood using realistic values. The hematocrit in the simulations in this work are calculated via

$$\phi = \frac{\sum_{k=1}^{P} \Omega_{RBC,k}}{V_{total}}$$

where $\Omega_{RBC,k}$ is the volume of the $k^{th}$ individual RBC, $P$ is the total number of RBCs, and $V_{total}$ is the total volume of the fluid domain considered. A hematocrit value of $\phi \approx 0.4$ is commonly considered a realistic volume fraction of RBCs, but many experiments are performed at reduced hematocrit values of 0.1-0.3. The range of hematocrit values simulated in this work range from 0.1-0.425 to compare with results from literature.

Suspension flows can be characterized using the Peclét number to emphasize the importance of Brownian motion. The Peclét numbers of the simulations in this work are infinite, i.e., $Pe \to \infty$, implying the strict hydrodynamic limit where Brownian motion is negligible. Large $Pe$ number suspensions are generally characterized as shear thinning where the viscosity decreases with shear rate. The Peclét number is defined as

$$Pe \equiv \frac{6\pi \mu \dot{\gamma} a^3}{k_B T}$$

where $k_B$ is Boltzmann’s constant and $T$ is temperature. The lattice-Boltzmann formulation used in this work does not consider thermal contributions and, therefore, cannot resolve the motions due to thermal oscillations. It is assumed, here, that the migration and motion due to deformation, hydrodynamic, and inter-particle forces
are much greater than that of Brownian motion.

The relative viscosity quantifies the additional resistance due to the presence of particles in Hagen–Poiseuille flow and can be used to describe the increase in the viscosity of a suspension due to the presence of particles in shear flows. The relative viscosity is defined as

\[ \mu_r \equiv \frac{\mu_a}{\mu} \]  

(6)

where \( \mu_a \) is the measured apparent (effective) viscosity and \( \mu \) is the viscosity of the suspending fluid. Furthermore, the presence of RBCs in blood strongly influences the relative viscosity, which can vary with factors such as vessels diameter, hematocrit, and shear rate (Pries et al., 1996). The calculation of the relative viscosity is different for simulations of RBCs in shear than those in Hagen–Poiseuille flow. The exact forms for these calculations will be given in context for clarity.

The migration and motion of RBCs is strongly dependent on their deformation. The capillary number represents the ratio of forces due to viscous fluid motion to the elasticity of the RBC membrane. The RBC capillary number is defined as

\[ Ca_G \equiv \frac{\mu \dot{\gamma} a}{G} \]

(7)

where, \( \mu \) is the viscosity of the suspending fluid, \( \dot{\gamma} \) is shear rate experienced by the RBC, \( a \) is the RBC radius, and \( G \) is the membrane shear modulus. Other capillary numbers are defined using the area modulus and Young’s modulus. For droplets, the capillary number is defined using surface tension instead of membrane shear modulus. Generally, RBCs tumble at low capillary numbers and undergo tank-treading motion at higher capillary numbers. Furthermore, as the capillary number is increased the amount of deformation also increases. The exact capillary numbers where tumbling and tank treading are observed vary based on the viscosity ratio of the internal to suspending fluid viscosities defined as

\[ \lambda \equiv \frac{\mu_{\text{interior}}}{\mu_{\text{exterior}}} \]

(8)
Physiologically, $\lambda \approx 5$ where suspending plasma has a viscosity of 1.2 cP and hemoglobin 6 cP. However, many experiments use viscous solutions containing dextran for the suspending fluid which reduces this ratio considerably. In general, a reduction in $\lambda$ reduces the shear rate threshold where the transition from tumbling to tank treading occurs (Abkarian et al., 2007).

The bending ratio for asymmetric shapes like RBCs is a measure for how easily they fold or buckle under certain flow conditions. The bending energy present in the RBC membrane can be described by the bending ratio (Li et al., 2005)

$$\chi \equiv \frac{\kappa_b}{GA_{\text{total}}}$$

where $\kappa_b$ is the bending energy of the membrane, $G$ is the membrane shear modulus, and $A_{\text{total}}$ is the total surface area of the membrane. An artificially high bending ratio can increase the stability of an RBC preventing deviations from its equilibrium shape other than stretching or elongations (Pozrikidis, 2001).

### 1.4 Characteristics of blood

At low shear rates, or for flows in the microvascular, blood is most accurately modeled as a non-Newtonian multiphase fluid. Its properties are strongly influenced by the number, shape, and properties of the suspended particles it contains. Accurately modeling it requires the incorporation of plasma, red blood cells (erythrocytes), white blood cells (leukocytes), and platelets (Bohle et al., 2003). Plasma is approximately 90% water and is commonly modeled as a Newtonian fluid with a density of 1,050 kg·m$^{-3}$ (Hinghofer-Szalkay & Greenleaf, 1987). Plasma, in vivo, has a measured viscosity of 1.2 cP, but is sensitive to temperature variations (Harkness & Whittington, 1970). One specific multiphase characteristic of blood is that its viscosity increases nonlinearly with hematocrit (Fung, 1993) and the hematocrit values of whole blood vary from approximately 30-45% depending on vessel size and location in the cardiovascular system.
Red blood cells are composed of a thin membrane filled with a viscous solution containing hemoglobin. The role of hemoglobin is to transport oxygen and carbon dioxide to and from cells throughout the body. Hemoglobin is an incompressible Newtonian fluid with a density approximately equal to that of plasma and a viscosity of 6 cP (Sugihara-Seki & Fu, 2005). Leukocytes, or white blood cells, are approximately spherical in shape, have a diameter of 7-8 µm, and are much less deformable than RBCs. As a result, they are modeled as rigid spheres (Munn & Dupin, 2008). Leukocytes are approximately 100 times less numerous than RBCs, but can contribute significantly to the resistance of flow in microvessels (Sun & Munn, 2005). The role of leukocytes is to deliver antibodies to counteract infections in the body and their volume fraction is an indicator of infection levels in a diseased patient. Platelets are less numerous than RBCs, but are fundamental in the hemostatic system of the body responsible for blood clotting and the formation of thrombi. Platelets have a maximum dimension of approximately 2 µm, and are commonly modeled as ellipsoid- or disk-shaped particles. However, platelet morphology has shown to vary from spherical to flat disks (Maxwell et al., 2006). Rigid platelet analogues, such as latex beads, are commonly used in experiments (Tilles & Eckstein, 1987; Eckstein et al., 1988).

Red blood cell aggregation has been observed in humans and in other athletic animals, but is absent in sedentary animals (Bishop et al., 2001). The presence of RBC aggregation can cause a reduction in the flow of blood in microcirculatory vessels and is a major factor contributing to the increase in flow resistance at extremely low shear rates in capillaries. The force adhering two RBCs is at a maximum when they are joined enface. This is commonly experienced when they form rouleaux formations (Fung, 1993) that resemble stacks of coins, but other complex aggregate clusters are also observed as well. After cells are adhered to each other, there is a threshold of shear stress required to separate them. The amount of shear stress required depends on the complexity of the aggregate and the suspending fluid properties, such as the
viscosity, the concentration of certain proteins, and the local flow conditions, e.g. the local shear rate. The effects of aggregation include an increase in the relative viscosity of blood up to ten times at shear rates as low as 0.01 sec$^{-1}$, but have relatively little impact at shear rates in excess of 10 sec$^{-1}$ (Chien, 1970). The process of RBC aggregation is enhanced with the addition of proteins such as fibrinogen and globulin in blood plasma (Wang et al., 2009). The formation of these aggregates can have dramatic effects on the transport of RBCs, and therefore oxygen, in microcirculation. This can manifest itself in shortness of breath and fatigue. Malaria can cause RBCs to become more rigid and more adhesive causing the formation of aggregates as well (Liu & Liu, 2006).

1.5 Blood rheology

The viscosity of blood is commonly modeled using power law formulations (Hussain et al., 1999) where the apparent viscosity takes a functional form such as $\mu_a=k(du/dy)^{(n-1)}$. The exponent $n$ is commonly referred to as the non-Newtonian behavior index. This approach has allowed the biomedical community to understand some of the complexities associated with blood flow through stents (Benard et al., 2006), elastic arteries (Kumar et al., 2005), stenosed blood vessels (Ro et al., 2008), small blood vessels (Khatir & Sequeira, 2004), coronary arteries (Goubergrits et al., 2008), and cerebral aneurysms (Bernsdorf & Wang, 2007). Data available for matching non-Newtonian behavior is only available at few shear rates and cannot be applied for flow through complex geometries where multiple shear rates, with various orders of magnitude, exist. Ideally, the exponent should also account for the various levels of hematocrit in blood. The possibility of simulating realistic blood flows with a formulations as simple as a power law formulation requires a vast survey of experimental design space for both shear rate and hematocrit levels. Complex modifications (Grigioni et al., 2005) also exist to improve the deficiencies of standard power law models in addition
to models utilizing multiple fluids (Sankar & Lee, 2008).

The methodology used to investigate the rheological properties of rigid particle suspensions can be applied to a suspension of deformable RBCs. Realistic blood is a dense suspension of RBCs where “dense” implies that RBCs are separated by less than a RBC radius (Stickel & Powell, 2005). In whole blood, the interactions of RBCs and platelets through inter-particle forces play a significant role in rheological properties. The simulations presented here assume that all the particles are neutrally buoyant so that the density of the solid phase is equal to the fluid phase, \( \rho_s = \rho \). For rigid particles, this allows the relative viscosity to be written as a function of only three dimensionless parameters \( \mu_r = f(\phi, Pe, Re) \). Assuming \( Re_{RBC} \ll 1 \) reduces the dependence to \( \mu_r = f(\phi, Pe) \) while assuming \( Pe \to \infty \) results in \( \mu_r = f(\phi, Re) \).

The deformation of the RBCs is also an important characteristic. This is quantified by the influence of the capillary number \( Ca_G \). Under the assumption that \( Pe \to \infty \) and \( Re_{RBC} \ll 1 \), the relative viscosity is \( \mu_r = f(\phi, Ca_G) \). The previous work by MacMeccan (2007) demonstrated little difference in \( \mu_r \) for simulations at \( \phi = 0.405 \) with \( Re_{RBC} = 0.1 \) and 0.7 even though these Reynolds numbers are significantly above the Stokes flow assumption of \( Re_{RBC} \ll 1 \). The relative viscosity for the LB-SL implementation is also insensitive to \( Re_{RBC} \) in this range which reiterates that viscosity is only a function of \( Ca_G \) and \( \phi \) in the regime considered here. Viscosity also varies with temperature and with disease state (Fung, 1993), but are not investigated in this work.

Simulations capable of capturing the microstructure and rheology of dense suspensions of deformable particles has just recently been investigated (Clausen & Aidun, 2010; Clausen, 2010; Clausen et al., 2011). Simulations of suspensions containing RBCs at realistic hematocrit values in cubical domains are performed in unbounded shear using the Lees–Edwards boundary condition (LEbc) (Lees & Edwards, 1972) in this work. The LEbc was originally developed for molecular dynamics simulations,

The effect of suspended RBCs on the rheology of blood can best be understood by calculating the ensemble averaged stresslet given in Batchelor (1970). The stress in blood can be split into the separate phases, fluid and solid, by

$$\langle \Sigma \rangle = \langle \Sigma^f \rangle + \langle \Sigma^p \rangle,$$

(10)

where the superscripts $f$ and $p$ identify the contributions of the suspending fluid and particles (or RBCs) respectively and $\langle \cdot \rangle$ denote ensemble averages. This average is calculated by performing the volume integral of the stress experienced by the RBCs via

$$\langle \Sigma \rangle = \frac{1}{V} \int \sigma dV.$$

(11)

For simulations exposed to an applied constant shear rate this volume average is appropriate (Clausen et al., 2011) while temporal averaging, for simulations, is done after initial transients have subsided. The average stress in a suspension subjected to shear, neglecting inertia at low $Re$, can be expressed as

$$\langle \Sigma \rangle = -(P_f)I + 2\mu E + \frac{1}{V} \sum_{i=1}^{N} S,$$

(12)

where $P_f$ is the mean pressure, $\mu$ is the suspending fluid viscosity, $E$ is the mean rate-of-strain tensor, $V$ is the volume of the domain, and the stresslet $S$ is given as the first moment of the traction vectors on the particle surface calculated via (Batchelor, 1970)

$$S_{ij} = \int_A \frac{1}{2} (\sigma_{ik} n_k r_j + \sigma_{jk} n_k r_i) - \mu (u_i n_j + u_j n_i) dA$$

(13)

where $\sigma_{ij}$ is the stress on the RBC surface, $u_i$ is the velocity of the RBC, $\mu$ is the viscosity of the plasma surrounding the RBC, $n_i$ is the outward pointing normal vector of the RBC surface, and $r_i$ is the vector from the center of the RBC to its surface. The relative viscosity is then calculated using this result by

$$\mu_r = \frac{\Sigma_{12}}{\mu \gamma},$$

(14)
where $\dot{\gamma}$ is the shear rate. In dense suspensions, anisotropy in the overall particle configuration generate negative first normal stress differences. This is certainly expected in blood since RBCs are not only deformable, but initially axisymmetric. The first and second normal stress differences are related to $\Sigma$ and are defined as

$$
\begin{align*}
N_1 & \equiv \Sigma_{11} - \Sigma_{22}, \\
N_2 & \equiv \Sigma_{22} - \Sigma_{33},
\end{align*}
$$

and are difficult to observe experimentally. In unbounded shear simulations, the entry $\Sigma_{11}^p$ describes the particle-phase normal stress in the flow direction, $\Sigma_{22}^p$ the velocity-gradient direction, and $\Sigma_{33}^p$ the vorticity direction. The particle-phase pressure is related to the trace of the particle-phase normal-stress tensor by

$$
\Pi_p = -\frac{1}{3} \Sigma_{ii}^p = -\frac{1}{3V} \sum_{i=1}^N S_{ii},
$$

and describes the difference in the pressures between the RBC phase and the suspending fluid. This is an osmotic pressure induced by the interactions and flow-induced hydrodynamic normal stresses between RBCs and platelets.

### 1.6 Microcirculation

Flow in the microvascular is strongly influenced by the presence of blood constituents, primarily RBCs. An apparent viscosity, $\mu_a$, is used to quantify the additional resistance due the presence of RBCs. The apparent viscosity of blood varies with RBC aggregation state and is also dependent on vessel geometry (Sun & Munn, 2005). The apparent viscosity represents the Newtonian fluid viscosity required to yield a measured flow rate for a given pressure-gradient force. Specifically, the apparent viscosity is formulated as

$$
\mu_a = \frac{\Delta p}{\Delta L} \frac{\pi R^4}{8Q},
$$

where $\Delta p/\Delta L$ is the pressure drop per unit length, $R$ is the vessel radius, and $Q$ is the measured volumetric flow rate. The comparison of *in vitro* and *in vivo* experiments
has shown significant differences in flow resistance (Pries & Secomb, 2005). One of the sources of these differences has been assumed to be due to the presence of the glycocalyx, a thin, negatively charged, macromolecular layer found on the lumenal surface of endothelial cells (Kamm, 2002). This work does not attempt to model the presence of glycocalyx.

It is well known that the addition of particles, rigid or deformable, in the presence of a pressure-gradient driven flow through a channel or pipe causes the velocity profiles to become “blunt” (Popel & Johnson, 2005) in comparison to the Hagen–Poiseuille parabolic profile for Newtonian fluids. Estimates for the blunting of the velocity profiles are given by Tangelder et al. (1986) through a simple modification of the form $u_x(r)=U(1-(r/R)^B)$ where $B$ is equal to 2.0 for Newtonian fluids and ranges from 2.4-4.0 for the flow of whole blood through arterioles. This blunting is most significant when the diameter of the arteriole is on the order of the RBC diameter. The cause of the blunting is the increase of viscosity in the core of the vessel from elevated hematocrit levels caused by the deformation-induced migration of RBCs. In the cell-depleted layer, the thin layer adjacent to the vessel wall absent of RBCs, the velocity profile fits the analytical solution for the same pressure gradient.

The importance of RBCs in blood lends itself to many physiological phenomena. The Fähraeus effect corresponds to dynamic measurements of hematocrit in tubes being smaller than values found in the discharge reservoirs (Popel & Johnson, 2005). This is related to the tendency of RBCs to migrate away from the tube wall. In these instances, a core of tightly packed RBCs moves with a significantly higher velocity than that of the cell-depleted wall layer. A parametric description of the reduction of tube hematocrit relative to discharge hematocrit has been developed via a vast survey of experiments in which whole blood was perfused through glass tubes with different diameters (Pries et al., 1990).

Blood flow in capillary tubes is different than the flow of a Newtonian fluid in
a pipe. More specifically, the Fähraeus–Lindqvist effect, demonstrated through in vitro experiments, has shown that the resistance to flow through small tubes can be less than a Newtonian fluid with a viscosity similar to that obtained from bulk measurements. This observation is primarily seen in experiments with tubes smaller than 500 µm in diameter. The reduction of apparent blood viscosity with decreasing tube diameter was found in tubes as small as 10 µm in diameter. As the tube diameter is decreased further, the apparent viscosity increases up to the minimum diameter of approximately 2.8 µm. A relationship for apparent viscosity for blood flow with a hematocrit value of 45% in glass tubes at shear rates >100 sec\(^{-1}\) has been determined empirically (Sugihara-Seki & Fu, 2005; Pries et al., 1996) from surveying experimental data.

The cell-depleted layer is the thin layer of plasma near a microvessel wall, absent of RBCs, important to the Fähraeus–Lindqvist effect. As the RBCs migrate toward the axis of the vessel, the hematocrit in the vessel core increases to values larger than the average hematocrit. This exposes a thin layer near the vessel wall. The presence of the cell-depleted layer is important as it is the region where platelets interact with endothelial cells and adhere to vessel walls. The cell-depleted wall layer thickness is mainly dependent on the hematocrit and on shear rate, but requires that the RBCs be deformable. Specifically, larger hematocrit values result in thinner cell-depleted layers while increasing the shear rate increases the cell-depleted layer thickness (Popel & Johnson, 2005). Increased shear rates lead to larger RBC deformation and larger vessel core hematocrit levels. In microvessel-sized tubes, the presence of a cell-depleted wall layer decreases the apparent viscosity. Experiments (Sakai et al., 2009) have shown that the suspending fluid viscosity also influences the cell-depleted layer thickness for dilute (\(\phi=0.015\)) suspensions of RBCs in tubes with diameters of approximately 25 µm. Specifically, as the suspending fluid viscosity is increased, the cell-depleted layer thickness increases. Others (Freund & Orescanin,
2011) have shown that for $\phi=0.30$ the thickness is dependent on shear rate up to 100 sec$^{-1}$ in vessels of approximately 10 $\mu$m in diameter.

In the absence of RBCs, platelets migrate to $r/R\approx0.6$ in small vessels, a phenomenon known as the *tubular pinch* effect. This location is well known as the Segré–Silberberg equilibrium position. The Segré–Silberberg equilibrium position of $r/R=0.6$ was discovered (Segré & Silberberg, 1962a,b) using macroscopic rigid spheres that were released in Poiseuille flow and the location of the particles was tracked using early laser tracking procedures that relied on the “blocking out” of light of two mutually perpendicular beams. Statistical analysis revealed that the equilibrium position for these macroscopic rigid spheres was $r/R\approx0.6$. However, when RBCs are added, platelets have a tendency to migrate toward the vessel walls (Aarts et al., 1988). Near the vessel wall, the convective and diffusive forces of blood constituents become comparable due to the lower velocities (Hathcock, 2006).

The phenomenon of platelets being expelled to the vessel wall is known as margination. The formation of thrombi is dependent on the accumulation of platelets on vessel walls and modeling this process is extremely difficult due to unknown underlying factors. After platelets have marginated to the cell-depleted layer, thrombi can accumulate and cause thrombotic occlusions (Para et al., 2011) in small or large vessels. However, platelet adhesion is a strong function of the wall shear rate and hematocrit (Aarts et al., 1988; Wootton & Ku, 1999). The migration of RBCs to the tube center is not surprising as it is a characteristic of deformable particles in Hagen–Poiseuille flow. However, platelet margination is less rapid than the migration of deformable RBCs to the vessel center. The margination process is thought to be driven entirely by interactions with RBCs and not by Brownian motion (Aarts et al., 1988; Eckstein et al., 1988) and the rotation of RBCs can enhance the diffusivity of platelets (Aarts et al., 1986). The important factors for margination have been determined experimentally (Aarts et al., 1988; Tilles & Eckstein, 1987; Zhang & Gay, 2007) to be
shear rate and hematocrit. The minimum hematocrit level was found to be $\phi=0.07$ for margination to occur, but is more readily observed for values of $\phi \geq 0.15$ (Tilles & Eckstein, 1987; Eckstein et al., 1988). Platelet margination has been studied with shear rates of 100-1000 sec$^{-1}$ in microvessels for the use of observing thrombosis formations experimentally (Aarts et al., 1988).

In the cardiovascular system, an abnormal region that becomes gradually narrower is known as a stenosis and the composition of a thrombosis is strongly dependent on the flow conditions (Wootton & Ku, 1999). Thrombosis is thought to begin with plaque rupture, vessel damage, or disfunctioning endothelium that expose tissue factor on vessel walls (Hathcock, 2006). At extremely low shear conditions, thrombosis consist of RBCs primarily, but at high shear rates, they are constructed primarily of platelets. The rate at which platelets adhere to form thrombi increases with shear rate. At the lower shear rates, this accumulation is roughly proportional to shear rate, but at higher shear rates, there are discrepancies associated with the rate of deposition (Wootton & Ku, 1999). More importantly, platelets tend to adhere at locations where high shear rate is present on collagen-containing surfaces such as the throat of a thrombosis. The presence of a collagen surface, excessively high shear rates, and whole blood are necessary for recreating an obstructed thrombus and the rate of platelet deposition is approximately linear with respect to shear rate for levels above 10,000 sec$^{-1}$ (Ku & Flannery, 2007). The growth of thrombosis is characterized by three mechanisms: platelet transport, platelet activation, and embolization (Wootton & Ku, 1999). The transport of platelets in microcirculation and in thrombosis is governed by the motion of RBCs and the non-uniform distribution of platelets. One factor for platelet activation can be tied to the shear stress exposure time experienced by platelets (Giersiepen et al., 1990; Tambasco & Steinman, 2003; Dumont, 2007). Embolization is the process regarding the removal of parts of a thrombus due to excessive exposure to high shear stress.
1.7 Red blood cell simulations

The field of computational fluid dynamics has grown at a rapid pace with the increased accessibility of computational resources and development of robust numerical methods. Research in the area of deformable suspensions has grown considerably in just the past five years. Most of the literature prior to 2007 was focused primarily on two-dimensional deformable or rigid three-dimensional rigid suspensions, but several capable methods have emerged recently for studying flows similar to the focus of this work. Simulations of cellular blood flow are discussed here by highlighting the recent findings in literature.

The dynamic behavior of RBCs undergoing tank-treading and tumbling motions are a common focus because many numerical methods are capable of simulating isolated cells in shear. Flipping motions are commonly observed at higher viscosity ratios, $\lambda$, at low shear rates while a reduction in $\lambda$ can cause a transition from the tumbling to tank-treading regime (Pozrikidis, 2003; Dupin et al., 2007; Pivkin & Karniadakis, 2008; Yazdani & Bagchi, 2011). An increase in shear modulus serves as a deterrent to tank-treading motion (Tsubota & Wada, 2010b) and the inclusion of membrane viscosity does not affect the amplitude and inclination angle of RBCs in tank-treading, but allows for better prediction with experiments due to an increase in viscous dissipation (Fedosov et al., 2010a).

Red blood cell aggregation models are commonly based on fitting potentials to adhesive energy measurements from experiments. Simulations in this field focus on the formation and disaggregation of small rouleaux shaped aggregates typically consisting of five or fewer RBCs. Findings include that by increasing the rigidity of cells, larger forces are required for disaggregation (Bagchi et al., 2005) which is consistent with observations of diseased cells. The peak in the adhesion energy was observed when the RBCs are along the compressive axis and at a minimum when they align with the flow (Liu & Liu, 2006). As a consequence, disaggregation is commonly observed
when the aggregates are aligned with the flow (Liu & Liu, 2006; Zhang et al., 2008) and shear stress was deemed a more effective method for break-up than the normal stress observed when clusters align along the extensional axis (Bagchi et al., 2005). The scaling of cluster sizes as it applies to RBC aggregation has also been studied in two-dimensions with rigid RBCs (Ding & Aidun, 2006) to give insight into the dependence of the size and number of RBC clusters observed at reduced hematocrit levels.

The advancements in parallel computing have allowed the simulation of realistic suspensions of RBCs. The shear-thinning characteristic of blood has been observed at low shear rates (MacMeccan et al., 2009; Wu & Aidun, 2009) limited to RBCs undergoing tumbling motion and were in good agreement with experimental results. The dependence on hematocrit, \( \phi \), at low shear rates, has also been accurately modeled (MacMeccan et al., 2009). Detailed probabilities of orientation angles and shear stress on platelets and RBCs at these low shear rates have also be reported (MacMeccan, 2007). However, a more detailed investigation of the normal-stress tensor of RBCs under these conditions is needed for a more complete rheological characterization.

The deformation of isolated RBCs in small vessels and capillaries has also been investigated using many numerical methods. Flows through capillaries and divergent geometries as small as 4 \( \mu \text{m} \) in diameter have been studied (Zhao et al., 2010; Freund & Orescanin, 2011) and have demonstrated the large increases in relative viscosity due to complete vascular blockage. Performing simulations in vessels less than the RBC diameter, 8 \( \mu \text{m} \), requires special care for initialization since an initial bi-concave shape cannot be used. In slightly larger vessels a characterization of the parachute shape of RBCs has also been investigated (Pozrikidis, 2005; McWhirter et al., 2009; Wu & Aidun, 2009; Fedosov et al., 2010a). The degree of velocity profile blunting is dependent on the rigidity of RBCs and their tendency to migrate toward the vessel core (Zhang et al., 2007; Dupin et al., 2007). This deformation induced migration
of RBCs has also been studied (Dupin et al., 2008) and the equilibrium location is dependent on Reynolds number at low hematocrit levels. Simulations of flow in larger vessels up to 30 µm in diameter have been performed (Liu & Liu, 2006; Doddi & Bagchi, 2009; Zhao et al., 2010) to demonstrate the Fåhraeus–Lindqvist effect and the change in cell-depleted layer thickness (Freund & Orescanin, 2011) with shear rate.

The process of platelet margination is now capable of being modeled mainly due to the increase in scalability of methods and parallel computing resources. The process of margination requires simulations in extremely long tubes due to the length and time scales in which the process occurs. Two- (Crowl & Fogelson, 2011) and three-dimensional (Zhao & Shaqfeh, 2011) simulations have reported that the process of margination occurs more rapidly for higher shear rates in Poiseuille flow. Hematocrit was also deemed an important factor and it was found that the diffusivity of platelets is dependent on their proximity to the wall. This is primarily due to the change in hematocrit and shear stresses experienced as platelets expel toward the wall. The diffusivity of platelets was predicted to scale linearly with wall shear rates in excess of 2,500 sec\(^{-1}\).

Currently, the largest simulations of deformable RBCs, to-date, are those presented in Rahimian et al. (2010). Leveraging the expertise from several institutions, they were able to parallelize the fluid and membrane models for CPU and heterogeneous CPU-GPU computations. In their largest simulation, they have shown the ability to simulate 260 million RBCs on 200,000 computational cores of the Jaguar supercomputer at Oak Ridge National Laboratory. These simulations earned the researchers the Gordon Bell prize for high performance computing. Current strong scaling results show an efficiency of 35% on up to 24,576 cores with 8,000 RBCs per core with \(N=84\) points used to represent each RBC membrane. The simulations were performed to display the scalability of the method and did not focus on a specific
physiological application, however.

The approach of this work is a direct numerical simulation of cellular blood flow and is limited to “small” arteries and veins due to the computational demand for realistic suspensions of deformable RBCs. It does have the advantage of capturing subtleties that a Newtonian fluid simulation or shear stress power-law non-Newtonian model simulation would fail to capture, however. The LB method is used due to its capability for resolving flows with inertia and capacity to scale well on parallel architectures. The linear FE implementation of MacMeccan (2007) & MacMeccan et al. (2009) is limited to low shear rates where RBCs undergo tumbling motions. Therefore, at locations near vessel walls, the linear FE RBCs do not exhibit the tank-treading behavior necessary for accurate migration toward the vessel core. The addition of the coarse-grained spectrin link membrane model of Pivkin & Karniadakis (2008) is used to extend the capabilities beyond a linear FE based membrane model. The computation framework of this work is based closely on the implementation of MacMeccan et al. (2009), but employs the distributed-memory parallelization techniques of Clausen et al. (2010). The details of this implementation are found in Reasor et al. (2011), but are discussed in more detail in Chapter II. The performance of the method is discussed in more detail in Chapter III comparing single-particle dynamics as well as the scaling on up to 4,096 cores with as many as 12,288 deformable RBCs. Investigations of the rheology and shear stress environment of platelets is presented in Chapter IV and the characterization of flows through small vessels, including platelet margination, are given in Chapter V.
Simulations of cellular blood require the modeling of RBC membranes and the fluid in which they are suspended. The numerical simulation of fluid-structure interaction problems is difficult due to instabilities that arise in the coupling of separate governing equations and the scalability of current algorithms. In this work, the lattice-Boltzmann (LB) method is coupled with a spectrin-link RBC membrane model. This implementation solves each phase independently, but couples the two phases through forces. The coupling is performed each time step as the particles (RBCs and platelets) move freely through the fixed Cartesian LB fluid domain. The hydrodynamic forces from the fluid are used for updating the particle dynamics and the particles influence the fluid phase through the forces arising from the standard bounce-back boundary condition that enforces the no-slip condition on the membrane surface.

2.1 Lattice-Boltzmann method

The lattice-Boltzmann method is based on the discretization of the continuous Boltzmann equation and was developed as an alternative to lattice gas methods. At low wavenumbers, the solution to the LB equation converges to the solution of the incompressible Navier–Stokes equations via the Chapman–Enskog expansion (see Chen & Doolen (1998)) using advective scaling. An alternative approach using diffusive scaling also shows (Junk & Yong, 2003; Junk et al., 2005) that the LB equation converges to the Navier–Stokes equations. These scalings are valid for low-Mach, low-Reynolds number flows with inertia which are characteristic of cellular blood flow. The use of entropic (Karlin et al., 1999) and multi-relaxation time LB methods (d’Humières, 1994) can be used to investigate higher Reynolds number flows. A review of the
methodology of these alternate LB approaches can be found in the recent review by Aidun & Clausen (2010) for complex flows including turbulence and particle-laden flows.

The LB method is an attractive numerical approach for suspension flows because of its ease in coupling the fluid and particle phases and due to the method scaling linearly with the number of particles (Ladd, 1994a,b). The local nature of the LB method also makes it an attractive method for efficient parallelization (Clausen et al., 2010) as opposed to suspension solvers based on Stokesian dynamics (Brady, 1988). The capability of the LB method to resolve inertia through the Navier–Stokes equations allows for computations of suspension flows where inertial effects are important (Ding & Aidun, 2000). The first simulations of rigid suspensions using the LB method coupled with the standard bounce-back boundary condition were performed by Ladd (1994a,b); Aidun & Lu (1995); Aidun et al. (1998); Ladd & Verberg (2001). Further development with suspensions of thin shells (Ding & Aidun, 2003) accounted for the influence of the fluid interior to particles and how accounting for those forces affects dynamics. Combining these efforts allowed for the simulation of suspensions of deformable linear FE based particles (MacMeccan et al., 2009; Clausen et al., 2011). The LB method with SBB, coupled with rigid and deformable particles, has shown the ability to match experimental observations of suspension viscosity and the discovery of trends in normal-stress differences and particle-phase pressures.

A three-dimensional LB variation is used in this work that limits velocities, $e_i$, of hypothetical fluid particles at locations, $x$, to 19 directions and is called the D3Q19 implementation. The evolution of the particle distribution, $f_i$, is governed by collision and streaming processes. The LB equation used (Chen & Doolen, 1998) updates the single particle distribution function, $f_i(x, t)$, explicitly via

$$f_i(x + e_i, t + 1) - f_i(x, t) = -\frac{1}{\tau}[f_i(x, t) - f_i^{eq}(x, t)],$$

where $f_i^{eq}$ is the equilibrium distribution function, $\tau$ is the single relaxation time,
and \( t \) is time. Operators of this form have been referred to as Bhatnagar–Gross–Krook (BGK) operators (Bhatnagar et al., 1954). The method used in this study has a pseudo-sound-speed of \( c_s = \sqrt{1/3} \), and the kinematic viscosity is related to the relaxation time via \( \nu = c_s^2 \rho (\tau - 1/2) \). A relaxation time of unity is chosen so that the suspending fluid kinematic viscosity is \( \nu = 1/6 \) in LB units. To consider the difference in viscosity ratio of the interior fluid to the exterior fluid, the relaxation time \( \tau \) is modified for the fluid enclosed by the RBC membrane. For the case of \( \lambda = 5 \), and assuming the interior and exterior fluids have equal densities, the kinematic viscosity of the interior fluid is \( \nu_{\text{interior}} = 5/6 \) which requires a relaxation time of \( \tau_{\text{interior}} = 3 \).

The equilibrium distribution function, suited for low-Mach flows, satisfying the Navier–Stokes equations is expressed as

\[
f_i^{(eq)}(x, t) = w_i \rho \left[ 1 + \frac{1}{c_s^2} (e_i \cdot u) + \frac{1}{2c_s^4} (e_i \cdot u)^2 - \frac{1}{2c_s^2} u^2 \right],
\]

where \( w_i \) are appropriate lattice weights set by the geometry of the lattice and isotropy. For the D3Q19 lattice the weights are defined as

\[
\begin{align*}
  w_i &= \begin{cases} 
    1/3 & \text{for } i = 0 \\
    1/18 & \text{for } i = 1 \ldots 6 \\
    1/36 & \text{for } i = 7 \ldots 18
  \end{cases}
\end{align*}
\]

where \( i = 0 \) is the rest, \( i = 1 \ldots 6 \) are the non-diagonal, and \( i = 7 \ldots 18 \) are the diagonal directions of the lattice.

The macroscopic fluid properties are found by the moments of the equilibrium distribution function, \( f_i^{(eq)} \). The first moment is the local density is given by

\[
\sum_i^Q f_i^{(eq)}(x, t) = \rho,
\]

and the solid phase density, \( \rho_s = \rho \), is chosen to match that of the LB fluid. The second moment is momentum, but the macroscopic velocity is given as

\[
\frac{1}{\rho} \sum_i^Q f_i^{(eq)}(x, t) \mathbf{e}_i = \mathbf{u}_\alpha,
\]
where $\alpha$ indicates a Cartesian direction, and the third moment is the pressure

$$\sum_{i}^{Q} f_i^{(eq)}(x, t) e_{i\alpha} e_{i\beta} = c_s^2 \rho \delta_{\alpha\beta} + \rho u_{\alpha} u_{\beta}. \quad (23)$$

In the LB formulation, the pressure is proportional to the density, i.e., $P_f = c_s^2 \rho = 1/3 \rho$. This equation of state makes the LB method pseudo-compressible and requires flows to be low Mach number. Single phase flows should limit the maximum velocities so that $Ma < \sqrt{3}/10 \approx 0.17$. However, to resolve the flow between particles in the case of dense suspensions, the velocities used are typically an order smaller in magnitude than this upper limit.

### 2.2 Spectrin-link method

The motivation of SL modeling of deformable RBC membranes is based on the physiological construction (see Fig. 1(a)). Fundamentally, this approach models the membrane of the RBC as a surface consisting of a triangular network of spectrin tetramers that are connected at their endpoints by actin. This is a realistic, but simplified, model of the RBC membrane cytoskeleton. Li et al. (2007) explain that realistic RBC membrane networks have the ability to undergo remodeling of the triangular network under large deformations in order to relax the in-plane elastic energy to zero. A realistic cell membrane has several constituents such as a lipid bilayer, cytoskeleton network, and many transmembrane proteins and is represented by the detailed image illustrated by Li et al. (2007) given in Fig. 1(b). These transmembrane proteins bind the cytoskeleton to the bilayer (Dao et al., 2006). Modeling the intricate details of binding the cytoskeleton to the lipid bilayer is computationally feasible, but would not be suitable for the simulation of a dense suspension of RBCs. As a result, the focus of this work is on the lower fidelity spectrin tetramer based model.

The basis for the RBC membrane model used in this work starts with the method developed by Li et al. (2005). It begins with the derivation of a spectrin-link membrane model to resolve the biconcave RBC shape through the minimization of Helmholtz
free energy. In their study, simulations were performed to mimic the optical-tweezer experiments of Mills et al. (2004) that measured RBC membrane deformation for forces up to 200 pN. Volume, area, bending, and in-plane energy contributions are considered in this model. The area and volume contributions ensure conservation of their respective properties and the bending energy is critical to the biconcave shape when the energy is minimized. The in-plane energy term includes a worm-like chain (WLC) potential as well as a model for the elastic energy stored in the lipid membrane. This initial investigation used 28,673 vertices to triangulate the surface of the RBC membrane with spectrin-link (tetramer) lengths $O(100)$nm similar in size to the proteins in an actual RBC (see scale in Fig. 1(a) from Liu et al. (1987)). The results obtained are more accurate than the first-order hyperelastic model, but not as accurate as the higher-order hyperelastic model of Mills et al. (2004). The results obtained for the SL model were the most accurate for the large deformations associated with an applied force $>150$ pN. Dao et al. (2006) continue the investigation of Li et al. (2005) and formally derive the material properties of the SL model. The level of fidelity used in the work of Li et al. (2005) is not suitable for the simulation of blood flow with realistic hematocrit values, but the use of a coarse graining SL approach (Pivkin & Karniadakis, 2008; Fedosov et al., 2009, 2010b) allows for the extension of the SL method to flows with thousands of deformable RBCs.

### 2.2.1 Geometric description of the RBC membrane

In the spectrin-link method, each RBC membrane consists of a network of points $\{x_n, n \in 1 \ldots N\}$, which are the vertices of its surface triangulation. The area of a triangle $\alpha \in 1 \ldots \Pi$ formed by the vertices $(l, m, n)$ is given by $A_{\alpha} = \frac{1}{2} \left| (x_m - x_l) \times (x_n - x_l) \right|$. The total area of the RBC membrane surface is given by $A_{\text{total}} = \sum_{\alpha \in \Pi} A_{\alpha}$ and the total volume is given as $\Omega_{\text{total}} = \sum_{\alpha \in \Pi} (x_{\alpha} \cdot n_{\alpha}) A_{\alpha}/3$ where $x_{\alpha} = \frac{1}{3} (x_m + x_n + x_l)$ is the center of triangle $\alpha$. The length of the link $i \in 1 \ldots S$ connecting two vertices $m$ and
Figure 1: Image of the spectrin network of a RBC membrane from negative staining electron microscopy courtesy of Liu et al. (1987) and a schematic of the RBC membrane cytoskeleton and a computational realistic model from Li et al. (2007).

$n$ is given by $L_i = |x_m - x_n|$. Figure 2 illustrates the geometric quantities used in this model. The lists of unique links and unique pairs of triangles are established using the connectivity data of the triangulated RBC surface prior to simulations. The lists of unique links and triangle pairs remain unchanged in the absence of cell rupture or death which is assumed in all the simulations presented in this work. The derivation of material properties of the SL based RBC membrane is based on a hexagonal surface triangulation like that seen in Fig. 2.

2.2.2 Helmholtz free energy

The contributions due to in-plane, bending, volume, and area can be represented by modeling the Helmholtz free energy of the membrane (Li et al., 2005). The Helmholtz free energy of the spectrin-link modeled system is given as

$$E\{x_n\} = E_{\text{in-plane}} + E_{\text{bending}} + E_{\text{volume}} + E_{\text{area}}.$$  \hspace{1cm} (24)

The in-plane contribution relevant to shear properties is modeled as

$$E_{\text{in-plane}} = \sum_{i \in \mathcal{S}} V_{\text{WLC}}(L_i) + \sum_{\alpha \in \mathcal{H}} C/A_{\alpha}.$$  \hspace{1cm} (25)
The force-length relationship is rooted in DNA mechanics (Marko & Siggia, 1995; Bustamante et al., 2003) and is written as

\[
f_{\text{WL C}}(L_i) = -\frac{k_{\text{in-plane}}}{p}\left\{\frac{1}{4(1-x_i)^2} - \frac{1}{4} + x_i\right\}.
\]  

(26)

The wormlike chain (WLC) potential, \(V_{\text{WL C}}\), for each individual link is obtained by integration as

\[
V_{\text{WL C}}(L_i) = -\int_0^L d\xi f_{\text{WL C}}(\xi) = \frac{k_{\text{in-plane}}L_{\text{max}}}{4p} \frac{3x_i^2 - 2x_i^3}{1 - x_i}.
\]  

(27)

where \(x_i = L_i/L_{\text{max}} \in (0, 1)\), \(L_{\text{max}}\) is the maximum length of the links and \(p\) is the persistence length which is \(\mathcal{O}(10)\)nm. The hydrostatic elastic energy in-plane is described by

\[
C = \frac{3\sqrt{3}k_{\text{in-plane}}L_{\text{max}}^3 x_0^4}{64p} \frac{4x_0^2 - 9x_0 + 6}{(1 - x_0)^2},
\]  

(28)

where \(x_0 = L_0/L_{\text{max}}\) and \(L_0\) is the average length of the links \(L_0 = 1/S \sum_{i \in S} L_i\). For an initially unstressed membrane, the formation of \(C\) is found after setting the Cauchy stress equal to zero. The derivation for the exact form of \(C\) is derived by considering the stress in the membrane (containing \(C\)) and that due to the WLC potential, \(V_{\text{WL C}}\).
The derivation for an unstressed two-dimensional hexagon lattice can be found by Dao et al. (2006).

The bending contribution takes into account the spontaneous and instantaneous angles between adjacent pairs of triangles. The bending contribution to the Helmholtz free energy of the system is given as

\[ E_{\text{bending}} = \sum_{\text{adjacent } \alpha, \beta \text{ pair}} k_{\text{bend}} [1 - \cos(\theta_{\alpha\beta} - \theta_0)] \] (29)

where \( \cos \theta_{\alpha\beta} = \mathbf{n}_\alpha \cdot \mathbf{n}_\beta \) and \( \sin \theta_{\alpha\beta} = \pm |\mathbf{n}_\alpha \times \mathbf{n}_\beta| \) with the + sign is taken if \((\mathbf{n}_\alpha - \mathbf{n}_\beta) \cdot (\mathbf{x}_\alpha - \mathbf{x}_\beta) \geq 0\) with the outward pointing normal of triangle \( \alpha \) is given as \( \mathbf{n}_\alpha = (\mathbf{x}_m - \mathbf{x}_l) \times (\mathbf{x}_n - \mathbf{x}_l)/2A_\alpha \) and \( \theta_0 \) is the spontaneous (or initial) angle between adjacent triangle pairs.

The constraint on volume ensures that the interior volume enclosed by the triangulated RBC membrane remains constant. For triangles of roughly the same size this takes the form

\[ E_{\text{volume}} = k_{\text{volume}} \left( \Omega_{\text{total}} - \Omega_{\text{desired}} \right)^2 / 2L_0^2 \Omega_{\text{desired}}^2, \] (30)

where \( \Omega_{\text{total}} \) is the instantaneous volume of the RBC and \( \Omega_{\text{desired}} \) is the desired or initial volume of the RBC. The fluid volume inside the particle is enforced due to the incompressible nature of the LB method.

The constraint on area takes a similar form to that of the volume and serves to conserve the surface area of the RBC. In experimental studies (Evans et al., 1976), RBC area conservation is observed for both small and large deformations. The SL method aims to capture this phenomenon that is not modeled accurately with Hookean and neo-Hookean approaches. The area contribution to the Helmholtz free energy is given as

\[ E_{\text{area}} = k_{\text{global}} \frac{(A_{\text{total}} - A_{\text{desired}})^2}{2L_0^2 A_{\text{desired}}} + \sum_{\alpha \in \Pi} k_{\text{local}} \left( A_\alpha - A_0^\alpha \right)^2 / 2L_0^2 A_0^\alpha, \] (31)

where \( A_{\text{total}} \) is the instantaneous surface area of the RBC, \( A_{\text{desired}} \) is the initial or desired area of the RBC, and \( A_\alpha \) is the instantaneous and \( A_0^\alpha \) is the initial area of triangle \( \alpha \). The first term of the area equation contributes to global area conservation.
while the second term contributes to local area conservation. The area constants $k_{\text{area}}$ are typically chosen such that the local contribution is much smaller than its global analog. The original coarse-graining model by Pivkin & Karniadakis (2008) does not contain a local area contribution, but Fedosov et al. (2009) included this term to ensure the surface area is conserved on a local as well as global basis.

The choice of $k_{\text{in-plane}}$, $k_{\text{bending}}$, $k_{\text{area}}$ and $k_{\text{volume}}$ are dependent on Boltzmann’s constant and temperature, when using fluid domain methods such as dissipative particle dynamics (Hoogerbrugge & Koelman, 1992), but since the LB method is independent of temperature and Brownian motion, these constants are arbitrary and are chosen to match non-dimensional parameters of interest. Specifically, $k_{\text{in-plane}}$ is chosen to match the capillary number $Ca_G$ and the other constants are chosen such that $E_{\text{volume}} > E_{\text{area}} > E_{\text{in-plane}} > E_{\text{bending}}$ similar to Dupin et al. (2007). The constant $k_{\text{bending}}$ can be modified to change the bending ratio $\chi$ independently of $Ca_G$ and the effects on rheological properties, primarily viscosity, and orientation are quantified in Chapter IV. It is important to note that all of the energy terms are dependent on relative calculations. This allows the evolution of the RBC membrane to be stored in a single coordinate system which reduces the memory footprint compared to the linear FE particles implemented in the work of MacMeccan et al. (2009).

### 2.2.3 Recovering material properties

The material properties of the RBC membrane and the suspending plasma, obtained from experimental studies, vary based on whether they are performed in vitro or in vivo. The material properties in vitro are relatively uncommon for the RBCs and platelets, but in vivo values are given in Table 1.

For the spectrin-link model, the shear modulus of the membrane for a regular hexagonal triangulation is given (Pivkin & Karniadakis, 2008) as

\[
G = \frac{\sqrt{3}k_{\text{in-plane}}}{4pL_{\text{max}}x_0} \left( \frac{3}{4(1-x_0)^2} - \frac{3}{4} + 4x_0 + \frac{x_0}{2(1-x_0)^3} \right). \tag{32}
\]
Table 1: Material properties of plasma, hemoglobin, RBCs and platelets from in vivo experiments.

<table>
<thead>
<tr>
<th>Material Property</th>
<th>in vivo</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>37°C</td>
<td></td>
</tr>
<tr>
<td>Plasma Viscosity</td>
<td>1.2 cP</td>
<td>Harkness &amp; Whittington (1970)</td>
</tr>
<tr>
<td>Hemoglobin Viscosity</td>
<td>6.0 cP</td>
<td>Hochmuth &amp; Waugh (1987)</td>
</tr>
<tr>
<td>RBC Shear Modulus</td>
<td>5.5±0.5×10⁻³ dynes/cm</td>
<td>Hochmuth &amp; Waugh (1987)</td>
</tr>
<tr>
<td>RBC Area Modulus</td>
<td>288±50 dynes/cm</td>
<td>Evans et al. (1976)</td>
</tr>
<tr>
<td>RBC Bending Stiffness</td>
<td>2.2±0.3×10⁻¹⁹ J</td>
<td>Hwang &amp; Waugh (1997)</td>
</tr>
<tr>
<td>Platelet Shear Modulus</td>
<td>570±600 dyne/cm²</td>
<td>Haga et al. (1998)</td>
</tr>
<tr>
<td>Platelet Young’s Modulus</td>
<td>1700±600 dyne/cm²</td>
<td>Haga et al. (1998)</td>
</tr>
</tbody>
</table>

A shear modulus value of 6.3×10⁻³ dynes/cm is assumed here which is near the upper limit of the measured experimental values. The elastic area compression modulus was originally (Dao et al., 2006) written as

\[ K = \frac{\sqrt{3}k_{\text{in-plane}}}{4pL_{\text{max}}(1-x_0)^2} \left( \frac{3}{2} \left( 6 - 9x_0 + 4x_0^2 \right) + \frac{1 + 2(1-x_0)^3}{1-x_0} \right), \]  
(33)

but was corrected (Fedosov et al., 2010a) to account for the contributions due to the local and global area constants to take the form

\[ K = \frac{\sqrt{3}k_{\text{in-plane}}}{4pL_{\text{max}}(1-x_0)^2} \left( \frac{3}{2} \left( 6 - 9x_0 + 4x_0^2 \right) + \frac{1 + 2(1-x_0)^3}{1-x_0} \right) + k_{\text{area}}^{\text{local}} + k_{\text{area}}^{\text{global}}. \]  
(34)

The Young’s modulus is calculated based on the values for the membrane shear modulus and the elastic compression modulus via

\[ E_y = \frac{4KG}{K+G}. \]  
(35)

Similarly, the Poisson ratio is calculated via

\[ \nu_{p} = \frac{K - G}{K + G}. \]  
(36)

As the area compression modulus \( K \to \infty \) the Poisson ratio \( \nu_{p} \to 1. \) Therefore, the modification of the area compression modulus (Fedosov et al., 2010a) to take into consideration the contributions due to the global and local area energy contributions yields estimates for the Poisson ratio that are closer to unity. The estimated value
for the Poisson ratio based on the experimental measurements given in Table 1 is \( \nu_p = 0.99 \).

### 2.2.4 Transient spectrin link and coupling with the LB method

Each of the vertices that combine to form the triangulated RBC membrane surface advance according to Newton’s equations of motion:

\[
\frac{dx_n}{dt} = v_n; \quad M \frac{dv_n}{dt} = f_n + f_{LB}^n + f_{PP}^n = f_{total}^n \tag{37}
\]

where \( v_n \) is the velocity of vertex \( n \) and \( M \) is a fictitious mass at each point chosen to yield the same membrane mass as previous linear FE studies by MacMeccan et al. (2009). The external forces, \( f_{LB}^n \) are the forces on the vertex due to the fluid-structure interaction (enforcing the no-slip boundary condition) and \( f_{PP}^n \) are the forces due to particle-particle interactions including lubrication, adhesion, or contact. The forces due to the SL model are denoted by \( f_n \). The forces due to the Helmholtz free energy contributions of the SL method are implemented from

\[
f_n = -\frac{\partial E\{x_n\}}{\partial x_n} \tag{38}
\]

where each contribution is an extensive exercise in chain rule differentiation. This implementation makes use of the analytic forms obtained via Mathematica’s symbolic manipulation capabilities as was done by Pivkin & Karniadakis (2008). This method aims to minimize the total energy given from Eqn. (24). In the absence of bending energy, the equilibrium shape will be a sphere with the volume specified by \( \Omega_{desired} \). When bending energy is present, the equilibrium shape is a biconcave disk representative of a RBC. As a result, spherical membrane meshes can be used as a starting point for RBC simulations.

Equations (37) are solved using a simple first-order temporally accurate forward Euler time integration scheme. Since the LB method is a temporally first-order accurate explicit fluid solver, a higher-order implementation for solving Newton’s equations of motion was deemed excessive due to its strong coupling with the LB fluid.
The first step for updating the SL based RBCs is to update the velocity, $v$ at time $t + 1$ for each vertex $n$ used to triangulate the RBC membrane via

$$v_{n}^{t+1} = v_{n}^{t} + \frac{f_{n,\text{total}}^{t}}{M} \Delta t. \quad (39)$$

Secondly, the location, $x$, of each node $n$ at time $t + 1$ is updated via

$$x_{n}^{t+1} = x_{n}^{t} + v_{n}^{t} \Delta t + \frac{1}{2} \frac{f_{n,\text{total}}^{t}}{M} (\Delta t)^2. \quad (40)$$

The SL based RBCs are updated every time step, $\Delta t$. All of the simulations performed are at very low Mach numbers of $Ma << 1$ so that the modified Courant number

$$Co = \frac{c_{s} \Delta t}{\Delta x} << 1, \quad (41)$$

where $c_{s}$ is the pseudo-sound-speed of $\sqrt{1/3}$ and $\Delta x = c$ is a unit LB length ($1/3 \mu m$). If $Co$ is less than unity, the integration scheme is stable.

### 2.2.5 Coarse-graining procedure

In order to model the RBCs using triangular networks that are larger than the spectrin links found on physical RBCs, a coarse-grained modeling procedure was developed by Pivkin & Karniadakis (2008). The goal of this coarse-grain modeling was to produce an RBC with physiological material properties similar to the high resolution studies of Li et al. (2005) & Dao et al. (2006). An image of the RBC for the high resolution studies is given in Fig. 3.

The coarse-graining procedure is performed by scaling the equilibrium length via

$$L_{c}^{0} = L_{f}^{0} \sqrt{N_{f}/N_{c}}$$

where the superscript $f$ denotes the fine grained model of Li et al. (2005) and $c$ denotes the coarse model. Here, $N_{c}$ and $N_{f}$ are the number of nodes that make up the triangulated RBC surface. The spontaneous angle is then scaled via

$$\theta_{c}^{0} = \theta_{f}^{0} \sqrt{N_{f}/N_{c}}$$

and the persistence length is adjusted via

$$p_{c} = p_{f} \sqrt{N_{c}/N_{f}}.$$
that membrane shear modulus, elastic area compression modulus, Young’s modulus, and Poisson ratio remain identical from fine to coarse grids (Pivkin & Karniadakis, 2008; Li et al., 2005). The capillary number and the viscosity ratio are the important dimensionless parameters for monitoring cell deformation and capturing tank treading and tumbling dynamics. As a result, many of the simulation results will use the capillary number as the dimensionless parameter for comparison to deformation quantities and normalized rheological properties.

2.2.6 Equilibrium RBC bi-concave shape

The effect on bending stiffness can drastically change the equilibrium shape of the deflated sphere. Li et al. (2005) found that using the a bending modulus of \( \kappa_b = 8.3 \times 10^{-20} \) J resulted in a “cup” shape. This corresponds to a \( k_{b\text{ending}} \) value of \( 69k_BT \) where \( k_B \) is Boltzmann’s constant and \( T \) is temperature. However, using \( k_{b\text{end}} = 200k_BT \) resulted in the bi-concave disk shape that resembles a typical RBC. This corresponds to a bending energy of \( \kappa_b = 2.4 \times 10^{-19} \) J which is close to the reported value of \( 2.2 \pm 0.3 \times 10^{-19} \) J (Hwang & Waugh, 1997). The value of \( k_{b\text{end}} = 200k_BT \) will yield an RBC shape, but any small fluctuation or mesh irregularities will cause it to become unstable and deform into a more cup-like shape. Li et al. (2005) report that
choosing $k_{\text{bend}} \approx 4000 k_BT$ results in a completely stable bi-concave disk shape, but results in a bending modulus of $\kappa_b \approx 5 \times 10^{-18}$ J which is a decade larger than the reported measured values. Li-Guo et al. (2010) also state that they see a competition between the bi-concave and cup shapes for $k_{\text{bend}} = 100-400 k_BT$ using the same coarse-grained spectrin-link RBC membrane model coupled with a coarse-grained molecular dynamics fluid solver.

For the bi-concave disk to be the state of minimization of energy the ratio of bending energy to in-plane energy in the membrane, i.e., $\chi = \kappa_b / G A_{\text{total}}$. Li et al. (2005) give a critical value, $\chi_c \sim 10^{-3}$, where exceeding this ratio results in a bi-concave disk shape for equilibrium shape. Choosing $k_{\text{bend}} = 1500 k_BT$ yields $\chi = 1.5 \times 10^{-3}$ while choosing $k_{\text{bend}} = 200 k_BT$ yields $\chi = 0.2 \times 10^{-3}$. Consequently, when modeling and RBC with physiological bending stiffness, the bi-concave disk equilibrium shape may not be dominant to the cup shape when the membrane is perturbed from equilibrium via hydrodynamic or inter-particle forces. Li et al. (2007) also comment on the difficulties of maintaining an equilibrium bi-concave shape through careful tuning of in-plane energy for the reference state.

In order to generate a baseline RBC shape, a spherical capsule mesh is deflated to 59% of its initial volume while keeping the surface area constant. This is similar to the method of Li et al. (2005). The deflation schedule is linear in time and is written as

$$\Omega_{\text{total}}^{\text{desired}}(t) = \Omega_{\text{total}}^{\text{desired}}(0) + \frac{t}{t_{\text{final}}} \left[ \Omega_{\text{total}}^{\text{desired}}(t_{\text{final}}) - \Omega_{\text{total}}^{\text{desired}}(0) \right].$$

(42)

Here $\Omega_{\text{total}}^{\text{desired}}(t_{\text{final}}) = 0.59 \Omega_{\text{total}}^{\text{sphere}}$. The equilibrium shape obtained after this process is a bi-concave disk due to the presence of sufficient bending energy and using the appropriate scaling for the spontaneous angle, $\theta_0^c$, between adjacent triangles based on the number of points used. The simulations here use 613 nodes to triangulate the surface so that the average spectrin link length is $L_0 = 1.5c$ (LB units). The evolution of the RBC shape is given in Fig. 4. This deflation procedure only needs
to be performed once to capture the equilibrium RBC shape. Once this shape is captured, the equilibrium spectrin link lengths are set to the values corresponding to this equilibrium shape. This shape is then used in the seed procedure for generating dense suspensions of RBCs for modeling whole blood.

**Figure 4:** Deflating a sphere to 59% of its initial volume to form the baseline RBC used ($N=613$): (a) $t_{LB}=0$; (b) $t_{LB}=5,000$; (c) $t_{LB}=10,000$; (d) $t_{LB}=15,000$; (e) $t_{LB}=20,000$; and (f) $t_{LB}=25,000$. Figure from Reasor et al. (2011).

### 2.3 Rigid particle modeling

The rigid particles used in this work to mimic the motion of platelets are updated using a simple Newtonian dynamics solver for rigid ellipsoidal shaped particles with assumed symmetry along their $x$ and $y$ axes. The time integration scheme used is the first order accurate explicit forward Euler scheme.

The fluid-solid coupling from the standard bounce-back operation and the particle-particle interactions generates the forces on each triangulated surface. These forces are summed for the entire particle to get the applied forces. The total forces applied on the particle are calculated via
\[
f_p(t) = \sum_{n \in N} f_n(t)
\]

where \( n \) denotes each node and \( N \) is the number of nodes used to triangulate the particle surface. The particle acceleration is obtained by \( a_p(t) = f_p(t)/M \) where \( M \) is the mass of the particle. The rigid body translation is updated in two steps by updating the particle velocity by

\[
v_p(t + \Delta t) = v_p(t) + a_p(t) \Delta t,
\]

and the location by

\[
x_p(t + \Delta t) = x_p(t) + v_p(t) \Delta t + \frac{a_p(t) (\Delta t)^2}{2}.
\]

The total torques acting on the rigid particles are calculated via

\[
T_p = \{T_x, T_y, T_z\} = \sum_{n \in N} \mathbf{r}_n \times \mathbf{f}_n,
\]

where \( \mathbf{r}_n \) is the radius from the particle center to node \( n \) and \( \mathbf{f}_n \) is the force applied to node \( n \). The multiplication factor for updating angular accelerations is given as a formulation based on the mass moments of inertia of the particle:

\[
\gamma = \frac{I_{zz} - I_{xx}}{I_{xx}}
\]

for \( I_{xx} = I_{yy} \). This equality is true for the spherical particles and the platelets used in this work which allows the updated angular accelerations to be written in simple analytical forms. The angular accelerations at time \( t \) are calculated from the angular velocities and moments of inertia via

\[
a_\theta = \frac{T_x \cos(\phi) + T_y \sin(\phi)}{I_{xx}} - \omega_\psi \sin(\theta) \left[ (1 + \gamma) \omega_\psi + \gamma \omega_\phi \cos(\theta) \right],
\]

\[
a_\phi = \frac{T_z}{I_{xx}} + \frac{\omega_\psi}{\sin(\theta)} (1 + \gamma) \omega_\psi - (1 - \gamma) \omega_\phi \cos(\theta) - \frac{\cos(\theta)}{I_{xx} \sin(\theta)},
\]
and

\[
a_{\psi} = \omega_{\theta} \omega_{\phi} \sin(\theta) - a_{\phi} \cos(\theta) + \sin(\theta) \frac{T_x \sin(\phi) - T_y \cos(\phi)}{I_{xx}(1 + \gamma)} + \frac{T_z \cos(\theta)}{I_{xx}(1 + \gamma)}.
\]

The angular velocities are then updated via

\[
\omega_{\theta,\phi,\psi}(t + 1) = \omega_{\theta,\phi,\psi}(t) + a_{\theta,\phi,\psi}(t) \Delta t.
\]

Similarly, the particle orientation angles are updated via

\[
x_{\theta,\phi,\psi}(t + 1) = x_{\theta,\phi,\psi}(t) + \omega_{\theta,\phi,\psi}(t) \Delta t + \frac{a_{\theta,\phi,\psi}(t)(\Delta t)^2}{2}.
\]

This implementation was originally used by MacMeccan (2007) and is not optimal due to the summation of forces, but the cost of the computation is insignificant compared to the fluid-solid interaction computations.

The moments of inertia for the ellipsoidal shaped platelets and disks used are calculated as

\[
I_{xx} = \frac{M}{5}(b^2 + c^2),
\]

\[
I_{yy} = \frac{M}{5}(a^2 + c^2),
\]

and

\[
I_{zz} = \frac{M}{5}(a^2 + b^2),
\]

where \(a\) is the axis along the \(x\) coordinate, \(b\) along the \(y\) coordinate, and \(c\) along the \(z\) coordinate in the body-fitted local coordinate system of the ellipsoid. All of the ellipsoids used in this study are symmetric \(I_{xx} = I_{yy}\) with \(a = b\). The mass for the rigid particles used in this work assumes that they have the same density, \(\rho_s = \rho\), as the suspending fluid they displace.

### 2.4 Fluid-solid coupling

The coupling between the LB fluid and the SL RBCs is done identically to the method previously described in Aidun & Qi (1998). This coupling is based on the LB lattice
vectors crossing the SL RBC membrane surface. This process has been referred to as forming “links”. The process of finding the links is done every LB time step as it was in the LB-FE method of MacMeccan et al. (2009). This must be done each time step due to the fact that the RBC membrane triangulation moves through the Cartesian LB fluid domain and the links from the previous time step are no longer valid.

The process of finding links is performed using the ray-tracing algorithm of Möller & Trumbore (1997) originally developed for graphics processing. The ray tracing algorithm performs projections and then tests for the links that intersect the triangulated surface. The algorithm of Möller & Trumbore reduces the memory footprint of other ray-tracing algorithms by 25-50% depending on the number of vertex sharing involved in the triangulation. This tracing is performed for rigid vessels only once upon initialization, but every time step for FE based capsules, rigid platelets, or SL RBCs. A schematic of the projection of the links crossing the SL boundary is given in Fig. 5(a). These links are determined according to the projections of the LB direction vectors $e_i$ from exterior fluid nodes to interior fluid nodes. This method relies on a coordinate system relative to the SL triangulation, known as the barycentric coordinate system, and returns the distance to the triangle intersection. A bounding box that encompasses the triangulated RBC surface is chosen to focus the computations in the vicinity of the particle, but still accounts for roughly 40% of the total computation time (Clausen et al., 2010) for FE edge lengths of $2.0c$. The amount of computation increases with the reduction of edge lengths (or triangle area) due the increased number of failure projections. In Fig. 5(b), a demonstration of the difference between the SL triangulation for the RBC membrane with $L_0=1.5c$ and the LB fluid discretization is given.
2.4.1 Bounce-back method

The most common boundary condition used in the LB method is standard bounce-back (SBB) boundary condition that enforces the no-slip condition on surfaces. The SBB method captures the boundary through the use of links that cross the solid boundaries which can include walls, rigid geometries such as vessels, or moving particle surfaces. The SBB condition is second-order accurate in space if the boundary resides at the midpoint between two fluid points (Ziegler, 1993). For the case of particles moving through the LB grid, the implementation is first-order accurate (Ginzburg & Adler, 1994; Noble et al., 1995).

Alternative methods that do not rely on the formation of links between fluid points crossing the boundary have shown promise for increased accuracy. Wu & Aidun (2009, 2010) make use of the external boundary force (EBF) implementation to enforce the no-slip condition as a cost-effective alternative to more traditional immersed boundary

Figure 5: Depiction of a link crossing the solid boundary of the RBC SL membrane with subsequent interpolation to neighboring SL membrane nodes is given in (a) (figure modified from Clausen (2010) to fit the SL methodology). A visualization of the difference between the fluid and solid phase discretizations for a SL RBC embedded in the LB fluid stencil is given in (b) where the $L_0=1.5c$. 
methods (Feng & Michaelides, 2004; Zhang & Gay, 2007). This method enforces the no-slip condition through the application of a force density to the LB fluid phase so that the velocities of the fluid and solid are identical at their interface. A counter force is used for updating the particle dynamics. Smoother force interpolations using the Dirac delta function (Peskin, 2002) and increased stability are both favorable characteristics of this implementation over the SBB method. This implementation has been applied (Wu et al., 2010) to dilute suspensions of rigid platelets in the hinge areas of bileaflet mechanical heart valves.

The concept of the link is seen in Fig. 5(a) as the ray that crosses the membrane surface that is connected on its endpoints by fluid particles in the LB domain. The links are determined along the lattice directions of the velocities $e_i$. The standard bounce-back procedure adjusts the particle distributions on link endpoints via

$$f_i(x, t + 1) = f_i(x, t^+) + 6\rho_i w_i \cdot e_i$$  \hspace{1cm} (56)

for a link in the $i'$ direction. Here $i'$ is the direction opposite of $i$, $t^+$ is the time after the collision process but prior to streaming, $u_b$ is the local solid velocity at the link intersection point. The corresponding traction force on the SL RBC is then given as

$$f^{(b)}(x + \frac{1}{2}e_{i'}, t) = -2e_i[f_i(x, t^+) + 3\rho_i w_i \cdot e_i].$$  \hspace{1cm} (57)

The standard bounce-back operation of Eqn. (57) must be interpolated to the nearest SL/FE nodes using a linear interpolation scheme for each $L_i$ greater than a LB fluid grid spacing, $c$. For the solid particles, such as platelets, the interior fluid does not impact dynamics. However, for fluid filled particles, such as RBCs, the effects of the interior fluid viscosity are extremely important. As the RBCs move throughout the domain LB fluid nodes are covered and uncovered by the domain inside the RBC membrane. As a result, the momentum of the particle must be adjusted to account for the covering and uncovering of nodes. The adjustment of covering takes the form

$$f^{(c)}(x, t + \frac{1}{2}) = \rho(x, t)[u(x, t) - u_b(x, t)]$$  \hspace{1cm} (58)
while uncovering changes the sign of this force. These adjustments must be made for the fluid filled RBCs used throughout this work to accurately resolve the momentum of each RBC. In the SL formulation, \( \mathbf{f}^{\text{LB}} = \mathbf{f}^{(b)} + \mathbf{f}^{(c)} \).

### 2.4.2 Coupling forces to spectrin-link red blood cells

The forces from the SBB operation are first found on individual surfaces of the triangulated discretization of the RBCs or platelets. However, updating the dynamics of the particles requires an interpolation of the forces from the surfaces to the surrounding nodes within a given tolerance. For the simulations in this work, a value of \( \sigma_c = 0.75 \ \mu m \) \((2.25c)\) is used as a distance tolerance from the link-surface intersection location to local nodal locations that get an interpolated weight of the calculated force. For each triangulated surface there are three points that need to be considered in addition to the nodes within the tolerance. The distance to the point that the link intersects is calculated via \( d_j = \| \mathbf{x}_{\text{link}} - \mathbf{x}_n \| \). The weighting on the \( j^{\text{th}} \) node for the link-wise force is assigned via

\[
g_j = \exp\left( -\frac{d_j^2}{\sigma_c^2} \right). \tag{59}
\]

These weights are normalized so that the sum of all weights is unity (MacMeccan et al., 2009). In this work where \( L_0 \approx 0.5 \ \mu m \) \((1.5c)\), the interpolation given in Eq. 59 very nearly mimics a linear interpolation. In instances where an LB length scaling of \( L_0 < 0.3 \ \mu m \) \((1c)\) is chosen, this function becomes very sensitive to the choice of \( \sigma_c \).

### 2.5 Subgrid modeling

When the gap between two particles or a particle and a tube wall is less than a lattice unit, the LB method fails to resolve the flow in that small gap. Therefore, a subgrid model must be used to capture the effects of contact. Subgrid modeling is also important in modeling the forces between to rigid particles or two approaching biological cells. In this section a discussion of the contact subgrid model originally derived in Ding & Aidun (2003) and used by MacMeccan et al. (2009), with the
improvements by Clausen (2010), as well as an adhesion model based on the work of Neu & Meiselman (2002), is given. The LB-FE code base including the contact model used by Ding & Aidun (2003) and MacMeccan et al. (2009), and including the implementation of the adhesion model of Neu & Meiselman (2002) is a contribution of this work.

2.5.1 Lubrication and repulsion model

The foundation for the use of lubrication theory for two particles near contact was established by Cox (1974) through derivations from the asymptotic expansion of the hydrodynamic equations in small gaps. The normal force between two spheres scales (to leading order) as $1/g$, where $g$ is the local gap, and the tangential forces scale as $\ln(1/g)$. As $g \to 0$ the normal force is much larger than the tangential component. Consequently, it is neglected in most lubrication models. Modeling the normal force captures the force singularity while the LB method resolves the interactions for gaps larger than a single lattice unit, $c$. The lubrication force given in Cox (1974) takes the form

$$ f_{\text{lub}} = \frac{3\pi \mu U_{\text{app}}}{2\epsilon^2 g} + \mathcal{O}(\ln(g^{-1})), \quad (60) $$

where $U_{\text{app}}$ is the approach velocity of two spheres and $\epsilon$ is a curvature approximation of the form

$$ \epsilon = \frac{1}{2} \left( \frac{1}{a} + \frac{1}{b} \right) \quad (61) $$

where $a$ and $b$ are the particle radii. Ding & Aidun (2003) use this result to define a surface stress element

$$ df = \frac{3\mu U_{\text{app}}}{2\epsilon g^2}, \quad (62) $$

where $g$ is the local gap between two particles at the surface element location. By integrating over the particle surface, the force given in Eqn. (60) is obtained. This integration is approximated through a summation over the LB links with a weighting coefficient, $\bar{q}$ and ultimately leads to a force on each link taking the form $df_{\text{lub}} = \bar{q}df$. 

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The approach velocity, $U_{app}$, is based on the centerline velocities for rigid spherical particles. As a result, the links crossing those surfaces do not provide any torque on the particle which is not the case for particles of arbitrary shape. Therefore, MacMeccan et al. (2009) modify the approach velocity so that it based on the local surface element velocity along the link, but this resulted in strong forces scaling as $1/g$ as particles slide past one another. These larger forces were corrected by projecting the force, velocity, and gap in the direction normal to the surface which leads to a reduction in the error associated with applying the strong singular forces. This modification takes the form

$$d\mathbf{T}_{\text{lab}}^{\text{rb}} = -\left(\frac{3\dot{q}\mu U_{\text{app}}}{2\epsilon g^2}\right)\mathbf{n}_{\text{avg}}.$$  (63)

The local gap, $g$, between particles is calculated via

$$g = (g'e_i) \cdot \mathbf{n}_{\text{avg}}$$  (64)

where $g'$ is the gap between surfaces along the LB link and the average surface normal is evaluated via

$$\mathbf{n}_{\text{avg}} = \frac{\mathbf{n}_{(a)} - \mathbf{n}_{(b)}}{||\mathbf{n}_{(a)} - \mathbf{n}_{(b)}||}.$$  (65)

between two triangles $a$ and $b$ where the normal vector of triangle $a$ is $\mathbf{n}_{(a)}$ and the normal vector of triangle $b$ is $\mathbf{n}_{(b)}$. This is performed between adjacent particles and particles interacting with walls. The corrected approach velocity is calculated via

$$U_{\text{app}} = -(\mathbf{u}_{b(b)} - \mathbf{u}_{b(a)}) \cdot \mathbf{n}_{\text{avg}}.$$  (66)

The curvature calculation is also modified (MacMeccan et al., 2009) for the treatment along the link. It is calculated via

$$\epsilon = \frac{1}{N} \sum_{i=1}^{N} \left| \frac{dT_{\text{surf}}}{ds} \right|,$$  (67)

where $s$ is the vector connecting triangular surface centroids, $T_{\text{surf}}$ is the tangent vector to the surface in the direction of $s$, and the summation is performed over the
adjacent three surfaces when a surface triangulation is used. The fitting parameter \( \bar{q} \) was found to be 0.6 in Ding & Aidun (2003), but the value of 0.4 used by MacMeccan et al. (2009) and Clausen et al. (2011) is employed in this work.

To prevent stability issues associated with RBCs overlapping, an additional contact force is used. The contact force to prevent overlap takes the exponential form (MacMeccan et al., 2009) of

\[
\mathbf{f}_{\text{contact}} = -A^* \exp \left( \frac{-g}{\sigma_c} \right) \text{ if } g \leq g_c, \quad (68)
\]

where \( A^* \) is a contact force scaling constant, \( g \) is the local gap, \( g_c \) is the cutoff gap specified, and \( \sigma_c \) determines the range of contact force. When implemented in the code, the form given by Eqn. 70 is modified via

\[
A^* = A_c 6\pi U \exp \left( \frac{g_c}{\sigma_c} \right), \quad (69)
\]

where \( U \) is a velocity scale, \( a \) is the particle radius. The multiplier \( A^* \) remains unchanged after the initialization stage, but the \( \exp(-g/\sigma_c) \) term is updated each time step. Simulations with an imposed shear field have a velocity scale of \( U=\dot{\gamma} a \). For Hagen–Poiseuille flow the velocity scale is \( U=f_x D a/4\mu \) where \( D \) is the tube diameter and \( f_x \) is the axial body force [F/L³]. The shear rate approximated is the wall shear rate \( \dot{\gamma}_w=f_x D/4\mu \) resulting in the similar formulation of \( U=\dot{\gamma} a \). The wall shear rate is independent of hematocrit in the cell-depleted layer adjacent to the vessel wall.

The contact force is written in a more general notation with the values normalized by the particle radius \( a \), and applied in the direction of the vector \( \mathbf{e}_i \) as

\[
\tilde{d}\mathbf{F}_{\text{contact}} = -\tilde{A}^* \exp \left( \frac{\tilde{g}_c - \tilde{g}}{\tilde{\sigma}_c} \right) \frac{\mathbf{e}_i}{\|\mathbf{e}_i\|}. \quad (70)
\]
The total contribution due to lubrication and contact modeling is

\[ d\mathbf{F}_{\text{lub}} + d\mathbf{F}_{\text{contact}} = \begin{cases} 
0 & \text{if } \tilde{g} > c_i/a, \\
-\bar{q} \frac{\bar{U}_{\text{app}}}{4\pi \lambda_{cg}^2} \mathbf{n}_{\text{avg}} - \tilde{A}_c \exp \left( \frac{g_c - \tilde{g}}{\tilde{\sigma}_c} \right) \frac{\mathbf{e}_i}{||\mathbf{e}_i||} & \text{if } \tilde{g} < \tilde{g} \leq c_i/a, \\
-\bar{q} \frac{\bar{U}_{\text{app}}}{4\pi \lambda_{cg}^2} \mathbf{n}_{\text{avg}} - \tilde{A}_c \exp \left( \frac{g_c - \tilde{g}}{\tilde{\sigma}_c} \right) \frac{\mathbf{e}_i}{||\mathbf{e}_i||} & \text{if } \tilde{g} \leq g_c,
\end{cases} \]  

(71)

where \( a \) is the particle radius, and \( \tilde{A}_c=5, \tilde{g}_c=0.03, \) and \( \tilde{\sigma}_c=0.005 \) are constants adjusted from Clausen (2010) & Clausen et al. (2011) which improve the behavior of the contact from the earlier work of MacMeccan (2007) & MacMeccan et al. (2009). The total force is then calculated by summing the contributions due to the standard bounce-back operation, the momentum adjustment for uncovering nodes as the particles move the LB domain, lubrication forces, and the contact force which results in the final form

\[ \mathbf{f}_{\text{link}} = \mathbf{f}^{(b)} + \mathbf{f}^{(c)} + d\mathbf{F}_{\text{lub}} + d\mathbf{F}_{\text{contact}} = \mathbf{f}^{\text{LB}} + \mathbf{f}^{\text{PP}}. \]  

(72)

### 2.5.2 Adhesion and repulsion model

At low shear rates, the formation of rouleaux, or a structure of RBCs mimicking a stack of coins, is observed. More often in clinical conditions, three-dimensional clumps are observed and are difficult to disperse and can cause the viscosity of blood to increase. In severe cases, these structures can increase the flow resistance through arteriole sized vessels and can induce blood sludging (Hathcock, 2006).

Figure 6 demonstrates the effect that adhesion has on the relative viscosity of whole blood at \( \phi=0.45 \) through the coaxial cylinder viscometer experiments of Chien (1970). The “normal” experiment consists of RBCs in plasma at 1.2 cP. The adhesion between RBCs was increased by using an 11% albumin-Ringer solution with the same viscosity as plasma. It is clear that adhesion does have a significant effect on the viscosity of blood at shear rates less than 5 \( \text{sec}^{-1} \). Hardening of RBCs was performed by washing them in a 0.5% solution of glutaraldehyde.
The effects due to hardening of RBCs and due to adhesion on the relative viscosity, $\mu_r$, of a suspension of RBCs at $\phi=0.45$ from Chien (1970).

The most numerous cell-cell interaction in the direct numerical simulation of cellular blood is that of RBC-RBC interactions. The effects of RBC aggregation on the rheology and the properties of blood flow in arteriole sized vessels are non-negligible. There is a general agreement that fibrinogen and other large plasma proteins increase RBC aggregation (Neu & Meiselman, 2002). Two typical ways of modeling theories for the aggregation of RBCs is “bridging” and “depletion”.

When investigating RBC-RBC interactions, the net negative charge on the RBC surface that is the source of the disaggregation forces (Neu & Meiselman, 2002) should be considered. The interaction energy between RBCs can be modeled by considering the isothermal charging process:

$$E = \frac{1}{2} \int_0^d \int_0^\rho \psi(\rho, x) d\rho dx$$  \hspace{1cm} (73)$$

in which $\psi$ is the electrostatic potential between the cells, dependent on the charge density, $\rho$. By solving the Poisson–Boltzmann equation, one can solve for the electrostatic potential, $\psi$. This potential can be used to approximate the interaction energy between RBCs as a function of the distance between cells.
One such potential that mimics the results found by solving the Poisson–Boltzmann
equation is the Morse potential given by

$$\phi(x) = D_e [e^{2\beta(x_0-x)} - 2e^{\beta(x_0-x)}],$$

(74)

where x is the distance between cells, $x_0$ is a cut-off distance in which no interaction
forces are present, $D_e$ is the surface energy, and $\beta$ is a scaling factor (Liu et al., 2004).

Upon differentiation of the Morse potential we obtain the RBC-RBC force

$$f(x) = -\frac{\partial \phi(x)}{\partial x} = 2D_e \beta [e^{2\beta(x_0-x)} - e^{\beta(x_0-x)}].$$

(75)

This force currently replaces the contribution of Eqn. (70), when invoked, but could
simply be added to it once it is modified into the form

$$df^{\text{adhesion}} = 2D_e \beta [\frac{e^{2\beta(x_0-x)} - e^{\beta(x_0-x)}}{||e_i||}] e_i,$$

(76)

to account only for the weak attraction forces. This force, in its general form, allows
for the weak attraction of RBCs at far distances and the strong repulsion at near
distances. The behavior of the dimensionless potential and force are given in Fig. 7. In
this plot, it is clearly demonstrated that the Morse force is attractive for distances $0 < \beta(x - x_0) \leq 3$ and strongly repulsive for distances $\beta(x - x_0) < 0$. In Fig. 8, the Morse
potential closely approximates the interaction energy measured from the experiments
of Neu & Meiselman (2002). This Morse potential based contact model has been
implemented into the LB-SL framework, but is not used for shear rates exceeding
5 sec $^{-1}$ where the experimental results of Chien (1970) showed that adhesion was
not significant. Morse-type adhesion models are used for numerous applications and
by implementing it into the LB-SL code it could be extended for use in future work
for platelet adhesion or other phenomena where adhesion is of primary importance.
Furthermore, the constants in the Morse potential function can also be altered so
that it is a purely repulsive model and therefore could replace the contact model
from MacMeccan et al. (2009) by fitting the parameters to match the exponential
formulation of that model.
Figure 7: Non-dimensionalized Morse potential and force (Liu & Liu, 2006).

\[ f(x) = 2D_e \beta [e^{2\beta(x_0-x)} - e^{\beta(x_0-x)}] \]
\[ \phi(x) = D_e [e^{2\beta(x_0-x)} - 2e^{\beta(x_0-x)}] \]

Figure 8: Cell interaction energy and the Morse potential function plotted against the distance between RBCs in nm and in LB units. Figure modified from Liu & Liu (2006) including the experimental interaction energy measurements of Neu & Meiselman (2002).
2.6 Lees–Edwards boundary condition

In order to study the rheological properties of blood under numerous shear rates, the Lees–Edwards boundary condition (LEbc) is used (Lees & Edwards, 1972). This boundary condition was initially used in Molecular Dynamics simulations. It is a periodic type boundary condition developed to model bulk systems in simple shear flow. The implementation of the LEbc in the current computational framework (MacMeccan, 2007; MacMeccan et al., 2009) was based on the implementation of Wagner & Pagonabarraga (2002). Lorenz et al. (2009) have also implemented the LEbc for suspensions using the lattice-Boltzmann method.

The LEbc is used to overcome the problem of maximum shear rate experienced in LB simulations and also to alleviate wall effects. Simulations using the LEbc with the LB-FE implementation were originally performed by Clausen (2010); Clausen & Aidun (2010); Clausen et al. (2011). In the shear (velocity-gradient) direction, periodic domains are shifted in time with a velocity equal to \( \pm \dot{\gamma} H \), where \( \dot{\gamma} \) is the shear rate and \( H \) is the domain length in the shear direction. In Fig. 9, a schematic of the LEbc is given. In the schematic, the simulation domain is indicated by the gray region with additional periodic images shown by the dashed box regions. There are also periodic images of a single RBC. The RBCs, platelets, or fluid that cross the top shear border undergo a shift in position in the flow direction equal to \( \dot{\gamma} H \Delta t \) and a shift in velocity in the flow direction of \( -\dot{\gamma} H \) before reappearing the bottom of the simulation domain (Clausen, 2010). In the LEbc, the flow and vorticity direction boundaries are treated like a typical periodic boundary where the flow and particles leave one side of the domain and enter the other at identical \( y \) and \( x \) locations respectively. Since the dynamics of the SL RBCs are updated differently than the body-fitted-based formulation of the linear FE method of MacMeccan et al. (2009), the passing of SL RBCs according to the rules of the LEbc must be done based on the global coordinate system of the LB stencil.
The LB fluid distributions must also be modified for the LEbc (Clausen, 2010). Wagner & Pagonabarraga (2002) propose the Galilean shift in the fluid distribution expressed as

\[ f_{i}^{GS} = f_{i} + f_{i}^{(eq)}(\rho, u \pm \dot{\gamma}H) - f_{i}^{(eq)}(\rho, u) \]  

(77)

where \( f_{i}^{GS} \) is the adjusted distributions. Since the location of the lattice changes according to \( \dot{\gamma}Ht \), the lattice used is no longer symmetric. The new distributions are linearly interpolated to the nearest lattice nodes.

Figure 9: Lees–Edwards boundary condition for the LB method, showing periodic domain images advecting with velocity \( \dot{\gamma}H \).

2.7 Orientation and the tensor of gyration

Due to the deformability and the tank treading behavior of the RBC, the initial minor and major axes do not describe the orientation of the RBC accurately for all time. Therefore, the tensor of gyration (Madi et al., 2009) is used to describe the orientation angle of the RBC with respect to the flow direction. The tensor of
gyration is calculated by

\[ G_{mn} = \frac{1}{N} \sum_{i=1}^{N} r_m^{(i)} r_n^{(i)} \]  

(78)

where \( r_m^{(i)} \) is the \( m \)th Cartesian coordinate of the position vector \( \mathbf{r}^{(i)} \) of the \( i \)th vertex on the RBC surface. \( G_{mn} \) is a non-negative definite symmetric tensor with real non-negative eigenvalues that can be diagonalized in the convenient form

\[
G = \begin{bmatrix}
\zeta_x^2 & 0 & 0 \\
0 & \zeta_y^2 & 0 \\
0 & 0 & \zeta_z^2
\end{bmatrix}.
\]

(79)

The output of \( G_{mn} \) is written for each deformable RBC at a specified time interval. The eigenvalues and eigenvectors of \( G \) are found using Jacobi’s iterative method (Sleijpen & van der Vorst, 2000) for determining the eigenvalues and eigenvectors of symmetric matrices during post-processing operations.

The eigenvalue and eigenvectors of the tensor of gyration are used to generate orientation angle and shape descriptors. When the eigenvalues are equal, the RBC is approximately spherical in shape. In general, the eigenvalues are not equal and the eigenvector corresponding to the largest eigenvalue is the direction in which the RBC is stretched the furthest. The orientation angle is calculated by

\[ \theta = \arccos(\mathbf{e}_x \cdot \mathbf{e}_{\min(\zeta)}) - \frac{\pi}{2} \]  

(80)

where \( \mathbf{e}_x \) is the unit vector in the direction of the flow and \( \mathbf{e}_{\min(\zeta)} \) is the normalized eigenvector corresponding to the smallest eigenvalue of \( G \), i.e., \( \min(\zeta_x, \zeta_y, \zeta_z) \). This orientation angle is described in Fig. 10.

The radius of gyration is calculated with the eigenvalues of \( G_{mn} \) via

\[ R_g = \sqrt{\zeta_x^2 + \zeta_y^2 + \zeta_z^2}. \]  

(81)

Physically, the radius of gyration is the root mean square of the distance of the nodes on the RBC surface to the center of the RBC. The shape descriptor known as
asphericity is calculated via

\[ \alpha = \frac{\zeta_x^2 - \frac{1}{2}(\zeta_x^2 + \zeta_y^2)}{R_g^2} \]  

(82)

and is zero for a perfect sphere. A typical RBC in the simulations in this work has an undeformed asphericity value of \( \alpha \approx 0.15 \). Deformation into a parachuting shape yield values of \( \alpha \approx 0.05 \).

2.8 Isolated RBC validation problems

To establish the feasibility and efficiency of coupling the LB and SL methods, a series of validating simulations were performed to ensure that the two methods in coordination with the SBB boundary condition was capable of generating results similar to those observed in literature. This section highlights the validation problems simulated.

2.8.1 Optical tweezer experiment

To validate the SL method with the optical tweezer experiments of Mills et al. (2004) and similar computational studies (Li et al., 2005; Dao et al., 2003), stretching simulations were performed. In these simulations, the RBC is initially at rest surrounded
by fluid with a viscosity ratio of $\lambda=5$ characteristic of realistic blood plasma and hemoglobin within. A force is then applied to 4% of the nodes (2% at the maximum $x$ coordinate and 2% at the minimum $x$ coordinate) to stretch the RBC. The deformation is then characterized by an axial diameter, $D_A$, and a transverse diameter, $D_T$. The axial diameter is the maximum diameter of the RBC and the transverse diameter is given as $2 \times \max_{n \in i...N} \sqrt{y^2_n + z^2_n}$.

The result for the simulation performed with a RBC with $N=613$ is compared with the literature in Fig. 11. This figure characterizes the deformation of an RBC undergoing a dynamic load of 0-200 pN. When the applied force is small, the SL method underestimates the deformation, but as the force is increased to $\approx 130$ pN, the axial diameter is well within the experimental error of Mills et al. (2004). For majority of the applied force range, the axial diameter is nearly identical to the solution by Li et al. (2005) using the SL method with $N=28,673$ nodes. As with the high resolution study, the transverse diameter deformation is underestimated with the SL method. The FE simulation of Dao et al. (2003) is the most accurate, but uses 12,000 3D four node shell elements for modeling half of the RBC (due to symmetry) computed with the commercial FE code ABAQUS and is not coupled with a fluid solver. Pivkin & Karniadakis (2008) obtained similar results using this coarse graining procedure and improvements were found using a modified in-plane energy term by Fedosov et al. (2009). The simulations from the current implementation are labeled as “Simulation A” and “Simulation B”, where A is based on the original formulation of for the area compression modulus of Dao et al. (2006) and B is based on the corrected form of Fedosov et al. (2010a). The modification of the area compression modulus, $K$, results in a larger Poisson ratio and better agreement with the experiments.
Figure 11: Axial, $D_A$, and transverse, $D_T$, diameters of the RBC versus applied force. The current simulation results are compared to the high resolution SL results of Li et al. (2005), the hyperelastic FE model of Dao et al. (2003), the linear FE model used in MacMeccan et al. (2009), and the experiments of Mills et al. (2004). Simulations were performed with $\lambda=5$ to mimic an RBC suspended in plasma (figure from Reasor et al. (2011)).

2.8.2 Tumbling and tank treading

The dynamics of RBCs in simple shear exhibit three primary dynamical modes. They are: tumbling at low shear rates; tank treading at high shear rates; and an intermediate regime when transitioning from tumbling to tank-treading. RBCs suspended in a low viscosity fluid, with a viscosity less than the internal fluid, tend to tumble for a large range of shear rates. Conversely, RBCs suspended in fluids more viscous than the internal fluid undergo tank-treading motions at most shear rates. Further, if an RBC is tank treading and the shear rate is lowered sufficiently, the shear stress on the RBC membrane reaches a point where it can no longer sustain tank treading and the RBC begins to tumble. This transition occurs when the shear stress is at a level that is no longer capable of generating the maximum value of the elastic energy in the RBC membrane (Skotheim & Secomb, 2007) and this maximum value is a function of the elastic properties of the membrane.
Experimental observations of Abkarian et al. (2007) have documented these dynamical regimes. In their study, they suspended isolated RBCs in a viscous solution of dextran with viscosities of 22, 31, and 47 cP. The RBCs were untreated and contained hemoglobin within with a viscosity of 6 cP. The simulations presented in this study were performed with a viscosity ratio of $\lambda = 0.27$ for tank-treading and tumbling simulations and $\lambda = 8.48$ for the “wheel” configuration simulations for isolated RBCs in shear. Tsubota & Wada (2010) report that the material properties, specifically the elastic properties of the membrane, play an important role in the motions of RBCs tank treading and tumbling. Therefore, the intermittent regime, is only observable in a very narrow parameter space. In the tank-treading regime, the power supplied to the RBC is equal to the power dissipated by the RBC membrane and the hemoglobin within (Tran-Son-Tay et al., 1984).

\[
\begin{align*}
C_{aG} & \\
\text{Oscillation Period [sec]} & \quad 0 \quad 0.02 \quad 0.04 \quad 0.06 \quad 0.08 \quad 0.1 \quad 0.12 \\
\text{Shear Rate [sec$^{-1}$]} & \quad 0 \quad 1 \quad 2 \quad 3 \quad 4 \quad 5 \quad 6 \quad 7 \quad 8 \\
\end{align*}
\]

**Figure 12:** Oscillation period plotted against shear rate for an isolated RBC in wall-bounded shear in dextran solution with a viscosity of 22 cP, $\lambda = 0.27$. The results of Pivkin & Karniadakis (2008) for $N = 500$ are given for comparison (figure from Reasor et al. (2011)).

As previously mentioned, RBCs can demonstrate different dynamics at different
shear rates when surrounded by a viscous medium such as dextran. The numerical simulations performed were done to mimic the experimental test cases of Abkarian et al. (2007) and the computations of Pivkin & Karniadakis (2008). In Fig. 12, the oscillation period is plotted against the shear rate for an isolated RBC in wall-bounded shear. The results from Pivkin and Karniadakis are given for their coarse case using $N=500$ and are compared to results from the present study with $N=613$. The exterior fluid was modeled as dextran with a viscosity of 22 cP yielding a viscosity ratio of $\lambda=0.27$ for these simulations. In the present study, a transition from tumbling to tank treading is observed between 1 sec$^{-1}$ and 1.5 sec$^{-1}$. Skotheim & Secomb (2007) predict that the tumbling regime is $\dot{\gamma}<1.169$ sec$^{-1}$ and that the tank treading regime is $\dot{\gamma}>1.357$ sec$^{-1}$ which is consistent with this work. Good agreement with the previous numerical investigation using the same SL model with a DPD fluid is evident in Fig. 12. This plot demonstrates the dependence of oscillation period against shear rate, but also demonstrates the transition from tumbling to tank treading as the shear rate is increased.

### 2.8.3 Deformation in the “wheel” configuration

From the experimental study of Yao et al. (2001) the deformation index of an RBC in shear in the “wheel” configuration is given as

$$DI = \frac{D_{\text{max}}/D_0 - 1}{D_{\text{max}}/D_0 + 1} \cdot 100\%.$$  \hspace{1cm} (83)

In these experiments, a dilute suspension of RBCs is placed in a rotational viscometer and measured via photography. For comparable simulations, a single RBC in the “wheel” configuration in a cubical domain with periodic boundary conditions in the $z$ and $x$ directions with the top and bottom moving a specified velocities in opposite directions is used. The LB fluid domain was $32 \times 32 \times 32$ in lattice units or a 10.6 µm cube. The deformation index is calculated by measuring the maximum and minimum diameter of the RBC in the “wheel” configuration. In the experimental study by Yao
et al. (2001) the RBC was contained in a viscous liquid with a viscosity of 0.707 cP. Therefore, the simulations performed here were performed with a viscosity ratio of $\lambda=8.48$. Even in the small domains used for these simulations, the agreement with the experimental data is good for the experimental shear rates. At the higher rates, there are discrepancies between the SL method and the linear FE method of MacMeccan et al. (2009) The SL method demonstrates strain hardening as the in-plane resistance increases of each link is stretched where $x_i=L_i/L_{\text{max}}$ approaches unity. The linear FE model does not exhibit strain hardening or strain softening since the effective stiffness matrix remains constant throughout the simulation explaining the differences at shear rates in excess of 100 sec$^{-1}$.

![Figure 13: Deformation index results for the experimental data from Yao et al., the LB-FE method from MacMeccan et al. (2009), and the current method for $\lambda=8.48$ (figure from Reasor et al. (2011)).](image)

2.8.4 Parachuting RBC in Hagen–Poiseuille flow

Isolated RBCs deform into a parachute-like shape in Hagen–Poiseuille flow while simultaneously migrating to the vessel center. To demonstrate the LB-SL capability
of capturing this phenomenon, a single RBC with diameter 8 µm is placed in a vessel with a diameter of 9.3 µm. A constant axial body force is used to mimic a constant pressure gradient and the boundary condition on the vessel wall is no-slip. The inflow and outflow boundary conditions are treated as periodic boundary conditions so that the RBC can reach a steady-state configuration without the use of an extremely long vessel. The vessel used in these simulations is approximately 40 µm in length with the aforementioned diameter. The parachuting behavior of the RBC is a function of the particle capillary number (or RBC velocity in this case). It is also a strong function of the vessel diameter as well since the shear rate experienced by a single RBC at the tube centerline reduces as the vessel diameter increases. This figure is given to display the LB-SL method’s ability to capture the parachuting behavior of RBCs through microvessels which was not obtainable using the LB-FE method.

Previous experimental studies of Tsukada et al. (2001) looked at the deformation index defined as $\Gamma = L/D$ where $L$ is the length of the RBC and $D$ is the deformed diameter. In the experimental studies the authors looked at the deformation index as a function of the RBC velocity. They used a microchannel with a width of 9.1 µm and a depth of 5 µm. For the present computations, a tube with a diameter or 9.3 µm is assumed. The experimental study also presented a correlation for converting the microchannel results to a glass tube with a diameter of 9.3 µm. The results for the deformation index are shown as a function of the RBC velocity in Fig. 14. In this plot, agreement between the experiment in the tube and the present study is clear.

2.9 Seeding of RBCs for dense simulations

The easiest way to generate an initial distribution of RBCs is to place them in ordered arrays that fit into a specified domain. However, this procedure becomes cumbersome in complicated geometries. For the simulations presented in this work, the initial distribution of RBCs could be generated in an orderly manner, but requirements of
realistic volume fractions make this very difficult. These ordered initial distributions also take a large amount of time to form the random distributions observed in blood.

The method for generating initial distributions of RBCs and platelets was first implemented by MacMeccan (2007). This method starts by generating random locations and orientations in the domain at a specified distance away from one another. Their distance is specified by the user, but a typical distance is 2.4 $\mu$m. The RBCs and platelets are then placed at these locations at approximately 30% of their final size. The RBCs and platelets are then “grown” rigidly allowing for strong particle-particle forces until they reach approximately 110% of their final size. The rate in which these particles are grown can cause overlap if not chosen wisely. A typical growth rate for realistic volume fraction is 0.004% per LB time step where they reach their final orientation in 20,000 LB time steps. This process can be time consuming for large simulations, but generates high quality “seeds” of RBCs and platelets.

Figure 14: Deformation index, $\Gamma$, plotted against RBC velocity for the parachuting RBC experiments of Tsukada et al. (2001) and current simulations in a 9.3 $\mu$m tube with $\lambda=5$ and $Re_{RBC}=0.001–0.008$ (figure from Reasor et al. (2011)).
The seeding process is performed in parallel using MPI for large simulations and are combined with a suite of utilities written in Python for future simulations. The time evolution of a seed is shown in Fig. 15 for a realistic concentration of $\phi=0.42$ with 196 RBCs.

Figure 15: Snapshots of growing RBC distributions for a $\phi\approx0.425$ simulation with 196 RBCs in preparation for an unbounded shear simulation.

For simulations that require sufficient statistical data from several radial locations in Hagen–Poiseuille flow, the seeds are grown assuming a homogeneous distribution of RBCs at an elevated hematocrit of approximately 45%. The seeds in rigid geometries, such as vessels, requires the large geometry so that the growing particles can interact with vessel walls. After the seed has been successfully generated, specific RBCs are replaced with platelets so that the platelet locations can be chosen at several radial positions needed for generating statistical data on platelet trajectories. The generation of these seeds can sometimes take more than one iteration if certain RBCs are “jammed” in locations where the contact force preventing overlap exceeds forces suitable to maintain stability. In these cases, the growing can be slowed to allow more time for particles to interact. These seeds can also be generated while exposed to a constant axial body force as well. Due to the random nature of this process, some seeds are successful after a single iteration and some take as many as five.
2.10 Conservation of RBC volume and surface area

The LB method generates approximate solutions to the incompressible Navier–Stokes equations but suffers from pseudo-compressibility effects associated with the equation of state \( P_f = \rho c_s^2 \). For single-phase flows, and those containing rigid particles, there are no incompressible effects in the low Mach number regime simulated. However, the SBB does not conserve mass exactly on a local level and the mixing of exterior and interior fluids can cause a gradual change in the volume of the deformable RBCs used here. This mixing is corrected by a density normalizing procedure found in Clausen (2010) as well an artificial pressure force that resists change in particle volume.

As a RBC deforms in shear, the surface area has to increase or the volume has to decrease. Limitations of Hookean and neo-Hookean membrane models do not conserve surface area, observed in experiments, as well as the spectrin-link model. The linear finite-element method of MacMeccan (2007); MacMeccan et al. (2009) revealed changes in volume of up to 2% and changes in area of up to 16% with standard deviations of 0.03% and 3% respectively. A comparison to the deviations from initial volume and area of the LB-FE method of MacMeccan (2007) and the LB-SL method are given in Table 2. The LB-SL method shows a slight increase in volume by 1.6% on average with maximum values exceeding the initial volume by 2.7% which is comparable to the previous LB-FE method. The mean surface area increase is 1.4% with a maximum value of 1.6%. Therefore, the spectrin-link RBC membrane model conserves the surface area better than the linear FE method results reported in MacMeccan (2007).

2.11 Limitations and assumptions

Matching \( Re_{RBC} \) and \( Ca_{RBC} \) simultaneously is very computationally expensive using the LB method for low \( Re \) flows. Specifically, matching \( Re_{RBC} \) requires taking extremely small velocities which, in turn, require \( O(10^7) \) LB time steps to simulate a
Table 2: Red blood cell surface area and volume statistical comparisons to MacMeccan (2007). Here \( A \) and \( \Omega \) denote the surface area and volume respectively and the subscript 0 denotes the initial values. The statistics from MacMeccan (2007) are for a dense suspension at \( \phi = 0.405 \) and the results from the LB-SL method are for a dense suspension at \( \phi = 0.425 \).

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Omega/\Omega_0 ) (MacMeccan, 2007)</td>
<td>1.000</td>
<td>0.003</td>
<td>1.020</td>
</tr>
<tr>
<td>( A/A_0 ) (MacMeccan, 2007)</td>
<td>1.080</td>
<td>0.030</td>
<td>1.160</td>
</tr>
<tr>
<td>( \Omega/\Omega_0 )</td>
<td>1.016</td>
<td>0.003</td>
<td>1.027</td>
</tr>
<tr>
<td>( A/A_0 )</td>
<td>1.014</td>
<td>0.003</td>
<td>1.016</td>
</tr>
</tbody>
</table>

single second of time. Therefore, \( Ca_G \) is assumed to be a more important parameter to match because the effects of RBC deformation are more critical than inertial effects for flows with \( Re_{RBC} = \mathcal{O}(0.1) \). All of the simulations presented in this study have \( Re_{RBC} < 0.7 \), but these values can be up to two orders of magnitude larger than their physical counterparts. For example, in an experiment a RBC subjected to a shear rate of 500 sec\(^{-1} \) would have \( Re_{RBC}^p \approx 0.007 \) and a corresponding capillary number of \( Ca_G = 0.83 \). The capillary number is matched in the simulations, but with a Reynolds number of \( Re_{RBC}^{LB} = 0.113 \). Therefore, in this example, the Reynolds number used would be approximately 16\( \times \) greater than the physiological case.

The coarse grained spectrin-link model implemented captures the elasticity of the RBC membrane through in-plane contributions. One neglected aspect of the RBC membrane is its viscosity. The elastic properties of the membrane describe the resistance to cell deformation, but the membrane viscosity describes the resistance to the rate of deformation (Hochmuth & Waugh, 1987). The membrane viscosity is neglected in almost all numerical simulations of RBCs, but experiments have shown that the membrane is a significant source of viscous dissipation demonstrated through the calculations of Evans et al. (1976). These calculations demonstrated that the viscous dissipation of the membrane is approximately two orders of magnitude greater than the viscous dissipation of the hemoglobin within the RBC. The time scale for a
red blood cell to recover to an unstressed state is given by

\[ t_c = \frac{\eta_{\text{membrane}}}{G}. \] (84)

The experiments of Hochmuth et al. (1979) revealed that this value is approximately \( t_c = 0.1 \) seconds. Therefore, if the membrane shear modulus is \( 5.5 \times 10^{-3} \) dyne/cm then the membrane viscosity is \( 5.5 \times 10^{-4} \) dyne sec /cm. The value of \( \eta_{\text{membrane}} \) is also dependent on hemoglobin concentration and temperature, and can change with shear rate as well. In the spectrin link membrane model, dissipative forces can be added to each link to account for the rate of deformation through the membrane viscosity. These forces take the form (Fedosov et al., 2010a)

\[ f_{\text{visc}}^i = -\gamma^T v_i - \gamma^C (v_j r_j) r_i \] (85)

where \( \gamma^C = \gamma^T / 3 \) and the membrane viscosity given as

\[ \eta_{\text{membrane}} = \sqrt{3} \gamma^T + \frac{\sqrt{3} \gamma^C}{4}. \] (86)

Equation 85 can be simplified to

\[ f_{\text{visc}}^i = -\frac{12 \eta_{\text{membrane}}}{13 \sqrt{3}} v_i - \frac{4 \eta_{\text{membrane}}}{13 \sqrt{3}} (v_j r_j) r_i \] (87)

where \( r_i = (x_m - x_n) / |x_m - x_n|, v_i = v_m - v_n, \) and \( \eta_{\text{membrane}} \) is the membrane viscosity. Again, all of these calculations are based on relative values from point-to-point along each spectrin link. These forces are added to the dynamics updates previously given, which are equally valued, but opposite in sign. The contributions can then be added to point \( j \) along the spectrin link.

The lattice-Boltzmann formulation used in this work does not consider temperature. However, experiments have shown that there are fluctuations on RBC membranes due to thermal fluctuations (Hale et al., 2009; Ben-Isaac et al., 2011). These fluctuations could be modeled by implementing small random forces that fit the statistical distribution of the fluctuations observed. However, modeling these fluctuations is not attempted in this work.
The parameter of interest for unsteady problems is the Womersley number, \( Wo \), which relates the unsteady inertial to viscous forces in these cardiovascular flows. Due to the complex nature of the human cardiovascular system, a range of Womersley numbers exist. When this parameter is small \( O(1) \), viscous forces dominate and when they are large \( (>10) \) unsteady inertial forces dominate (Ku, 1997). The study of biomedical flows in larger blood vessels requires the use of Womersley-based boundary conditions for pressure and velocity. However, for smaller vessels, those <100 \( \mu m \) in diameter, this parameter is small and cellular effects are more important. Therefore, the focus in this work is on the flow of blood in small vessels where \( Wo \) is negligible.

It is well known that arteries in the human body are not rigid and can deform due to numerous reasons. An extensive summary of mechanical modeling of arteries can be found in a study by Kalita & Schaefer (2008). More advanced studies of cardiovascular fluid-structure interaction have been performed by van de Vosse et al. (2003). Variations in pressure are related to the elasticity of large arteries (Westerhof et al., 2007). The arterial wall structure is very complex, containing muscles, elastin, collagen, ground substance, tunica intima, and tunica media. Complicated models can be implemented to account for many of its characteristics, but many are modeled with novel finite-elements with effective stiffness, elasticity, and density. For the smaller vessels studied here, it is assumed that the deformation of the vessels is negligible due to their small size. As a result, the small vessels modeled in this work will be treated as rigid boundaries with the no-slip condition enforced through the standard bounce-back LB boundary condition.
CHAPTER III

IMPLEMENTATION AND COMPUTATIONAL PERFORMANCE

3.1 Motivation

The study of dense suspensions of rigid or deformable particles is a formidable computing task. The computational demands of solving the fluid and solid phases, the calculation of fluid-structure interaction forces, and coupling the fluid and solid grids creates problems that can easily go beyond the capabilities of a modern workstation. The memory footprint required for such computations in addition to the need for the investigation of multiple parameters make parallel computing a priority.

In order to obtain useful statistics for simulations of whole blood, a sufficient number of RBCs must be used and these simulations must simulated for enough time to eliminate initial transients. The parallelization techniques used in the development of this hybrid LB-SL solver use the message passing interface (MPI) for distributed memory high performance computing resources. In this chapter, the computational demands of the SL RBC model are compared with rigid body dynamics and the linear FE model of MacMeccan (2007) & MacMeccan et al. (2009). The parallelization techniques and methodology are then discussed and compared with the previous parallel implementation of Clausen et al. (2010) including the amount of MPI communication associated with this implementation. The computational performance of the code is also evaluated in detail to identify the bottlenecks of this computational approach using profiling software packages.
3.2 Implementation

Implementing the SL method into the existing LB-FE code (MacMeccan et al., 2009) required the addition of a new particle type to ensure the capability to simulate rigid and deformable particle simultaneously. This particle type has added data structures, but can reduce memory footprint by eliminating the mass, stiffness, and damping matrices required for the linear FE method. The additional data structures for the SL includes the addition of the lists of unique links between nodes and a list of the unique triangle pairs in the membrane triangulation. These lists are equal in length for a closed triangulated surface, are built \textit{a priori}, and remain unchanged after initialization. An additional data structure for the SL method was created to keep the vectors of normalized link lengths, angles, etc. separate from the rigid or linear FE particle methods. User option flags are used to turn the spectrin-link method on or off if linear FE capsules are simulated. All of the additional data relevant to the next time step was added to the restart capabilities recently implemented by Clausen et al. (2010). This capability is mandatory for simulations due to limited wall times on TeraGrid resources.

Since the SL method forces are calculated based on the global coordinates by their master rank each time step, many of the parameters and details are not communicated via MPI. However, since the area and volume contributions depend on the initial area and volume, they must be communicated as the particles pass from one rank to the next. The initial angles between adjacent triangle pairs are communicated in a similar manner. This additional communication is performed using non-blocking send/receives and is the only additional communication added to the previously published parallel LB-FE method of Clausen et al. (2010).
3.3 Individual computational expenses

The efficiency of a given algorithm is determined by many variables. When analyzing the performance on a single core, one of the major factors is how well the data fits into the memory hierarchy. The memory hierarchy consists of processor registries, processor cache, random-access memory (RAM), and hard drives. In the present simulations, it would be impossible to run simulations in any feasible amount of time if the physical hard drive were accessed repeatedly. Therefore, the problems simulated in this work are small enough to fit into the RAM allocated to each processor. The structure of the data and how it fits into each subsequent level of the memory hierarchy is a major factor that determines the computational efficiency of a given algorithm or a set of algorithms.

Modern processors used for high performance computing are configured with as little as 2 GB of RAM (IBM BG/P) and as much as 128 GB of RAM (Longhorn at TACC). Cache is commonly divided into three classes namely L1, L2, and L3 which increase in size and decrease in expense from L1 to L3. All the processors used in the computations of this work are multicore and commonly share L3 cache while L2 cache can be shared or dedicated to each core depending on the architecture. The amount of L3 cache typically ranges from 2 MB to 6 MB with an average of 512 kB per core. L2 and L1 cache are available in smaller amounts. The peak GFLOP ($10^9$ floating point operations) ratings are given on a core level and on a total system level for most of the TeraGrid facilities used in this work. TAU (Shende & Malony, 2006) is used to profile the LB-SL code revealing the computational times, GFLOPs, and L2 cache misses.

The lattice-Boltzmann method has been praised for its ease of implementation and scalability, but one major drawback is its massive memory requirement. Each LB grid point using the D3Q19 formulation requires a minimum of 19 double precision variables at 8 bytes each. Furthermore, each local subdomain can contain 33,000 to
250,000 grid points corresponding to a range of 5 MB to 38 MB. Therefore, when the LB kernel is performing the streaming and collision tasks associated with the BGK operator, not all of the data fits into the cache of the processor due to its large size. Optimizing problems to fit into cache-sized blocks of memory is one area that is of considerable interest in the computational community for numerous applications. When an algorithm accesses data that is not available in cache it is called a cache miss. Cache misses ultimately lead to underutilization of the CPU.

Williams et al. (2008) reported a % peak FLOPs of 35% for single-phase LB with a D3Q27 stencil on AMDx2 architectures while the present code performance is only 3.34% of the theoretical peak values based on the 9.2 GFLOPs peak value of each core of the AMD Barcelona processors on Ranger at TACC. Williams et al. (2008) found that their original code, prior to block optimization, suffered greatly due to cache misses. Pohl et al. (2003) investigate multiple blocking schemes to better optimize the LB fluid data into cache sized blocks and demonstrated outstanding results in two-dimensional implementations while only seeing a slight reduction in L2 cache misses in three dimensions. They argue that the large data sizes associated with three-dimensional simulations only make L3 cache, with sizes on the order of MB, improvements feasible.

The poor peak GFLOP performance of the current LB implementation is due to poor cache management and has not undergone any single-core-level optimization. Ranger at TACC is used for the large simulations performed in this study. Each node on Ranger has four cores, a L3 cache size of 2MB, a L2 cache size of 512 kB × 4 (dedicated to each core), and L1 cache size of 64 kB. The smallest possible subdomain allowed for simulations is 32×16×16 due to the size of the RBCs in LB units and typically results in poor node balancing for the solid phase (SL RBCs and rigid platelets). This size subdomain requires a minimum of 1.25 MB for the particle distributions \( f_i \) for each core which corresponds to 5 MB per node. This is approximately 2.5× the
amount of L3 or L2 cache available. It is obvious that this implementation suffers from considerable cache misses. Therefore, reducing subdomain sizes to the level of cache is not feasible for the three-dimensional simulations of interest in this work. A multi-block approach that breaks each subdomain into smaller subdomains would decrease the number of cache misses and increase the performance overall.

The percentages of the L2 cache misses in the LB-SL code are given in Table 3 for a typical $\phi=0.425$ simulation in shear. This table highlights the major routines where large amounts of access to data are not readily available in cache. The largest percentage of cache misses is in the LB kernel where the BGK operation is performed. Secondly, is the calculation of the SBB on the surface of each RBC. The reason that this operation encounters a large percentage of cache misses is that it accesses the stored links from the link finding algorithm that cross the boundary of the RBC membrane. The number of links increases roughly as $\Pi^2$ where $\Pi$ is the number of SL triangles used to represent the RBC surface. Thirdly, the link finding algorithm incurs a comparable amount of the total cache misses. The spectrin-link method calculations are based on the links, triangles, and adjacent pairs of triangles on each RBC and are far less numerous requiring less memory access than the links or the fluid distributions. This fact is reflected in that the largest operation of the SL method accounts for only 0.232\% of the total L2 cache misses.

The individual computational costs of the main functions used in the LB-SL code are also given in Table 3. For the simulations using the SL based RBCs with average spectrin link lengths of $L_0=1.5c$, the link finding algorithm accounts for approximately 50\% of the computational time. Clausen et al. (2010) reported a value of 40\% using a comparable edge length of $L_0=2.0c$. The link finding algorithm is the fundamental calculation for determining the standard bounce-back operation that enforces the no-slip condition on the RBC surfaces. The algorithm starts with a bounding box around each particle and computes where each link between LB nodes intersects the RBC
Table 3: Exclusive computational cost of each routine for a simulation of 143 RBCs at $\phi=0.425$ on a single 16 core node. Total time to run simulation for 1,000 LB time steps is 771.1 seconds. Average per core performance in GFLOPs is also given and compared to the theoretical peak performance per node. Average percentage of total L2 cache misses is also included.

<table>
<thead>
<tr>
<th>Routine</th>
<th>%Time</th>
<th>GFLOPs</th>
<th>%Peak GFLOPs</th>
<th>%Cache Misses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Link Finding</td>
<td>50.4%</td>
<td>0.123</td>
<td>1.34%</td>
<td>15.6%</td>
</tr>
<tr>
<td>FSI Calc.</td>
<td>12.4%</td>
<td>0.128</td>
<td>1.39%</td>
<td>17.2%</td>
</tr>
<tr>
<td>LB Kernel</td>
<td>4.82%</td>
<td>0.307</td>
<td>3.34%</td>
<td>39.9%</td>
</tr>
<tr>
<td>Determine Interior Fluid</td>
<td>2.54%</td>
<td>0.066</td>
<td>0.717%</td>
<td>8.90%</td>
</tr>
<tr>
<td>Contact Force Calc.</td>
<td>0.766%</td>
<td>0.304</td>
<td>3.30%</td>
<td>1.20%</td>
</tr>
<tr>
<td>Curvature Calc.</td>
<td>1.94%</td>
<td>0.576</td>
<td>6.26%</td>
<td>0.846%</td>
</tr>
<tr>
<td>SL Bending Forces</td>
<td>0.891%</td>
<td>1.26</td>
<td>13.7%</td>
<td>0.021%</td>
</tr>
<tr>
<td>SL In-plane Forces</td>
<td>0.311%</td>
<td>0.956</td>
<td>10.4%</td>
<td>0.058%</td>
</tr>
<tr>
<td>SL Angle Calc.</td>
<td>0.255%</td>
<td>0.402</td>
<td>4.37%</td>
<td>0.232%</td>
</tr>
<tr>
<td>SL Area Forces</td>
<td>0.114%</td>
<td>1.02</td>
<td>11.1%</td>
<td>0.002%</td>
</tr>
<tr>
<td>SL Volume Forces</td>
<td>0.044%</td>
<td>1.83</td>
<td>19.9%</td>
<td>0.001%</td>
</tr>
<tr>
<td>SL Area &amp; Volume Calc.</td>
<td>0.042%</td>
<td>0.464</td>
<td>5.04%</td>
<td>0.001%</td>
</tr>
<tr>
<td>SL Dynamics Update</td>
<td>0.029%</td>
<td>0.502</td>
<td>5.46%</td>
<td>0.021%</td>
</tr>
</tbody>
</table>

membrane surface where SBB operation is enforced at the midpoint of each link.

The SL membrane model is fairly efficient with certain functions reaching up to 19.9% of the peak GFLOPs performance. The small percentage of cache misses reported is due to the data structures in each SL RBC being much smaller than the fluid phase data structure associated with the LB fluid stencil. The amount of computation due to the force contributions of in-plane, bending, area, and volume are dependent on how many vertices are involved in the point based derivatives used to derive those forces. The in-plane contribution is based on a two-point derivative for the WLC potential and hydrostatic elastic energy terms and both the area and volume contributions are based on three-point derivatives. The bending contribution is based on a four-point derivative for each vertex because it is dependent on two adjacent triangles that share two points. The complex four-point derivatives corresponding to the bending energy term taking the largest amount of computational time in the SL method.
3.4 Computation comparisons of RBC dynamics

All of the force terms in the SL method are dependent on differences between nodal points or angles between adjacent triangles of the RBC membrane. As a result, the SL method is invariant to rotations and translations and each vertex location only needs updating in the global coordinate system. In the LB-FE method, the particle dynamics for rigid and linear FE governed particles require a local and global coordinate system for updating their dynamics.

Comparisons of the average amount of time it takes to update RBC dynamics in seconds for rigid, linear FE, and SL models for an isolated RBC computed on a single computational core of an Intel Core i5 2.4 GHz laptop processor are given in Table 4. Each result is the average time in seconds of 1,000 LB time steps and does not include additional overhead associated with the LB fluid, fluid-solid coupling, or MPI. The RBC membrane mesh used in these benchmarks contains $N=254$ vertices. From these results, it is evident that the average time it takes to update the dynamics of a single RBC is quite small for the rigid and SL methods and is orders of magnitude less than the linear FE method. The linear FE method is the slowest overall due to the multiplication of the $(3N)^2$ inverse ($N=$ number of vertices) of the effective stiffness matrix with an effective force vector. This is performed for each particle each time step. The forces used in the linear FE method and rigid implementation must go through rotations into the local coordinate system. Since the amount of MPI communication differs for each of the methods, benchmarks of dense suspensions of RBCs are needed to better quantify computational cost.

Table 4: Average computational time [sec] comparisons for updating the dynamics of an isolated RBC using the rigid body dynamics, the linear FE formulation of MacMeccan et al. (2009), and the SL method. These are the average times of 1,000 updates.

<table>
<thead>
<tr>
<th></th>
<th>$t_{\text{Rigid}}$</th>
<th>$t_{\text{FE}}$</th>
<th>$t_{\text{SL}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>$2.6 \times 10^{-5}$</td>
<td>$2.3 \times 10^{-3}$</td>
<td>$9.0 \times 10^{-6}$</td>
</tr>
</tbody>
</table>
3.5 Parallelization

The current MPI implementation (Clausen et al., 2010) discretizes the full LB fluid domain into a set of Cartesian subdomains using the standard Cartesian topology functions defined by MPI. Specifically, the `MPI_Cart_create` is used to partition the uniform spaced LB domains employed in this work. A flow chart showing the order of communications and computation is shown in Fig. 16.

![Flowchart for single time step iteration highlighting communication and major computations (modified from Clausen et al. (2010)).](image)

The fluid phase relies on `MPI_Sendrecv` to communicate a set of ghost nodes in the three Cartesian directions, shown for a two-dimensional case in Fig. 17(a). This communication occurs once per time step. Each direction (x, y, and z) are treated independently with care taken for treatment of the specific boundary conditions used. The particles, RBCs or platelets, are tracked as Lagrangian particles that are “handed-off” between subdomain ranks as they travel through the simulation domain. The handing off procedure allocates and deallocates the particle data as the center of mass moves from subdomain to subdomain. The particle data structures are
stored as a C array of pointers, which are dynamically allocated only if the particle is visible, which keeps the memory footprint from growing as the simulation progresses and also prevents issues when scaling to larger number of processors. For a given time step, a list of all particle indices near the subdomain border is created for each subdomain, which are treated as “visible particles”. This list is then synchronized among neighboring ranks by sending it to all the neighboring domains (8 for 2 dimensions and 27 for 3 dimensions) through MPI_Sendrecv operations, shown in Fig. 17(b). Next, the particle geometry necessary to perform the bounce-back coupling is sent in a point-to-point process using nonblocking send, MPI_Isend, and receive, MPI_Irecv, operations from the rank owning the particle to all ranks where the particle is visible. After the fluid-solid boundary condition is applied, forces are communicated back using blocking, MPI_Send and MPI_Recv, operations to the owning rank and appropriately summed so that they can be used in conjunction with the SL forces. The dynamics of each RBC are calculated by the rank owning the subdomain where the center of the mass of the particle is located. This MPI implementation was optimized to its current state using TAU (Shende & Malony, 2006) on Surveyor, the porting machine at Argonne National Laboratories, and on the larger IBM BG/P installation known as Intrepid. Many of the MPI communication deficiencies associated with the simulation of \( \mathcal{O}(1,000) \) deformable particles were not obvious for simulations on 128-512 cores, but led to memory growth and considerable slow downs when moving to 8,192-16,384 cores.

### 3.6 MPI communication overhead

The implementation of the SL membrane model into the framework of the existing LB-FE code required several modifications to allow for simultaneous use of rigid, linear FE, and SL governed particles. In allowing for this flexibility, an independent data structure was created to handle the geometric and material properties of RBCs
Figure 17: Schematic of MPI communication procedure simplified for two dimensions. The communication algorithm is performed in two separate phases: (a) the fluid ghost nodes are communicated in each Cartesian direction, and (b) a list of particles near the subdomain border is synchronized with neighboring ranks, then particles are sent in a point-to-point fashion using nonblocking communications (modified schematic from Clausen et al. (2010)).

governed by the SL formulation. The SL method requires the communication of additional information that is not required by rigid RBCs or linear FE governed RBCs. The MPI implementation for SL governed RBCs followed the previous implementation to ensure compatibility.

The first comparison of MPI implementations for the LB-rigid method and the LB-SL method is given in Table 5 and gives the percentage of the total run time that each MPI protocol uses during a model simulation. This table demonstrates that the percentage of the run time is nearly identical for both methods with the LB-rigid method utilizing slightly more run time for computation than communication, i.e., 11.28% for the rigid particle implementation and 11.37% for the LB-SL method. The majority of the communication is performed with MPI_Sendrecv and MPI_Allreduce operations. Additionally, each protocol as a percentage of the MPI communication is given in the parentheses in Table 5. The MPI_Sendrecv operations are non-blocking communication protocols used to communicate LB fluid information to local neighboring subdomains. The global communication protocols of MPI_Allreduce are used
for gathering results used in post-processing. Specifically, the ensemble averaging required by the stresslet calculation for rheological studies. The `MPI_Isend`, `MPI_Irecv`, and `MPI_Recv` operations associated with the particle information and forces are considerably less expensive than the LB fluid domain communication.

Table 5: Comparison of MPI costs for LB-Rigid and LB-SL implementations. Average % of total simulation time per LB time step is given. The percentage of MPI time is given in parentheses. Results were generated using mpiP on the Queen Bee cluster at LONI-LSU.

<table>
<thead>
<tr>
<th></th>
<th>LB-Rigid</th>
<th>LB-SL</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPI_Sendrecv</td>
<td>3.55% (31.4%)</td>
<td>3.53% (31.1%)</td>
</tr>
<tr>
<td>MPI_Allreduce</td>
<td>3.36% (29.8%)</td>
<td>3.01% (26.4%)</td>
</tr>
<tr>
<td>MPI_Isend</td>
<td>1.46% (12.9%)</td>
<td>1.40% (12.3%)</td>
</tr>
<tr>
<td>MPI_Recv</td>
<td>1.30% (11.5%)</td>
<td>1.16% (10.2%)</td>
</tr>
<tr>
<td>MPI_Allgather</td>
<td>0.96% (8.52%)</td>
<td>1.64% (14.4%)</td>
</tr>
<tr>
<td>MPI_Irecv</td>
<td>0.18% (1.59%)</td>
<td>0.17% (1.53%)</td>
</tr>
<tr>
<td>...</td>
<td>0.47% (4.29%)</td>
<td>0.46% (4.07%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>11.28% (100%)</strong></td>
<td><strong>11.37% (100%)</strong></td>
</tr>
</tbody>
</table>

3.7 Parallel computational comparisons

The primary motivation of implementing a new membrane model with the ability to capture large deformations that the previous LB-FE model failed to resolve. However, the difference in the computational cost is of utmost importance when performing simulations on 100’s to 1,000’s of processor cores with simulation times measured in tens of hours. In Table 6, the simulation time for three repetitions of a characteristic simulation with 45% RBC by volume were obtained assuming the particles behaved rigidly, deformable with the linear FE method, and deformable with the SL method. These simulations were performed on the Louisiana Optical Network Initiative (LONI) Queen Bee cluster at LSU courtesy of NSF’s TeraGrid. It is important to do these benchmarks with dense simulations because the number of particle-particle interactions and communication is at a maximum and results may be skewed for an
isolated RBC in shear for example. These timings disregard initialization procedures that are done only once during a simulation. Comparisons of average times for a single time step update in seconds and averaged over 1,000 LB time steps using 32 Intel Xeon 2.33 GHz computational cores connected with a 10 Gb/sec Infiniband interconnect. The fluid subdomains are $64 \times 64 \times 64$, the total number of RBCs is 1,090, and the total LB fluid domain for these simulations is $512 \times 128 \times 128$. Each RBC membrane mesh used in these benchmarks contains $N=254$ vertices.

Table 6: Average time step [sec] comparisons averaged over 1,000 LB time steps for the coupled LB-Rigid, LB-FE, and LB-SL methods using MPI containing 1,090 RBCs at 45% hematocrit using 32 computational cores.

<table>
<thead>
<tr>
<th></th>
<th>$t_{LB\text{-Rigid}}$</th>
<th>$t_{LB\text{-FE}}$</th>
<th>$t_{LB\text{-SL}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rep 1</td>
<td>1.451</td>
<td>1.942</td>
<td>1.474</td>
</tr>
<tr>
<td>Rep 2</td>
<td>1.475</td>
<td>1.936</td>
<td>1.461</td>
</tr>
<tr>
<td>Rep 3</td>
<td>1.462</td>
<td>1.929</td>
<td>1.454</td>
</tr>
<tr>
<td>Average</td>
<td><strong>1.462</strong></td>
<td><strong>1.936</strong></td>
<td><strong>1.463</strong></td>
</tr>
</tbody>
</table>

The results in Table 6 reveal that updating the dynamics of the rigid particles, including the MPI communication overhead, is slightly more efficient than the LB-SL method. The rigid particles use a local coordinate system and must be rotated every time step after the forces are applied, but the dynamics are much simpler and less computationally demanding than the deformable SL method. Table 4 reveals that the RBC dynamics calculations are more efficient with the SL than rigid, but by accounting for the MPI communication overhead results in near similar total run times for the benchmarks performed in Table 6. The LB-SL method is still approximately 25% faster per time step than the LB-FE method. Being able to capture larger deformations and additional dynamics with a method that is more efficient is a major innovation for this solver. Consideration for traditional non-linear FE methods were given, but the computation expense of constructing and solving the large FE matrices was seen as a major drawback. It would have ultimately led to a reduction in scale,
but an increase in accuracy. The SL method scales similar to the linear FE method and also reduces the computational cost of the individual RBC dynamics.

3.8 Strong scaling

One way of evaluating the performance of the LB-SL method on parallel architectures is through strong scaling benchmarks. Strong scaling is used to determine how much speedup an algorithm gets with an increase in computational resources. Therefore, total problem size is fixed while the problem size on each computational core reduces as the number of cores is increased. One must choose a problem size large enough to make the computation a significant portion of the cost for the largest number of cores used. For the simulations in this work, a minimum subdomain size is typically a $32^3$ in LB units which is large enough to have as many as 4.5 RBCs for a $\phi=0.40$ simulation. Ideally, the computational time reduces linearly with a corresponding increase in number of cores used. However, node balancing, the tendency for subdomains to contain an uneven amount of RBCs, can impact the performance. Also, as the subdomain size is reduced, the ratio of communication cost to computational cost is increased. This has significant effects in the case of global communication where each core must communicate to all others. In this implementation, the amount of global communication is only needed for output of results that need spatial averaging over the entire domain such as hematocrit profiles or flow rates. Therefore, the benchmark simulations presented in this section correspond only to the computational and communication cost of the algorithms and do not include post-processing.

A scaling study on Ranger at TACC has been performed for simulations ranging from 128 to 4,096 cores. This is the maximum number of cores available on the TeraGrid allocation used in this study. The performance of the LB-SL method with a fixed domain size for several different number of processors was used to determine the strong scaling performance. The domain size was chosen as a fixed $512^3$ cube with
12,288 deformable RBCs in unbounded shear. The hematocrit is at a reduced value of $\phi=0.27$ which corresponds to ideal linear arrays of RBCs. This method was chosen because it is similar to what was used in the Gordon Bell prize award winning work of Rahimian et al. (2010) and can be easily used for many different domain sizes. The seeding algorithm used for generating compact rheological simulations is too expensive to use for generating seeds for the large domains used for benchmarking, but the given values yield fair estimates of how the code scales without any node balancing issues that are prevalent when subdomains do not have an equal amount of RBCs. Table 7 gives a summary of the strong scaling simulations performed and lists the subdomain sizes, computational time for 1,000 LB time steps, speedup, and efficiency based on the computational time for 128 cores, the smallest number of cores with access to enough memory for performing this domain size. The strong scaling speedup is also demonstrated in Fig. 18. The speed-up of the code can be increased by $17.7 \times$ as the number of cores is increased from 128 to 4,096 cores at a 55.4% efficiency. Using subdomain sizes of $64 \times 32 \times 32$ the efficiency is greater than 70% on 2,048 cores with each subdomain containing 6 RBCs and also demonstrates the ability to do nearly $T=3$ LB time steps per second.

**Table 7:** Strong scaling simulation results for $\phi=0.27$ with a fixed LB domain size of $512^3$ with 12,288 RBCs. All simulations were computed for 1,000 LB time steps on Ranger at TACC. Speedup and scaling efficiencies are based on the 128 core case. $T$ is the number of LB time steps per second.

<table>
<thead>
<tr>
<th>Cores</th>
<th>Subdomain Size</th>
<th>Time [sec]</th>
<th>Speedup</th>
<th>Efficiency</th>
<th>$T$</th>
</tr>
</thead>
<tbody>
<tr>
<td>128</td>
<td>$128 \times 64 \times 128$</td>
<td>3939.4</td>
<td>–</td>
<td>–</td>
<td>0.254</td>
</tr>
<tr>
<td>256</td>
<td>$128 \times 64 \times 64$</td>
<td>2418.6</td>
<td>1.63</td>
<td>81.4%</td>
<td>0.413</td>
</tr>
<tr>
<td>512</td>
<td>$64 \times 64 \times 64$</td>
<td>1055.4</td>
<td>3.73</td>
<td>93.3%</td>
<td>0.948</td>
</tr>
<tr>
<td>1024</td>
<td>$64 \times 32 \times 64$</td>
<td>620.34</td>
<td>6.35</td>
<td>79.4%</td>
<td>1.61</td>
</tr>
<tr>
<td>2048</td>
<td>$64 \times 32 \times 32$</td>
<td>335.18</td>
<td>11.8</td>
<td>73.4%</td>
<td>2.98</td>
</tr>
<tr>
<td>4096</td>
<td>$32 \times 32 \times 32$</td>
<td>222.29</td>
<td>17.7</td>
<td>55.4%</td>
<td>4.50</td>
</tr>
</tbody>
</table>
3.9 Weak scaling

Weak scaling simulations with a fixed subdomain size of $32^3$ LB units was used to demonstrate the scalability of the LB-SL method for larger simulations. The results for simulations of $\phi=0.27$ for several domain sizes are given in Table 8 for up to 4,096 cores on Ranger at TACC. The method does not exhibit the ideal scaling for equal LB time steps / second ($T$), but does perform at a 63% efficiency for 1,024 cores with the initial scale set for 16 cores. For 12,288 RBCs in a $512^3$ cube on 4,096 cores, $T\approx4.5$ is achieved which is sufficient for performing simulations in a reasonable amount of computational time at an efficiency of 51.6%. The 16 core case, performed on a single node, does not use a high-speed interconnect.

3.10 Discussion

The implementation of the coarse-grained spectrin-link RBC membrane model was done in a manner so that it could be used in conjunction with legacy particle models in the LB-FE implementation of MacMeccan et al. (2009); Clausen et al. (2011). The
Table 8: Weak scaling simulation results for $\phi=0.27$ with a fixed LB subdomain size of $32 \times 32 \times 32$. All simulations were computed for 1,000 LB time steps on Ranger at TACC. The number of LB time steps per second is denoted by $\mathcal{T}$.

<table>
<thead>
<tr>
<th>Cores</th>
<th>LB Domain Size</th>
<th>RBCs</th>
<th>Time [sec]</th>
<th>$\mathcal{T}$</th>
<th>Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>64\times64\times128</td>
<td>48</td>
<td>114.8</td>
<td>8.708</td>
<td>-</td>
</tr>
<tr>
<td>32</td>
<td>128\times64\times128</td>
<td>96</td>
<td>121.3</td>
<td>8.244</td>
<td>94.7%</td>
</tr>
<tr>
<td>64</td>
<td>128\times128\times128</td>
<td>192</td>
<td>126.8</td>
<td>7.886</td>
<td>90.6%</td>
</tr>
<tr>
<td>128</td>
<td>128\times128\times256</td>
<td>384</td>
<td>140.6</td>
<td>7.112</td>
<td>81.7%</td>
</tr>
<tr>
<td>256</td>
<td>256\times128\times256</td>
<td>768</td>
<td>162.2</td>
<td>6.165</td>
<td>70.1%</td>
</tr>
<tr>
<td>512</td>
<td>256\times256\times256</td>
<td>1536</td>
<td>168.5</td>
<td>5.935</td>
<td>68.2%</td>
</tr>
<tr>
<td>1024</td>
<td>256\times256\times512</td>
<td>3072</td>
<td>180.5</td>
<td>5.540</td>
<td>63.6%</td>
</tr>
<tr>
<td>2048</td>
<td>512\times256\times512</td>
<td>6144</td>
<td>195.2</td>
<td>5.123</td>
<td>58.8%</td>
</tr>
<tr>
<td>4096</td>
<td>512\times512\times512</td>
<td>12288</td>
<td>222.3</td>
<td>4.498</td>
<td>51.6%</td>
</tr>
</tbody>
</table>

MPI framework and methodology of Clausen et al. (2010) was followed for the implementation, but additional data structures were added to the communication. The SL membrane model demonstrated improved performance for individual dynamics over the linear FE method. Computations at realistic hematocrit values showed that simulations with rigid particles perform better than the SL method, but not significantly. The LB-SL method showed an approximate 25% speedup from the LB-FE for the same study. Strong and weak scaling studies on as many as 4,096 cores and 12,288 RBCs were performed with efficiencies good enough for computing simulations in a reasonable amount of time. The LB-SL method does not scale to the extent of the work by Rahimian et al. (2010), primarily due to the amount of resolution used for the RBC membranes ($N=613$ vertices) compared to coarser resolution ($N=84$) used in their studies. Node-balancing, memory, and the amount of computation due to the fluid-solid coupling scaling is extremely sensitive to the number of vertices used to triangulate the surface.
CHAPTER IV

CELLULAR BLOOD IN SHEAR

The dynamics of deformable particles including capsules, vesicles, and RBCs can effect the bulk rheological properties of the fluid. These effects are typically characterized as non-Newtonian and are seen in dilute suspensions but the effects are more significant in dense suspensions such as whole blood. In suspensions, non-Newtonian effects are caused by the random orientation of particles, hydrodynamic effects, and particle-particle interactions (Brady & Morris, 1997; Morris & Katyal, 2002). In this chapter, an examination of the rheological properties of blood including viscosity, the particle-phase normal stress tensor, normal stress differences, and the particle-phase pressure is presented. The relative viscosity and shear stress from simulations is compared to experimental and numerical results from literature. A discussion on the diffusivity of RBCs and the shear stress environment experienced by platelets is also included.

4.1 Dependence on domain size

In order to determine the adequate number of RBCs needed to capture rheological properties, a series of simulations was performed at a realistic hematocrit of $\phi=0.425$ for three different domain sizes with an increasing number of RBCs and platelets. The simulations performed are summarized in Table 9 and include the converged results for the orientation angle and rheological properties. All of these simulations were computed at an identical shear rate of 55 sec$^{-1}$, $Ca_G=0.04$, and $Re_{RBC}=0.095$. The viscosity ratio for these simulations is set to the physiological ratio of $\lambda=5$. The bending energy for these simulations is $\kappa_b=2.4 \times 10^{-19}$ J similar to reported experimental measurements of Hwang & Waugh (1997). The domains are not exactly divisible by the RBC volume so the volume fractions vary from 0.424 to 0.428. The converged
results are obtained by taking the time average starting with $\dot{\gamma}t=10$ to $\dot{\gamma}t=30$. The orientation angle $\theta/\pi$ for the three simulations is similar, but there a slight variation due to the tumbling motion and random orientations at the low shear rate of $55$ sec$^{-1}$ and the difference in the number of RBCs from the small case to the larger case is observed. The relative viscosity for these simulations is similar and the slight variations could be attributed to the difference in hematocrit. The normalized normal stress differences and particle pressure exhibit similar behavior and are included to demonstrate that the number of RBCs used is sufficient for rheological studies.

**Table 9:** Simulations of varying numbers of RBCs and platelets with $\lambda=5$, $\dot{\gamma}=55$ sec$^{-1}$, $\kappa_b=2.4\times10^{-19}$ J, $Ca_G=0.04$, and $Re_{RBC}=0.095$. The time-averaged results for rheological properties are also given for comparison.

<table>
<thead>
<tr>
<th>Domain [μm$^3$]</th>
<th>30.6×30.6×20</th>
<th>37.3×37.3×25.3</th>
<th>42.6×42.6×26.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBCs</td>
<td>75</td>
<td>140</td>
<td>192</td>
</tr>
<tr>
<td>Platelets</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>$\phi$</td>
<td>0.428</td>
<td>0.426</td>
<td>0.424</td>
</tr>
<tr>
<td>$\theta/\pi$</td>
<td>0.147</td>
<td>0.144</td>
<td>0.146</td>
</tr>
<tr>
<td>$\mu_r$</td>
<td>3.737</td>
<td>3.682</td>
<td>3.674</td>
</tr>
<tr>
<td>$N_1/\mu_\dot{\gamma}$</td>
<td>1.556</td>
<td>1.509</td>
<td>1.507</td>
</tr>
<tr>
<td>$N_2/\mu_\dot{\gamma}$</td>
<td>-0.482</td>
<td>-0.448</td>
<td>-0.458</td>
</tr>
<tr>
<td>$\Pi_p/\mu_\dot{\gamma}$</td>
<td>0.201</td>
<td>0.172</td>
<td>0.167</td>
</tr>
</tbody>
</table>

The time history of the instantaneous and average relative viscosity, $\mu_r$, is given in Fig. 19(a). The bold lines correspond to the running time average starting with $\dot{\gamma}t=10$. The time integral average relative viscosity, $\mu_r = \langle \Sigma_{12} \rangle / \mu_\dot{\gamma}$, is relatively insensitive to the domain size for those simulated starting with $\dot{\gamma}t=10$. This is consistent with the size dependence studies of MacMeccan (2007) & Clausen et al. (2011) using the LB-FE method. The average orientation angle is given in Fig. 19(b) as well. The average RBC orientation is also fairly insensitive to the domain sizes chosen. The large domain size is chosen for the remaining simulations in this work to study the additional rheological properties because the computational cost between
the medium size and large size is not significant and the statistics are better for the larger case.

Figure 19: (a) Instantaneous and time integral averaged relative viscosity, $\mu_r$, and (b) average orientation angle, $\theta/\pi$, plotted as a function of time, $\dot{\gamma} t$, of the three domain sizes chosen for $Ca_G=0.04$, $Re_{RBC}=0.095$, and $\lambda=5$. Bold lines indicate running time averages beginning with $\dot{\gamma} t=10$.

4.2 Reynolds number effects

One of the limitations associated with the LB method for the simulation of dense suspensions is the added computational time associated with simulating low Reynolds number flows. MacMeccan (2007) simulated blood at $Re_{RBC}=0.1$ and 0.7 and showed that the suspension viscosity using the LB-FE method was relatively insensitive to Reynolds number effects in that range. The capillary number is the dominant dimensionless parameter for determining RBC deformation and MacMeccan concludes that it is the most important for determining viscosity as well. Here, a similar numerical experiment to that of MacMeccan for $Re_{RBC}=0.01–0.38$ has been performed and the results are presented in Fig. 20. The results from the LB-SL simulations demonstrate the same insensitivity reported in MacMeccan (2007) for the relative viscosity. This is an important finding since the $Re_{RBC}$ for physiological RBC at 55 sec$^{-1}$ is approximately 0.001 which is ten times smaller than the smallest RBC simulated here. The
time averages for the $Re_{RBC}$ case are not reported due to the extremely large number of time steps required, but the results follow the same trend as the other cases (see Fig. 20).

Table 10: Simulations of varying $Re_{RBC}$ with $\lambda$=5, $\dot{\gamma}$=55 sec$^{-1}$, $\kappa_b$=2.4×10$^{-19}$ J, $Ca_G$=0.04, and $\phi$=0.425 using 192 RBCs and 4 platelets. The time averaged results for rheological properties are also given for comparison with the averages beginning at time $\dot{\gamma}t$=10.

<table>
<thead>
<tr>
<th>$Re_{RBC}$</th>
<th>0.01</th>
<th>0.048</th>
<th>0.095</th>
<th>0.190</th>
<th>0.380</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\theta/\pi$</td>
<td>-</td>
<td>0.143</td>
<td>0.147</td>
<td>0.153</td>
<td>0.155</td>
</tr>
<tr>
<td>$\mu_r$</td>
<td>-</td>
<td>3.66</td>
<td>3.67</td>
<td>3.71</td>
<td>3.72</td>
</tr>
<tr>
<td>$N_1/\mu\dot{\gamma}$</td>
<td>-</td>
<td>1.53</td>
<td>1.51</td>
<td>1.49</td>
<td>1.43</td>
</tr>
<tr>
<td>$N_2/\mu\dot{\gamma}$</td>
<td>-</td>
<td>-0.469</td>
<td>-0.458</td>
<td>-0.450</td>
<td>-0.432</td>
</tr>
<tr>
<td>$\Pi_p/\mu\dot{\gamma}$</td>
<td>-</td>
<td>0.163</td>
<td>0.167</td>
<td>0.210</td>
<td>0.201</td>
</tr>
</tbody>
</table>

Figure 20: Reynolds number study for 192 RBCs and 4 platelets: (a) instantaneous relative viscosity, $\mu_r$, and (b) average orientation angle, $\theta/\pi$, plotted as a function of time, $\dot{\gamma}t$, for the five $Re_{RBC}$ values simulated. Bold lines represent running averages starting with $\dot{\gamma}t$=10.

### 4.3 Hematocrit dependence

In infinite Peclét number, low Reynolds number suspensions, the viscosity is a strong function of the volume fraction. By adding the complexity of deformation, it is also a function of RBC capillary number. To demonstrate the strong dependence on
hematocrit, simulations for $Ca_G=0.02$ or a shear rate of 28 sec$^{-1}$ were performed using four hematocrit values of $\phi=0.10$ (46 RBCs), $\phi=0.20$ (91 RBCs), $\phi=0.30$ (136 RBCs), and $\phi=0.425$ (192 RBCs). The instantaneous $\mu_r$ values are given in Fig. 21(a) and the ensemble averaged results for simulations using the LB-SL method are compared to the LB-FE method of MacMeccan et al. (2009) and the Couette-type viscometer experimental results of Fung (1993) in Fig. 21(b). The well known Krieger–Dougherty formula (Krieger & Dougherty, 1959) for suspensions of rigid spheres

$$\mu_r = \left(1 - \frac{\phi}{\phi_m}\right)^{-[\eta]\phi_m}$$

is also presented with parameters $\phi_m=0.72$ and $[\eta]=2.3$ from Tao & Huang (2011) to match results for whole blood in a viscometer. In this figure, the viscosity is strongly dependent on $\phi$ and the $\langle \mu_r \rangle$ results for the LB-SL method are in good agreement with those from literature.

**Figure 21:** Dependence on hematocrit displayed through (a) relative viscosity, $\mu_r$ plotted as a function of time, $\dot{\gamma}t$, for $\phi=0.10$, 0.20, 0.30, and 0.425; (b) ensemble averaged $\langle \mu_r \rangle$ plotted against hematocrit, $\phi$, both for $\lambda=5$ and $Ca_G=0.02$, $Re_{RBC}=0.095$, $\kappa_b=2.4\times10^{-19}$ J, $\dot{\gamma}=28$ sec$^{-1}$ compared to the numerical results of MacMeccan et al. (2009) and the rotational viscometer results from Fung (1993). The Krieger–Dougherty formula (Krieger & Dougherty, 1959) is given with $\phi_m=0.72$ and $[\eta]=2.3$. 

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4.4 Bending energy effects

The effect of bending modulus in RBC modeling is highly disputed due to difficulties arising in using realistic values in simulations. When the bending modulus of RBCs using the SL model is reduced to physiological conditions the bi-concave disk shape is not necessary the preferred shape depending on the flow conditions. In Fig. 22, a demonstration of the RBC shape with two different bending energy values is presented. Here, \( \kappa_b = 2.4 \times 10^{-19} \text{ J} \) corresponds to \( k_{\text{bend}} = 200k_B T \) and \( \kappa_b = 1.8 \times 10^{-18} \text{ J} \) corresponds to \( k_{\text{bend}} = 1500k_B T \). The deformed shape of the RBCs at low shear rates, with the realistic bending energy, differs from the typical bi-concave shape seen in most computations from literature. The lower bending modulus allows for folding and truly random orientations at low shear rates. Rheological results for the two bending energies discussed here are given throughout the remainder of this chapter.

![Image of RBC distributions for two different bending modulus values](image)

**Figure 22:** Instantaneous RBC distributions for two different bending modulus values with \( \phi = 0.42.5, \dot{\gamma} = 14 \text{ sec}^{-1} \). The bending modulus of \( \kappa_b = 2.4 \times 10^{-19} \text{ J} \) is similar to the physiological measurements whereas the higher value of \( \kappa_b = 1.8 \times 10^{-18} \text{ J} \) is used to ensure a stable bi-concave disk shape.
4.5 Rheological properties

The normal stress differences and particle pressure have been studied in suspensions of rigid spherical particles (Zinchenko & Davis, 2002), but have just recently been explored with deformable spherical capsules (Clausen et al., 2011). In the work of Clausen et al., normal stresses are observed to be compressive in nature when exposed to a constant shear rate. As the shear rate is increased, the particles transition from compressive on average to being in tension. This analysis has been extended to simulations with SL membrane based RBCs in this work.

In Figure 23, the instantaneous and time averaged rheological properties are plotted as a function of time, $\dot{\gamma}t$. The time averaged values are given as bold lines with the same pattern with averaging beginning at $\dot{\gamma}t=10$. In Fig. 23(a), the instantaneous relative viscosity does not exhibit large variations but the lowest shear rate of 14 sec$^{-1}$ does exhibit more noise than the highest shear rate of 440 sec$^{-1}$. A similar trend is observed for $\Pi_p/\mu\dot{\gamma}$ in Fig. 23(b). The first and second normal stress differences (Fig. 23(c and d)) at the lowest shear rate of 14 sec$^{-1}$ exhibit high amounts of noise due to the tumbling dynamics and buckling deformations that the RBCs undergo. At low shear rates, the RBCs do not align with the flow as they do at higher shear rates.

One of the most common ways to describe the non-Newtonian nature of blood at low shear rates is shear thinning. This is best demonstrated by plotting the viscosity versus the shear rate. In Fig. 24, the ensemble averaged relative viscosity, $\langle \mu_r \rangle = \langle \mu_a \rangle/\mu$, is plotted against the RBC capillary number, $Ca_G$. The experimental results of Fung (1993) and Merrill et al. (1963) obtained using whole blood in rotational viscometers are given for comparison. The effect of bending energy on the relative viscosity at the low end of the shear rate range is apparent, but for $Ca_G>0.1$ the difference is less substantial. The higher bending energy simulations underestimate the viscosity at the low shear rates because the RBCs have less of a tendency to fold
Figure 23: Rheological properties plotted as a function of time, $\dot{\gamma} t$: (a) relative viscosity, $\mu_r$, (b) normalized particle-phase pressure $\Pi_p/\mu \dot{\gamma}$, (c) normalized first normal stress difference, $N_1/\mu \dot{\gamma}$, and (d) normalized second normal stress difference, $N_2/\mu \dot{\gamma}$, with $\lambda=5$, $\phi=0.425$, $\kappa_b=2.4 \times 10^{-19}$ J, for $\dot{\gamma}=14, 28, 55, 110, 220, & 440$ sec$^{-1}$. The key given in (a) is identical for the plots and bold lines denote running averages starting with $\dot{\gamma} t=10$. 

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and bend. The results for the lower bending energy value of $2.4 \times 10^{-19} \text{J}$ match the experimental observations fairly well, but still under predict the literature slightly. Contact modeling is used to prevent RBCs and platelets from overlapping. These repulsive inter-particle forces lead to larger gaps between particles and, ultimately, a reduction in viscosity. Under prediction of viscosity is demonstrated in simulations (Sierou & Brady, 2002; Clausen et al., 2011) of rigid spheres due to this effect. Forsyth et al. (2011) have recently postulated, based on experiments, that deformation is not the dominant cause of non-Newtonian characteristics, but that the transition from tumbling to tank-treading causes the reduction in viscosity with increasing shear rate.

![Diagram](image)

**Figure 24:** Relative viscosity, $\langle \mu_r \rangle$, plotted against $Ca_G$ for $\lambda=5$, $\phi=0.425$ compared to the numerical results of MacMeccan et al. (2009), and the rotational viscometer results of Fung (1993) and Merrill et al. (1963).

The deformable capsule simulations of Clausen et al. (2011) saw a dramatic decrease in the particle-phase pressure with the onset of deformation. Figure 25 includes the results of Clausen et al. (2011) with the results of deformable RBC simulations.
The effect of bending modulus is less apparent in the particle pressure, but the overall trend is consistent with the observation with initially spherical capsules. Large positive particle pressure values are present at low shear rates where inter-particle forces cause the RBCs to be in compression on average. Negative particle pressures are observed at $Ca_{G,eff}>0.2$ indicating that the RBCs are in tension for high shear rates.

Figure 25: Normalized particle pressure, $\langle \Pi_p \rangle / \mu \dot{\gamma}$, plotted against $Ca_{G,eff}$ for $\lambda=5$, $\phi=0.425$ compared to the results of Clausen et al. (2011).

As the shear rate is increased RBCs transition to tension and align with the flow (Bishop et al., 2001). The shear modulus of the cell is the primary influence on rheological properties in such instances. In Fig. 26, it is clear that the RBCs undergo a change from compressive to tensile forces as the shear rate increases. At the lowest shear rate simulated, all the normal stress components are in compression which is similar to what is observed in suspensions of rigid particles. The change in sign for $\langle \Pi_p \rangle / \mu \dot{\gamma}$ is due to the change in sign for the particle-phase normal stress.
in the flow direction, $\Sigma_{11}^p$. The particle-phase normal stress in the velocity-gradient direction, $\Sigma_{22}^p$, increases, but remains in compression. This indicates that as the RBCs align with the flow the interactions between layers of RBCs keep them in a compressive state. The particle-phase normal stress in the vorticity direction, $\Sigma_{33}^p$, increases reaching a near equilibrium value at the highest shear rate simulated. These observations indicate that as the RBCs align with the flow, they become in tension in the flow direction while remaining in compression in the velocity-gradient direction.

Figure 26: Individual normal stress components of the particle-phase stress tensor, $\langle \Sigma_{ii}^p \rangle/\mu \dot{\gamma}$, plotted against $Ca_{G,\text{eff}}$ for $\lambda=5$, $\phi=0.425$. The hollow shapes are for the bending energy of $\kappa_b=2.4 \times 10^{-19}$ J and the solid shapes are for the bending energy value of $\kappa_b=1.8 \times 10^{-18}$ J.

Derivatives of the individual normal stress components of the particle-phase stress tensor are the first and second normal stress differences. The shear rate dependence of these properties is given in Figs. 27 and 28. The first normal stress difference, $N_1=\Sigma_{11} - \Sigma_{22}$, gives a sense to the differences in stress in the flow direction versus that in the velocity-gradient direction. As the shear rate is increased, the stresses in
both directions transition from compressive to tensile, but do so at a relatively con-
sistent trend. This causes the relative insensitivity in the first normal stress difference
illustrated in Fig. 27 and shows that the axisymmetric shape of the RBCs allow for sig-
nificantly different stress characteristics depending on orientation with the flow. This
difference reaches a relatively steady value at the higher shear rate levels when the
RBCs orientation is less random. The second normal stress difference, \( N_2 = \Sigma_{22} - \Sigma_{33} \),
represents the difference in normal stress between the velocity-gradient direction and
the vorticity direction. The values of \( N_2 \) remain negative because the normal stresses
in the velocity-gradient direction are more compressive due to the formation of lay-
ers of RBCs than the side-by-side orientation of the RBCs in the vorticity direction.
However, there is additional surface area in the velocity-gradient direction due to the
RBCs aligning in the flow direction which allows for more area where the RBCs can
interact through inter-particle forces. A similar trend was observed for deformable
capsules and the value of \( N_2 \approx -0.4 \) at the highest \( Ca_G \) simulated by Clausen et al.
(2011) is near the value observed in the simulations containing RBCs.

The non-Newtonian effects of blood are the most prevalent at low shear rates.
Merrill (1969) demonstrate this through the non-linear response of effective shear
stress, \( \tau_{\text{eff}} \), with increasing shear rate. A popular method of expressing the rheological
properties, namely the shear-stress dependence on shear rate, of blood is based on
Casson’s model (Casson, 1959) which compares the square root of shear stress to the
square root of shear rate. MacMeccan (2007) and Merrill (1969) both discuss the
effective shear stress using a Casson’s equation of the form

\[
\sqrt{\tau_{\text{eff}}} = \sqrt{\tau_{\text{yield}}} + \sqrt{\gamma \mu_a}
\]

which states that the square-root of the effective shear stress in the suspension should
have a linear relation with \( \sqrt{\gamma \mu_a} \). A Casson plot is given in Fig. 29 comparing the
present results with those of MacMeccan (2007) and Merrill (1969). In this plot, it
is seen that there is a nearly linear dependence for all of the results. Specifically,
Figure 27: Normalized first normal stress difference, $\langle N_1 \rangle / \mu \dot{\gamma}$ plotted against $Ca_{G, eff}$ for $\lambda=5$, $\phi=0.425$ compared to the results of Clausen et al. (2011).

Figure 28: Normalized first normal stress difference, $\langle N_2 \rangle / \mu \dot{\gamma}$ plotted against $Ca_{G, eff}$ for $\lambda=5$, $\phi=0.425$ compared to the results of Clausen et al. (2011).
the numerical results using the LB-SL method agree well with the experiments of Merrill (1969) while are slightly less than that reported by MacMeccan (2007). The experimental results of Merrill (1969) demonstrate a difference in slope for the three separate regimes. The yield stress, $\tau_{\text{yield}}$ is a constant dependent largely on the hematocrit, material properties of the RBCs, and properties of the suspending fluid and is significant in clinical studies. The yield stress for the present simulations can be extrapolated to be approximately equal to the value reported by Merrill (1969) of 0.04 dynes/cm$^2$ for $\phi=0.405$ based on the agreement in the Casson region, but is strongly dependent on adhesive forces between RBCs in the regime of $\dot{\gamma}<1$ sec$^{-1}$. Therefore, an extrapolation of $\tau_{\text{yield}}$ would not be valid without considering adhesive effects.

![Figure 29: Casson plot of the square root of effective shear stress, $\sqrt{\tau_{\text{eff}}}$, as a function of square root of shear rate, $\sqrt{\dot{\gamma}}$, compared to the numerical results from MacMeccan (2007) and the experimental results of Merrill (1969).](image)
4.6 Orientation

The changes in the overall configuration of the RBC suspension can result in changes in the rheological properties discussed previously. In the case of tank-treading capsules, particles tend to align with the flow direction. Therefore, the orientation angle, one parameter capable of quantifying the microstructure of blood, is used here. A presentation of the orientation angle, $\theta$, for RBCs at $\phi=0.425$ at several shear rates is given. This orientation angle is identical to that defined previously. The orientation of the RBCs is inherently random due to the large number of interactions at realistic hematocrit levels. However, as the shear rate is increased the RBCs tend to align with the flow so that there is a minimal cross-sectional area (Bishop et al., 2001). In Fig. 30, demonstrations of the RBC orientations for various shear rates are presented. The change in orientation of the RBCs can be seen from these images, but is further quantified by the orientation angle.

There are several ways to analyze the change in orientation. Statistically, the cumulative distribution function of the orientation angle can be compared to previous numerical results. In Fig. 31, a comparison of the cumulative distribution function of the simulation performed by MacMeccan (2007) and the experimental results of Goldsmith & Marlow (1979) is given. The experimental results of Goldsmith & Marlow (1979) are not an optimal case for comparison due to the reduced hematocrit and different flow conditions, but is included nevertheless. The results of MacMeccan (2007) show that the orientation angle at time $\dot{\gamma}t=10$ maintain a random configuration at the low shear rate of 55 sec$^{-1}$. The LB-SL results in this work fall between the numerical results of MacMeccan (2007) and the experimental results of Goldsmith & Marlow (1979), demonstrating that the majority of the RBCs are aligned at an angle $\leq45^\circ$ relative to the flow direction. The inherent tendency for RBCs to tumble in the LB-FE method at all shear rates is the most likely factor in the random orientation seen in the results of MacMeccan (2007). At low shear rates, the LB-SL method
Figure 30: Instantaneous RBC distributions for different shear rates with $\phi=0.425$, $\kappa_b=2.4 \times 10^{-19}$ J. At lower shear rates the RBCs maintain a random orientation while at high shear rates they align in the flow direction.
does allow for the RBC membrane to tank tread somewhat if shear stresses are large enough. This allows for RBCs to slide past one another instead of flipping under certain conditions.

**Figure 31:** Cumulative $\theta$-orientation probability distribution of RBCs in unbounded shear for $\phi=0.425$ at $\dot{\gamma}t=10$. The results of MacMeccan (2007) are for $\phi=0.405$ and $\dot{\gamma}=55$ sec$^{-1}$ at $\dot{\gamma}t=10$. Goldsmith & Marlow (1979) results are for RBCs in Hagen–Poiseuille flow at $\dot{\gamma}=66$ sec$^{-1}$.

In Figs. 32 & 33, a comparison of the cumulative distribution functions of the same suspension of RBCs at $\phi=0.425$ at several shear rates ranging from 14 sec$^{-1}$ to 440 sec$^{-1}$ at two times $\dot{\gamma}t=5$ & 10 is given. As the shear rate is increased, the overall distribution becomes more favorable for particles aligning with the flow direction which is consistent with observations of isolated RBCs in shear and the observations of Bishop et al. (2001). For the higher shear rates, all of the RBCs are within 45 degrees of the flow direction at time $\dot{\gamma}t=10$. For the low shear rate of 14 sec$^{-1}$ as few as 55% of RBCs are in that range.

The average orientation angle relative to the flow direction is another way to characterize the microstructure. The average orientation angle is plotted against
Figure 32: Cumulative $\theta$-orientation probability distribution of RBCs in unbounded shear with $\phi=0.425$ for several shear rates at $\dot{\gamma} t=5$.

Figure 33: Cumulative $\theta$-orientation probability distribution of RBCs in unbounded shear with $\phi=0.425$ for several shear rates at $\dot{\gamma} t=10$. 
capillary number in Fig. 34. Here, it is seen that with increasing shear rate, the orientation angle reduces. This reiterates what was demonstrated in the cumulative distribution plots (Figs. 32 & 33). The error bars represent one standard deviation of the orientation angle. As the shear rate is increased, the average angle aligns with the flow, and the material properties of the RBC become the determining factor in rheological properties as the RBC transitions from compressive to tensile states in the flow direction. The effect of bending modulus is clearly evident; with the lower bending energy value allowing the RBCs to fold and deform significantly more at low shear rates. This results in the average orientation angle at lower shear rates to have a tendency not to align with the flow, but to tumble and buckle. As the shear rate increases, the orientation angle becomes less significant between the two values as they are in an elongated state due to the higher shear stress. The orientation of RBCs can be manipulated experimentally (Tao & Huang, 2011) using magnetic fields to align RBCs in the flow direction leading to a reduction viscosity. The present simulations show that by increasing the bending energy of the RBCs similar results can be obtained at low shear rates.

4.7 Red blood cell self-diffusion

Another phenomena of interest is that of RBC self-diffusion. The diffusion of particles in a rigid suspension of spherical particles is primarily driven by particle-particle interactions. In the case of the present simulations, the non-symmetric shape and the tendency of the RBCs to align with the flow direction yield interesting results that are not necessarily represented by the observations of particle self-diffusion in spherical particle suspensions. The particle self-diffusion is measured using the mean-squared displacements of the particle locations in the directions normal to the flow. This self-diffusion is calculated via

$$\langle \Delta y \Delta y \rangle \sim 2D_{yy}t,$$

(90)
where $\Delta y$ is the $y$ displacement and $D_{yy}$ is the diffusion constant corresponding to the velocity-gradient, $y$, direction. These values are obtained in the $z$ (or vorticity) direction similarly. Diffusion in the $x$ direction requires careful treatment as the displacements due to the flow are significant. The exact value of the normalized diffusion constant, $D_{yy}^*$, is estimated via

$$D_{yy}^* \sim \frac{1}{2\gamma a^2} \frac{\partial \langle \Delta y \Delta y \rangle}{\partial t}.$$  \hspace{1cm} (91)

The diffusion constants are commonly normalized via $D_{yy}/\gamma a^2$ where $a^2$ is the effective RBC radius $a=(3\Omega_{\text{total}}/4\pi)^{1/3} = 2.95$ $\mu$m. The mean-square displacements are calculated via

$$\langle \Delta y \Delta y \rangle = \langle [y(t) - y(0)]^2 \rangle - \langle y(t) - y(0) \rangle^2.$$  \hspace{1cm} (92)

Table 11 presents the normalized diffusion coefficients for the simulations performed showing the general trend that the normalized diffusion coefficients reduce as the shear rate is increased, but exhibit significant variation. The existing literature indicates large variations of $D_{yy}^*$ a volume fraction of $\phi=0.40$ for rigid suspensions.
(Sierou & Brady, 2004). Eckstein et al. (1977) report the value for $D_{yy}^*$ for 100 \( \mu \)m diameter rigid spheres to be approximately 0.015 for a shear rate of 10 \( \text{sec}^{-1} \) at a volume fraction of \( \phi=0.40 \). Diffusion coefficients were not measured for particles as small as RBCs, but were shown to increase with particle diameter. Clausen et al. (2011) show a decrease in $D_{yy}^*$ with increasing $Ca_G$ using deformable spherical capsules. The capillary numbers studied in Clausen et al. (2011) would correspond to shear rates ranging from 0-157.5 \( \text{sec}^{-1} \) for the simulations presented here. The diffusion coefficients are larger in magnitude for capsules than those observed for RBCs. The difference in particle shape, from spherical capsules to RBCs, would lead to significant differences in diffusion because RBCs tend to align with the flow whereas spherical capsules at low $Ca_G$ values still maintain a low aspect ratio. The dimensional velocity-gradient direction diffusion coefficient, $D_{yy}$, scale as $m\dot{\gamma}^n$ where $n\approx0.7$ as seen in Fig. 35. Platelet diffusion has been demonstrated to show similar scaling characteristics (Aarts et al., 1986) for flow through tubes. The upper and lower bounds from that study for $\phi=0.40$ are included for comparison.

**Table 11:** RBC diffusion coefficients of simulations at $\phi=0.425$, $\kappa_b=2.4\times10^{-19}$J.

<table>
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<tr>
<th>$\dot{\gamma}$ [(\text{sec}^{-1})]</th>
<th>$Ca_G$</th>
<th>$D_{yy}^*$</th>
<th>$D_{zz}^*$</th>
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<tr>
<td>14</td>
<td>0.01</td>
<td>0.011±0.010</td>
<td>0.012±0.009</td>
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<tr>
<td>28</td>
<td>0.02</td>
<td>0.006±0.069</td>
<td>0.005±0.057</td>
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<td>55</td>
<td>0.04</td>
<td>0.005±0.006</td>
<td>0.008±0.007</td>
</tr>
<tr>
<td>110</td>
<td>0.08</td>
<td>0.004±0.004</td>
<td>0.005±0.004</td>
</tr>
<tr>
<td>220</td>
<td>0.16</td>
<td>0.003±0.005</td>
<td>0.004±0.002</td>
</tr>
<tr>
<td>440</td>
<td>0.32</td>
<td>0.002±0.004</td>
<td>0.004±0.003</td>
</tr>
</tbody>
</table>

### 4.8 Shear stress on platelets

The shear stress on platelets is an extremely important factor in determining “blood damage” that can cause platelet activation and thromboembolic events. Accurately
Figure 35: Velocity-gradient direction diffusion coefficient, $D_{yy}$, plotted against shear rate, $\dot{\gamma}$, for $\phi=0.425$. Fit curves used take the form $m\dot{\gamma}^n$ with the range of $m$ and $n$ given from the measurements of Aarts et al. (1986) for $\phi=0.40$.

Modeling the shear stress on platelets is difficult computationally, especially in realistic geometries and in implant devices. In order to model the shear stress on platelets, a platelet-shaped particle must be used to accurately capture the hydrodynamic interactions between the platelet and the surrounding plasma. Another important contribution is that of platelet-RBC interaction forces that can cause localized increases in shear and normal stresses.

Most numerical investigations approximate the shear stress on platelets by accounting for the invariance of the stress tensor along a particle pathline in single-phase flow. Improved modeling accounts for the presence of platelet-shaped particles, but still only models them in a single-phase fluid. The objective of this study is to determine the significance of the multiphase nature of blood on the shear stress and how it can be used to improve estimates of models that simulate platelets in a single-phase fluid.
4.8.1 Isolated platelet in shear

The assumption that the shear stress on a platelet is equal to the invariance in the stress tensor along a pathline is not a well-founded one, but without the capability to model particles in the flow, the options are limited. The simplest case to test is that of an imposed constant shear stress in a semi-infinite domain using the LEbc. The shear stress on an individual platelet is monitored and shows that the average shear stress is nearly equal to the shear stress in the fluid, $\mu_0 \dot{\gamma}$, but the maximum shear stress is greater.

Figure 36 presents the average shear stress, $\bar{\tau}$, and the maximum shear stress, $\tau_{\text{max}}$, on the platelet surface for an isolated platelet exposed to a constant shear stress of 2.85 dynes/cm². The average shear stress the platelet experiences is approximately 5% higher than the applied shear stress with an average value of 2.99 dynes/cm². There is an increase in viscosity due to the finite size of the platelet. The viscosity is increased from 1.2 cP to 1.25 cP. The maximum shear stress the platelet experiences is much higher than the average value with values exceeding 6 dynes/cm². Therefore, assuming that the shear stress on a platelet is equal to the local shear stress of a single phase fluid is not an accurate assumption due to the local increase in viscosity and the finite size of the particle. In Fig. 36, the platelet Reynolds number, $Re_p = \dot{\gamma} a^2 / \nu$, does not have a significant effect on the average or maximum shear stress for the values simulated.

4.8.2 Platelets in blood

The average shear stress on platelets suspended in a suspension of RBCs is affected by the numerous interactions with RBCs and ultimately affected by the increase in viscosity. In Fig. 37, the normalized maximum and average shear stress of platelets and RBCs in shear is plotted as a function of time for a shear rate of 55 sec⁻¹. From this plot, it is clear that the rigid platelets experience higher levels of shear stress than
Figure 36: Normalized average shear stress, $\bar{\tau} / \mu \dot{\gamma}$, and normalized maximum shear stress, $\tau_{\text{max}} / \mu \dot{\gamma}$, plotted versus strain units, $\dot{\gamma}t$. This plot is for a single isolated rigid platelet shaped particle exposed to a constant shear rate of $\dot{\gamma}=237.4$ sec$^{-1}$ in a suspending fluid with a viscosity of 1.2 cP corresponding to a shear stress of $\mu \dot{\gamma} = 2.85$ dynes/cm$^2$.

The deformable RBCs due to their increased rigidity and difference in shape. The average shear stress above that of the apparent stress in the fluid of $\mu \dot{\gamma}$ by $\xi \approx 1.73$. In Fig. 38, the cumulative probability distribution is given for the time averaged shear stress magnitude and compared to the results of MacMeccan (2007). In the current simulations there are a few platelets experiencing high values of average shear stress that elevate the time history average. The cumulative probability distributions for the time-averaged maximum shear stress are given in Fig. 39. The maximum shear stresses experienced by the RBCs and platelets is well above the apparent stress with some values reaching as high as $7.5 \mu \dot{\gamma}$ and are larger than those predicted by MacMeccan (2007).

The time that platelets are exposed to high levels of shear stress has been determined to be an important parameter to predict platelet activation. Various experimental (Dumont, 2007; Giersiepen et al., 1990; Tambasco & Steinman, 2003) and
Figure 37: Normalized time-integral average shear stress, $\bar{\tau}/\mu\dot{\gamma}$, and time-integral averaged normalized maximum shear stress, $\tau^{\text{max}}/\mu\dot{\gamma}$, plotted versus strain units, $\dot{\gamma}t$, for RBCs and platelets. This simulation is for an imposed constant shear rate of $\dot{\gamma}=55$ sec$^{-1}$ in a suspending fluid with a viscosity of 1.2 cP.

Figure 38: Cumulative probability distribution for the time-average shear stress magnitude on surface of platelets and RBCs for $\dot{\gamma}=55$ sec$^{-1}$. The results of MacMec- can (2007), composed from simulations of 22-55 sec$^{-1}$, are given for comparison.
Figure 39: Cumulative probability distribution for the maximum shear stress magnitude on surface of platelets and RBCs for $\dot{\gamma}=55$ sec$^{-1}$. The results of MacMeccan (2007), composed from simulations of 22-55 sec$^{-1}$, are given for comparison.

computational methods (Wu et al., 2010) have been used to model this phenomena. The experimental investigations focus on correlating protein levels at a given applied shear.

Dumont (2007) created a blood damage index (BDI) model based on a linear relationship between the average shear stress on the platelet and the exposure time. This formulation is written as

$$B_D = \frac{1}{N} \sum_{i=0}^{N} \tau_i \cdot \Delta t_i. \quad (93)$$

In their study, they released 15,000 passive particles in the flow through a mechanical heart valve and the shear stress was obtained along each of the particle trajectories via

$$\tau_{ij} = \mu \left( \frac{\partial u_j}{\partial x_i} + \frac{\partial u_i}{\partial x_j} \right). \quad (94)$$

Dumont (2007) assumed that platelets were activated if the shear-stress accumulation reached a value of 35 dynes·sec/cm$^2$. 

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Giersiepen et al. (1990) argued that the importance of shear-stress magnitude was more important than the exposure time and developed a modified model to match their experimental measurements more accurately. The importance of the shear stress, \( \tau_i \), carries a larger exponent than the exposure time, \( \Delta t_i \). This model is written as

\[
\text{BDI}_G = \frac{1}{N} \sum_{i=0}^{N} \tau_i^{3.075} \cdot \Delta t_i^{0.77}.
\] (95)

Alternatively, Tambasco & Steinman (2003) assume that the most important parameters for characterizing blood damage are the average shear stress on platelets that exceeded a threshold value and the length of time they are exposed to these high levels of shear stress. Therefore, in their study, they only compute an accumulation of blood damage if the shear stress exceeds a threshold value of \( \tau^* = 105 \text{ dynes/cm}^2 \). They write this formulation as

\[
\text{BDI}_T = \frac{1}{N} \sum_{i=0}^{N} \bar{\tau}_{\text{max}}^* \cdot \Delta t_i^*.
\] (96)

where \( \bar{\tau}_{\text{max}}^* \) is the average of two successive maximum shear stresses along a platelet’s trajectory that exceeds \( \tau^* \), and \( \Delta t^* \) is the residence time between two points where the shear stress threshold is exceeded. One reason this methodology was adopted was to correct for high values of activation in recirculation regions where platelet residence times were relatively large.

In Fig. 40, a comparison of the Dumont and Giersiepen BDI models for the present simulations is given. The Tambasco & Steinman model was not considered because the shear stresses investigated do not reach the threshold level of 105 dynes/cm\(^2\) of the low shear rates simulated. The average shear stress of the platelets was observed to be larger than the applied shear stress in the fluid. This results in higher BDI\(_D\) values than the accumulation of stress in the fluid, i.e., \( \mu^* \gamma t \) (see in Fig. 40(a)). This effect is magnified greater in the Giersiepen BDI model due to the larger weight put on the shear stress in Fig. 40(b). It is clear in Fig. 40 that the BDI model predictions, just using the apparent shear stress in the fluid, lead to an underestimate to what
is experienced by the platelets in the simulation. However, the estimate is improved when the average shear stress on each platelet is assumed to be $\xi = 1.73$ times higher than the apparent shear stress in the fluid, as was the case in Fig. 37. By accounting for the higher than average shear stress on the platelets, an improvement is apparent for the estimate of the BDI model in Fig. 40 for the cases with the $\xi$ correction factor. Notably, the Dumont BDI model agrees very well, as expected, but the larger exponent on the shear stress in Giersiepen model makes it more sensitive to elevated shear stresses.

4.9 Discussion

In this chapter the LB-SL method, using the LEbc, has shown the ability to match experimental viscosity measurements for several shear rates at a realistic volume fraction and for several hematocrit values at low shear rates. Similar results for rheological properties and orientation angle were obtained for the number of RBCs ranging from 75 to 192 and Reynolds number effects were shown to be of little influence for the range of 0.01-0.38. By increasing the bending energy of the RBC the stability of the bi-concave shape is increased which prevents buckling and folding deformations in the low shear rate regime. This increase in bending energy was shown to reduce the relative viscosity and significantly reduce the average orientation angle of RBCs at low shear rates. The shear stress experienced by platelets was shown to be greater than the average shear stress in the total suspension which could ultimately lead to poor estimates in shear stress accumulation models if not considered.

The normal stresses of RBCs in these configurations have not been investigated prior to this work due to the difficulty in measuring them experimentally. Few numerical methods are robust enough to simulate dense suspensions and obtain these quantities. Results show that the particle-phase pressure undergoes a sign change as the shear rate is increased. This sign change is due to the normal stress...
Figure 40: Time evolution of the normalized (a) Dumont and (b) Giersiepen BDI models of the average shear stress on platelets compared to the accumulation of apparent shear stress, $\mu_a \dot{\gamma}$, and the corrected apparent shear stress, $(\xi \cdot \mu_a \dot{\gamma})$, using the same model. The simulation performed was for $\dot{\gamma} = 55 \text{ sec}^{-1}$ in unbounded shear.
experienced by RBCs in the flow direction exceeding the shear stress in the suspending fluid, $\mu \dot{\gamma}$. The first normal stress difference was shown to be relatively insensitive to shear rate due to the large dependence on $\Sigma_{11}^p$. The second normal stress difference exhibits similar behavior of deformable capsules showing that the compressive forces in the velocity-gradient direction are larger than those in the vorticity direction.
CHAPTER V

BLOOD FLOW IN MICROVESSEL Sized TUBES

5.1 Characteristics of blood flow in a microvessel

The flow of blood in microvessel-sized tubes is strongly influenced by the presence of RBCs. In vessels with diameters less than 10 µm, RBCs align in a single-file formation deformed into parachute or bullet like shapes. As the diameter increases, the interaction between RBCs and their alignment becomes more complex. One such example is the transition to “zipper” formations where RBCs interlock. This phenomenon is demonstrated in Fig. 41 for vessels slightly larger than one RBC diameter.

![Figure 41: Blood flow through a microvessel demonstrating the zipper formation: (a) in rat mesentery with a diameter of 12 µm from Pries & Secomb (2011) and (b) simulation with a diameter of 11.3 µm.](image)

To demonstrate the influence of RBCs in microvessel sized tubes, a presentation of results for simulations in an 11.3 µm diameter vessel is given. This size vessel was chosen because data is available from Freund & Orescanin (2011) and it is a size where
a transition from single-file formations to more complex interactions occur (Pries & Secomb, 2011) as demonstrated by the instantaneous distribution in Fig. 41. The simulations performed are summarized in Table 12. In these simulations, the inlet and outlet boundary conditions are treated as periodic so that the computational domain can be reduced and so a continuous seed of deformable RBCs, at the specified hematocrit, does not need to be initialized at the inlet.

**Table 12:** Summary of simulations in a 11.3 μm diameter vessel. The length of the tube is 45.3 μm and the LB fluid domain used is 136×34×34 with $Re_D < 6.7$ and $Re_{RBC} < 0.5$. The bending energy used for these simulations is $2.4 \times 10^{-19}$ J.

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<th>$\delta$ [μm]</th>
<th>$Ca_G$</th>
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</tbody>
</table>

The presence of RBCs in microvessel-sized tubes causes the velocity profile to become severely blunted in the tube center and the hematocrit profiles reveal a relatively thick cell-depleted layer relative to the tube size. Both of these aspects are demonstrated in Fig. 42(a) & (b), respectively. The radial profiles of $\langle \phi(r) \rangle$ are calculated via

$$\langle \phi(r) \rangle = \frac{1}{2\pi LT} \int_{t_0}^{T} \int_{L}^{L} \int_{0}^{2\pi} \phi(r, \theta, x, t) d\theta dx dt$$  \hspace{1cm} (97)$$

where $t_0$ is the time after the initial transients of the flow have subsided after accelerating from an initially quiescent state to within 20% of the final flow rate. This procedure is repeated for $\langle u_x(r) \rangle$.

The ensemble averaged hematocrit, $\langle \phi \rangle$, profile in Fig. 42(a) shows a gradual
increase from zero at the tube wall to a plateau level in the vessel core. The ensemble averaged axial velocity, $\langle u_x \rangle / U$, profile given in Fig. 42(b) demonstrates a typical parabolic profile in regions of nearly zero hematocrit, but severe blunting in the vessel core region. As the shear rate is increased, the slope of the velocity profile in the cell-depleted region shows the trend indicated in the figure due to the peak velocity increasing consistent with the results of Freund & Orescanin (2011).

Figure 42: Ensemble averaged hematocrit (a) and normalized velocity (b) profiles for several shear rates at $\phi=0.30$, $D=11.3$ μm vessel, and $λ=5$.

The viscosity of blood is strongly dependent on shear rate which was demonstrated in the unbounded shear simulations in the previous chapter. However, in Hagen–Poiseuille flow, there is a range of shear rates from zero at the vessel center to a maximum at the tube wall. The resistance to flow in a vessel due to the presence of RBCs can be estimated by the relative viscosity which is determined using the volumetric flow rate for the axial body force used. In order to compute the apparent viscosity of a dense suspension simulation such as pressure-gradient driven flow through a rigid tube, the spatially averaged volumetric flow rate is computed via

$$
\bar{Q}(t) = \frac{1}{L} \int_0^L \int_0^{2\pi} \int_0^R u_x(r, \theta, x, t) r dr d\theta dx.
$$

where $x$ is the axial coordinate and $L$ is the length of the tube. MPI protocols are
used to calculate the flow rate across all the computational cores to minimize the post-processing of the very large LB fluid data sets. Once the average volumetric flow rate is found, the relative viscosity is computed via

\[
\mu_r(t) = \frac{\mu_a(t)}{\mu} = -\frac{dp}{dx} \frac{\pi R^4}{8\bar{Q}(t)} = \frac{f_x \pi R^4}{8\bar{Q}(t)}
\]

(99)

where \(f_x\) is an axial body force used to mimic a constant pressure gradient and \(R\) is the tube radius. The average flow rate is monitored to determine if the flow has converged. This can vary depending on the diameter and length of the tube as well as hematocrit and shear rate. The relative viscosity of the flow through the 11.3 \(\mu\)m tube is plotted against shear rate in Fig. 43(a) for \(\phi=0.10\) & 0.30 along with the numerical results from Freund & Orescanin (2011) for \(\phi=0.30\). Both methods indicate there is a sharp drop in viscosity as the shear rate is increased and yield results on the upper range of the 1.19±0.1 value reported by the survey of experiments of Pries et al. (1992).

The cell-depleted layer thickness is sensitive to the interactions of RBCs with each other and the vessel wall (Pries et al., 1996). For the present study, the cell-depleted layer thickness arbitrarily defined by Freund & Orescanin (2011) as

\[
\phi(D/2 - \delta) = 0.01
\]

(100)
is used. This definition gives an estimate for the distance from the tube wall where the radial averaged hematocrit profile is equal to 1%. In Fig. 43(b), a comparison of the cell-depleted layer results of the LB-SL method to the numerical results of Freund & Orescanin (2011) is presented. The results for the cell-depleted layer thickness are in relatively good agreement and show that a maximum value is observed as the shear rate exceeds 100 sec\(^{-1}\). The cell-depleted layer does not evolve further because the RBCs have reached a state where they are tightly packed in the vessel center at that shear rate magnitude.
Figure 43: The relative viscosity, $\mu_r$, (a) and cell-depleted layer thickness, $\delta$, (b) dependence on shear rate for $\phi=0.10$ & $0.30$, $D=11.3$ $\mu$m vessel, and $\lambda=5$. The boundary integral method numerical results of Freund & Orescanin (2011) for $\phi=0.30$ are given for comparison.

5.2 Fähraeus–Linqvist effect

The Fähraeus–Linqvist effect demonstrates that the viscosity of the blood in microvessel-sized tubes is a function of the tube diameter at shear rates above $100$ sec$^{-1}$. This phenomenon has been studied extensively experimentally. A survey of experimental data was compiled by Pries et al. (1992) to develop best fits for several hematocrit values. The accepted correlation from Pries et al. (1996) for $\phi=0.45$ takes the form

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

(101)

and this viscosity dependence on tube diameter is demonstrated in Fig. 44. The reason the viscosity increases with tube diameter is related to the cell-depleted layer thickness. At high shear rates, the cell-depleted layer thickness in tubes with diameters $>10$ $\mu$m is relatively constant. However, in tubes with diameters smaller than the RBC diameter, the viscosity is higher because the cell-depleted layer is essentially non-existent and the RBCs come in contact with the wall. As the diameter of the tubes increases to values larger than that of the RBC, the cell-depleted layer
becomes an important characteristic that determines the viscosity. The thickness of the cell-depleted layer does not vary significantly with the hematocrit and shear rate held constant. However, the ratio of the cross-sectional area of the cell-depleted layer to that of the tube cross section is important. As the tube diameter increases, the percentage of the total area represented by the cell-depleted layer decreases causing a relative increase in viscosity due to the large percentage of area with significant hematocrit. Figure 45 shows a typical RBC distribution with $\phi=0.45$ with 1,090 deformable RBCs in a 42.6 $\mu$m diameter vessel from an LB-SL simulation.

![Figure 44: The Fåhraeus–Lindqvist effect demonstrated through an increase in relative viscosity with tube diameter. Experimental results of Gerbstaedt et al. (1966); Reinke et al. (1986), the fit for $\phi=0.30$ and correlation for $\phi=0.45$ from Pries et al. (1996), and the numerical results of Zhao et al. (2010) are given for comparison.](image)

The Fåhraeus–Linquist effect is demonstrated in Fig. 44. In this plot, there is a clear transition where the tube diameter reaches the RBC diameter (approximately 8 $\mu$m) and a trend of increasing viscosity with increasing tube diameter follows. Simulations with a hematocrit of $\phi=0.30$ were performed with tube diameters of 11.3 $\mu$m, 21.3 $\mu$m, 32 $\mu$m, and 41.3 $\mu$m at a shear rate of approximately 100 sec$^{-1}$. The LB-SL
simulations demonstrate the increasing trend in viscosity with increasing diameter, but the results fall slightly above the fit for $\phi=0.30$ from Pries et al. (1996) from \textit{in vitro} experiments.

![Image](image.png)

**Figure 45:** Instantaneous snapshot of RBCs after 110,000 LB time steps for a $Ca_G=0.5$ simulation in a 42.6 $\mu$m diameter vessel with $\phi=0.45$ (1,090 RBCs) (Reasor et al., 2011).

## 5.3 Platelet margination

### 5.3.1 Setup and simulations performed

The flow of suspending fluid and particles is driven by an axial body force used to mimic a constant axial pressure gradient. Therefore, the Womersley number is identically zero for all simulations. The rigid tubes used in these simulations have a diameter of 41.3 $\mu$m (124 LB units); the length of the tube is 1.45 diameters or 60 $\mu$m (180 LB units); the number of LB fluid grid points used is 2.77 million for all of the simulations. A detailed list of the simulations performed is given in Table 13 which compare the influence of the shape of rigid particles with identical volume, viscosity ratio of the internal and external fluids of the RBCs, and hematocrit. A total of 40 rigid particles are used in all simulations and are distributed with random axial locations. The initial radial locations are all chosen within $r/R \leq 0.8$ to ensure every particle has to travel a minimum distance of 4 $\mu$m outward in the radial direction to reach the tube wall and are chosen to yield statistical information for all radial locations as the particles migrate. The initial platelet locations are identical for the
three hematocrit simulations as well. The number of platelets chosen yields a greater number (by volume) than that observed physiologically and the basis for this decision was for gathering better statistics.

**Table 13:** Summary of the margination simulations performed for different hematocrit, viscosity ratios, and rigid particle shapes. The RBC capillary number based on the wall shear rate of $\dot{\gamma}_w = 355.1 \text{ sec}^{-1}$ is $Ca_G=0.271$.

<table>
<thead>
<tr>
<th>Hematocrit, $\phi$</th>
<th>RBCs</th>
<th>Rigid Particles</th>
<th>$\lambda$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.20</td>
<td>144</td>
<td>40 Platelets</td>
<td>Rigid RBCs</td>
</tr>
<tr>
<td>0.20</td>
<td>144</td>
<td>40 Platelets</td>
<td>5.0</td>
</tr>
<tr>
<td>0.20</td>
<td>144</td>
<td>40 Platelets</td>
<td>1.0</td>
</tr>
<tr>
<td>0.20</td>
<td>144</td>
<td>40 Platelets</td>
<td>0.5</td>
</tr>
<tr>
<td>0.20</td>
<td>144</td>
<td>40 Disks</td>
<td>5.0</td>
</tr>
<tr>
<td>0.20</td>
<td>144</td>
<td>40 Spheres</td>
<td>5.0</td>
</tr>
<tr>
<td>0.30</td>
<td>216</td>
<td>40 Platelets</td>
<td>5.0</td>
</tr>
<tr>
<td>0.40</td>
<td>288</td>
<td>40 Platelets</td>
<td>5.0</td>
</tr>
</tbody>
</table>

The axial body force magnitude is identical for all the simulations and the overall shear rate, $\dot{\gamma}=2U/D$ where $U$ is the centerline velocity and $D$ the tube diameter, is lower for the higher hematocrit simulations due to the corresponding increase in viscosity. The wall shear rates are identical due to the presence of the cell-depleted layer. The platelet shaped particles have a major diameter of 2.3 $\mu$m and a thickness of 1.0 $\mu$m, the disk shaped particles have a major diameter of 3.26 $\mu$m and a thickness of 0.523 $\mu$m, and the spherical shaped particles have a diameter of 1.73 $\mu$m.

Descriptive images are given in Fig. 46 to better illustrate the process of margination of a rigid platelet. This is done through highlighting a single platelet in the $\phi=0.40$ simulation. The RBCs are rendered transparent for easily visualizing the platelet of interest. As the platelet travels from its initial location, it rotates and slides between the deformable RBCs before reaching the cell-depleted layer. This particular platelet migrates from approximately 10 $\mu$m from the vessel wall in 330
μm. This is a shorter distance than average, but demonstrates the margination process observed in the simulations effectively.

![Diagram](image)

**Figure 46:** The path of an individual platelet that marginates in approximately 330 μm from its initial radial location of 10 μm from the tube wall for a simulation with φ=0.40 and λ=5. Image (a) is a view of the entire length of the tube in which the platelet travels, (b) and (c) are detailed views emphasized by the colored boxes in (a). The centerline and tube walls are indicated by the dashed and solid lines respectively. The translucent rendering of the RBCs allows for the visualization of the platelet of interest.

### 5.3.2 Radial averaging of platelet concentrations

Zhao *et al.* (2007) investigated the consequences of the radial averaging bin resolution, $w$, on platelet concentration profiles. In their experiments they used a hematocrit of φ=0.20 and three different widths for grouping platelets when presenting concentration profiles. The widths used were $w=1$ μm, 2 μm, and 5 μm. Using the finest resolution they revealed that there was a peak in the platelet concentration approximately 2 μm from the wall which was not seen in previous experiments of Aarts *et al.* (1988) that used less fidelity. In Fig. 47, a presentation of the resolution study is given with numerical results from this work for the φ=0.20 simulation with platelet-shaped
particles. What is revealed in this plot is that the peak time-averaged concentration is at 1.75 µm near the approximated peak location of 2 µm by Zhao et al. (2007). The choice of the bin width, \( w \), can clearly lead to misleading conclusions. When \( w=5 \) µm, as in the historical experiments of Aarts et al. (1988) and Eckstein & Belgacem (1991), a clear decrease in the concentration from the wall to the centerline is observed and the near-wall gap is not captured. Therefore, it is important for experiments to strive to obtain at least a 1 µm resolution during acquisition of results and performing radial averages of platelet concentrations.

![Figure 47](image.png)

**Figure 47:** Time averaged platelet concentration profiles in a tube with a diameter of 41.3 µm, \( \phi=0.20 \), with \( \lambda=5 \). Four different bin widths, \( w \), were used to compare where the local peak in concentration occurs similar to the study of Zhao et al. (2007). The peak with \( w=0.5 \) µm is at 1.75 µm from the vessel wall.

### 5.3.3 Dependence on platelet shape

In order to determine whether the shape of platelets is an important factor in margination, numerical simulations using three different shapes were performed. In these simulations the volume of the rigid particles is held constant at approximately 23 µm³. The details of the volume, axes, and moments of inertia are provided in Table 14.
The mass of the particles is chosen to be equal to the volume (in LB units) so that the density of the rigid particles is equal to that of the suspending fluid ($\rho=\rho_s=1$).

The first shape is a rigid sphere with a diameter of 3.91 $\mu$m, the second shape is an estimated platelet shape based on experimental measurements, and the third shape is a disk that was created by stretching the radius of the platelet while reducing its thickness. The sphere- and disk-shaped particles were selected as limiting cases.

**Table 14:** Volume, dimensions, and mass moments of inertia for rigid particles used in LB units.

<table>
<thead>
<tr>
<th>Particle</th>
<th>Volume</th>
<th>$(a, b, c)$</th>
<th>$I_{xx}$</th>
<th>$I_{yy}$</th>
<th>$I_{zz}$</th>
<th>$AR$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sphere</td>
<td>634</td>
<td>(5.32, 5.32, 5.32)</td>
<td>7179</td>
<td>7179</td>
<td>7179</td>
<td>1.00</td>
</tr>
<tr>
<td>Platelet</td>
<td>634</td>
<td>(7.00, 7.00, 3.10)</td>
<td>7433</td>
<td>7433</td>
<td>12429</td>
<td>2.25</td>
</tr>
<tr>
<td>Disk</td>
<td>634</td>
<td>(9.80, 9.80, 1.57)</td>
<td>12493</td>
<td>12493</td>
<td>24360</td>
<td>6.24</td>
</tr>
</tbody>
</table>

For all the shape study simulations performed the hematocrit is $\phi=0.20$ and the initial locations of the rigid particles and RBCs are nearly equal, but differ due to the difference in their size and proximity to the deformable RBCs. In Fig. 48, the average trajectories of the three simulations are given using the physiological viscosity ratio of $\lambda=5$. The aspect ratio is denoted as $AR$ in the figure where $AR_{\text{sphere}}=1$, $AR_{\text{platelet}}=2.25$, and $AR_{\text{disk}}=6.24$. This plot demonstrates that the different shapes have unique average margination rates, but confirm that all the shapes investigated experience margination. The tendency of the disk shaped particles to reach a final position against the RBCs on the edge of the cell-depleted layer, results in larger average distance-to-the-wall values than the spherical- or platelet-shaped particles. The spherical shaped particles migrate the most rapidly and the majority reach the outer layer after traveling an average distance of 6 mm.

In Figure 49 a presentation of the transition from initial radial distribution of platelet to time $t=100D/\bar{u}$ is given for the three different particle shapes. This figure, along with the average platelet trajectories in Fig. 48, give the reader a better feel for the time evolution of the margination process. The initial distributions are similar,
but not exact due to the tightly packed orientations of RBCs on the initial conditions. As the simulation progresses, spherical- and platelet-shaped particles clearly migrate more rapidly than the disk-shaped particles. The orientation of the particles once they have reached the cell-depleted layer is also interesting. The disk-shaped particles are aligned adjacent to the RBCs that form a barrier between the high hematocrit core and the cell-depleted layer. The platelet and spherical shapes interact with the vessel wall and RBCs simultaneously.

To better quantify the difference in margination due to shape, the diffusivity in the wall-normal direction, $D_{rr}$, is used (Goldsmith & Marlow, 1979). Since each platelet center is tracked, estimates of the diffusivity can be obtained using the mean-square displacements in the radial direction which are calculated via

$$\langle \Delta r^2 \rangle = \langle [r(t) - r(0)]^2 \rangle$$  \hspace{1cm} (102)
Figure 49: Temporal evolution of platelet distributions for $\phi=0.20$ for (a) spheres, (b) platelets, and (c) disk shaped particles with $\lambda=5$. At $2ut/D=200$ the platelet concentrations are labeled. The bin width for the concentration profiles is $w=1$ $\mu$m. The initial and ending end views of the tube are also given to display the distribution of platelets before and after margination.

and $D_{rr}$ is half of the slope of the $\langle \Delta r^2 \rangle$ when presented as a function of time, i.e.,

$$D_{rr} = \frac{1}{2} \frac{\partial \langle \Delta r^2 \rangle}{\partial t}.$$  \hspace{1cm} (103)

Estimates for the diffusivity of platelets has been studied experimentally (Aarts et al., 1986) as well as numerically (Zhao & Shaqfeh, 2011) to determine its dependence on shear rate. In Fig. 50, the average diffusivity of 40 platelets is plotted against time. There is an initial spike in diffusivity as the platelets accelerate from their initial state, but reach a relatively constant value as the majority of platelets migrate to the walls. Aarts et al. (1986) report diffusivity values ranging from $0.4-1.3 \times 10^{-7}$ $\text{cm}^2 \text{sec}^{-1}$ for wall shear rates of 200-1200 $\text{sec}^{-1}$. The simulations presented here with a wall shear rate of 355 $\text{sec}^{-1}$, report values in the $0.4-1.4 \times 10^{-7}$ $\text{cm}^2 \text{sec}^{-1}$ range which is the same order as those reported by Aarts et al. (1986).

The average diffusivity of all the platelets as a function of time is interesting, but single phase simulations using convection-diffusion models (Bark, 2010) rely on
diffusivity values for RBCs and platelets and additional data can only increase their accuracy. Using the radial binning procedure previously discussed, these values can be evaluated as a function of radial coordinate. Figure 51 demonstrates that there is a peak in the diffusivity near the vessel wall which is most significant for the sphere- and platelet-shaped particles. This is expected as the particles are observed to migrate rapidly toward the vessel wall once they reach the 4 μm vicinity. The two-dimensional Poiseuille flow simulations of Crowl & Fogelson (2011) report diffusivity values on the order of $10^{-6}$ cm² sec⁻¹ which is a magnitude greater than the simulations presented in this work. The platelet trajectories presented in Crowl & Fogelson (2011) also show rapid platelet margination once they get within 10 μm of the wall, but they report a drop in diffusivity as opposed to the peak values observed in the Hagen–Poiseuille simulations presented here.

Zhao & Shaqfeh (2011) performed simulations at a capillary number of $Ca_G = 0.25$
Figure 51: Wall-normal diffusivity, $D_{rr}$, of particles plotted as a function of radius for $\phi=0.20$ for spheres, platelets, and disk shaped particles with $\lambda=5$, $Re_D=6.14$, $Ca_G=0.27$, and $\dot{\gamma}_w = 355.1 \text{ sec}^{-1}$ in the 41.3 $\mu$m diameter vessel.

and are compared to the present results using the root-mean-square wall-normal velocity fluctuations and average axial velocities in Fig. 52. Their simulations were performed in a channel at $\phi=0.20$ with a height of 33.84 $\mu$m to focus on the effects of shear rate. Their results are plotted against $z/H$ instead of $r/R$. The average axial velocities for all particles are similar and agree well with the results from Zhao & Shaqfeh (2011) and don’t indicate any motion pertinent to the margination process. Of more interest are the RMS wall-normal velocity fluctuations, $\sqrt{u_{\perp}^2/\dot{\gamma}_w a}$. The present results for the model platelet shape and the results of Zhao & Shaqfeh (2011) are in relative agreement in magnitude and in trend, but a peak at a location closer to the vessel wall is observed in the present study than what was shown in their work. What is clear from the RMS wall-normal velocities is that the spherical particles experience larger fluctuations than the model platelets and thin disks especially in near the $r/R=0.7$ location (6.2 $\mu$m from the wall). Thin disks have a greater tendency to slide between RBCs allowing for lower RMS wall-normal velocities fluctuations than
the lower-aspect-ratio particles, such as spheres, that cannot easily slide between RBCs without interaction.

**Figure 52:** Averaged normalized RMS wall-normal velocities, \( \frac{\sqrt{u_\perp^2}}{\gamma_w a} \) (dashed lines), and average axial velocities, \( \frac{u_x}{\gamma_w a} \) (solid lines), for spheres, platelets, and disks in Hagen–Poiseuille flow normalized by the wall velocity scale \( \dot{\gamma}_w a \). The tube diameter is 41.3 \( \mu \)m, \( \phi=0.20, \lambda=5, \) \( Ca_G=0.27, \dot{\gamma}_w=355.1 \sec^{-1} \), and \( Re_D=6.14 \) compared to the Poiseuille flow simulations of Zhao & Shaqfeh (2011) for \( Ca_G=0.25 \).

The shear stress experienced by the platelets as they marginate from locations in the core region to the cell-depleted wall layer is of interest for the application of platelet shear-stress history and its relation to activation and adhesion. The average shear stress, \( \bar{\tau}/\mu \dot{\gamma}_w \), and maximum average shear stress, \( \bar{\tau}_{\text{max}}/\mu \dot{\gamma}_w \), profiles are given in Fig. 53. The average shear stress of the spherical particles is greater than that of the platelet- and disk-shaped particles as seen in (a) which is primarily due to the large maximum shear stresses experienced by these particles seen in (b). Since the spherical particles cannot slide easily between RBCs, there are larger shear stresses experienced as they marginate from the core to the cell-depleted layer. The disk shaped particles have the lowest average shear stress due to their tendency to slide between RBCs as they marginate. The maximum shear stress plot reveals peaks in
the shear stress for the disk shaped particles due to their tendency to flip as they move toward the wall. The maximum shear stress near the wall is greatest for the spherical particles because they continuously interact with the vessel wall and the RBCs at the edge of the cell-depleted layer. The platelet-shaped particles can align adjacent to the RBCs without interacting with the wall, but also undergo flipping motions as well.

**Figure 53:** Averaged platelet (a) shear stress, $\bar{\tau}/\mu\dot{\gamma}_w$ and (b) average maximum shear stress, $\bar{\tau}_{\text{max}}/\mu\dot{\gamma}_w$, profiles for three shapes in Hagen–Poiseuille flow. The tube diameter is 41.3 μm, $\phi=0.20$, $\lambda=5$, $Ca_G=0.27$, $\dot{\gamma}_w=355.1$ sec$^{-1}$, and $Re_D=6.14$.

The ensemble averaged hematocrit, $\langle \phi \rangle$, and normalized axial velocity, $\langle u_x \rangle/U$, profiles for the fluid phase are given in Fig. 54 for the present simulations. The hematocrit profiles are largely unaltered by the different particle shapes, but the peak location near the $r/R=0.7$ location resembles the volume exclusion effect (Nott & Brady, 1994) seen in Stokesian dynamics simulations. Simulations using the LB-FE method that did not allow for RBC tank treading resulted in peak locations closer to the wall and the RBCs were observed to slide against the vessel wall instead of migrating toward the core of the vessel. This peak location of hematocrit is at roughly the same location where the peaks in RMS wall-normal velocity of the particles are observed. The peak in hematocrit at this location is due to the formation of a
“barrier” of RBCs that have migrated away from the wall to form the cell-depleted layer. The peaks observed are likely due to the platelet particles interacting with this barrier. The axial velocity profiles demonstrate the degree of blunting due to the $\phi=0.20$ concentration of RBCs.

Figure 54: Ensemble averaged hematocrit (a) and axial velocity (b) profiles for simulations with rigid spheres, platelets, and disks in Hagen–Poiseuille flow. The tube diameter is 41.3 $\mu$m, $\phi=0.20$, $\lambda=5$, $Ca_G=0.27$, $\dot{\gamma}_w=355.1$ sec$^{-1}$, and $Re_D=6.14$.

5.3.4 Dependence on hematocrit

One of the most commonly studied parameters in the margination process is hematocrit. It is commonly observed that a larger percentage of platelets will marginate at realistic hematocrit levels than at reduced values. In Fig. 55, the average platelet trajectories for the $\phi=0.20$, 0.30, and 0.40 simulations are given for a physiological viscosity ratio of $\lambda=5$. In these simulations, the axial body force used is identical which results in identical wall shear rates, but a reduction in flow rate as the hematocrit is increased. Emphasized in the figure, the rate of margination is increased with increasing hematocrit. For the physiological hematocrit of $\phi=0.40$ nearly all the platelets have marginated after traveling only 3 mm whereas the $\phi=0.20$ takes over 8 mm to achieve the same result. The difference in slope of these results highlights
the increase in margination rate for the same axial pressure gradient.

Figure 55: Average platelet trajectories for three hematocrit values Hagen–Poiseuille flow. The tube diameter is \( 41.3 \, \mu m \), \( \phi = 0.20, 0.30, \& 0.40 \) for these simulations with \( \lambda = 5 \), \( Ca_G = 0.27 \), and \( \dot{\gamma} = 355.1 \, \text{sec}^{-1} \).

The time evolution of the platelet distributions is given in Fig. 56. In this figure, the time scaling \( t = 100D/\bar{u} \) results in similar distributions at the individual times observed. However, the distance required for the majority of platelets to marginate for the realistic hematocrit is less than the reduced value as demonstrated in Fig. 55. The flow rate is reduced due to the strong relative viscosity dependence on \( \phi \), demonstrated in Fig. 57. Of interest in the application to platelet shear stress accumulation and adhesion is the location of the particles once they reach the cell-depleted layer. It is notably different for the \( \phi = 0.40 \) than the \( \phi = 0.20 \) case. For the \( \phi = 0.40 \) case, the final location is closer to the vessel wall due to the reduced cell-depleted layer thickness and the platelets align themselves so that their minimum dimension (thickness coordinate) is aligned with the radial coordinate. This maximizes the surface area subjected to the wall shear stress, \( \mu \dot{\gamma}_w \), adjacent to the vessel wall.

The average wall-normal diffusivity for the three hematocrit values is given in
Figure 56: Temporal evolution of platelet distributions for (a) $\phi=0.40$, (b) $\phi=0.30$, and (c) $\phi=0.20$ for platelet shaped particles with $\lambda=5$. At $2\bar{u}t/D=200$ the platelet concentrations are labeled. The bin width for the concentration profiles is $w=1$ $\mu$m. The initial and ending end views of the tube are also given to display the distribution of platelets before and after margination.

Figure 57: Ensemble averaged relative viscosity, $\langle \mu_r \rangle$ plotted versus hematocrit, $\phi$, for the three hematocrit values simulated with $\lambda=5$, $C_{\alpha G}=0.27$, and $\dot{\gamma}_w = 355.1$ sec$^{-1}$ in a 41.3 $\mu$m diameter tube in Hagen–Poiseuille flow compared to the results of Reinke et al. (1986) for a 41 $\mu$m tube and Pries et al. (1996) for a 41.3 $\mu$m diameter tube.
As expected, there is an increase in $D_{rr}$ with increasing $\phi$ and the magnitude between the $\phi=0.20$ and $\phi=0.40$ but are still on the same order. Initial transients result in the largest diffusivity values and the simulations approach a final value as the majority of the platelets have reached a final marginated state by five seconds. The radial distribution of wall-normal diffusivity, $D_{rr}$, is given in Fig. 59 for the three hematocrit values simulated. Increasing the hematocrit reduces the cell-depleted layer thickness at the same wall shear rate. The largest diffusivity values are observed near the cell-depleted layer location. Notably, the largest peak in diffusivity is for the $\phi=0.40$ case which is much greater than $\phi=0.20$ and 0.30 and the location of peak is observed closer to the wall as well.

![Graph of $D_{rr}$ against time](image)

**Figure 58:** Temporal evolution of the average $D_{rr}$ of 40 platelets for $\phi=0.20$, 0.30, and 0.40 in a 41.3 μm diameter vessel with $\lambda=5$, $Ca_G=0.27$, and $\dot{\gamma}_w = 355.1$ sec$^{-1}$.

A significant difference in the RMS wall-normal velocity fluctuations, $\sqrt{u_\perp^2}/\dot{\gamma}_w a$, was demonstrated for the three shapes simulated. However, when examined for different hematocrit levels in Fig. 60, a noticeable trend is not apparent. The axial
velocities of the platelets in the $\phi=0.40$ case is considerably lower due to the increased viscosity. This leads to the $\phi=0.40$ case having the lowest $\sqrt{u_\perp^2/\dot{\gamma}_w a}$ values in the vessel core. The three simulations are in relative agreement for $r/R>0.8$ and the hematocrit does not seem to be a significant factor driving the magnitude of velocity fluctuations.

The average and maximum average shear stress profiles for the three hematocrit values are given in Fig. 61. The average shear stress remains relatively unchanged as the increase in interactions for the $\phi=0.40$ case is counteracted by the reduction in shear rate due to the elevated hematocrit. The $\tau^{\text{max}}/\mu\dot{\gamma}_w$ profile emphasizes the effect of inter-particle forces on the shear stress. Due to the doubling of the hematocrit, a strong increase in the average maximum shear stress experienced by the platelets is observed. The increase in the number of RBC-platelet interactions is thought to be one of the dominant factors that margination is more pronounced with higher hematocrit levels and these results indicate that the interactions at higher hematocrit

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure59.png}
\caption{Wall-normal diffusivity, $D_{rr}$, profiles plotted as a function of radius for $\phi=0.20$, 0.30, and 0.40 platelets in 41.3 $\mu$m diameter vessel with $\lambda=5$, $Ca_G=0.27$, and $\dot{\gamma}_w = 355.1$ $\text{sec}^{-1}$.}
\end{figure}
Figure 60: Normalized RMS wall-normal velocities, $\sqrt{u_{\perp}^2}/\gamma_w a$, for platelets in Hagen–Poiseuille flow for $\phi=0.20$, 0.30, & 0.40. Tube diameter is 41.3 µm, $\lambda=5$, $Ca_G=0.27$, and $\dot{\gamma}_w = 355.1$ sec$^{-1}$ compared to the Poiseuille flow simulations of Zhao & Shaqfeh (2011).

levels result in higher maximum average shear stresses.

The ensemble averaged hematocrit, $\langle \phi \rangle$, and axial velocity, $\langle u_x \rangle/U$ of the fluid phase are given in Fig. 62. It is clear that the increase in $\phi$ causes the peak near the cell-depleted layer to become more pronounced for the realistic $\phi=0.40$ than that for the $\phi=0.20$ value. The peak location is also pushed closer to the vessel wall and causes the reduced cell-depleted layer thickness. The velocity profile reveals that the degree of blunting is more severe as the hematocrit is increased.

In the presence of significant concentrations of the glycoprotein, Von Willebrand factor (VWF), platelets have shown to form aggregates that attach to vessel walls called platelet strings (Dong et al., 2002; Bernardo et al., 2004; Nolasco et al., 2005; Huang et al., 2009). This research does not focus on effects due to adhesive forces, but observed in the simulations with $\phi=0.40$ were platelets aligning in these train like formations (as seen in Fig. 63) in the cell-depleted layer. The formation of such a
Figure 61: Averaged platelet (a) shear stress, $\bar{\tau}/\mu\dot{\gamma}_w$ and (b) average maximum shear stress, $\bar{\tau}_{\max}/\mu\dot{\gamma}_w$, profiles for three hematocrit levels in Hagen–Poiseuille flow. The tube diameter is 41.3 $\mu$m, $\phi=0.20$, 0.30, & 0.40 with $\lambda=5$.

Figure 62: Ensemble averaged (a) hematocrit and (b) axial velocity profiles for three initial hematocrit values in Hagen–Poiseuille flow. The tube diameter is 40.6 $\mu$m, $\phi=0.20$, 0.30, & 0.40 with $\lambda=5$.
string without the presence of adhesive forces could be coincidental, but shows that platelets have somewhat of a preference for aligning in these structures in the cell-depleted layer with only inter-particle and hydrodynamic forces considered. Notably, this train-like formation is minimal drag configuration.

![Image of platelets forming a string](image)

**Figure 63:** Multiple strings of platelets are observed in the simulations containing as many as seven platelets. The tube diameter is 41.3 µm, φ=0.40, and λ= 5.

### 5.3.5 Dependence on viscosity ratio

The ratio of the interior fluid of the RBC membrane to that of the suspending fluid, λ, is an important dimensionless parameter in RBC dynamics. As λ decreases, the shear rate ˙γ where tank treading is observed also decreases. Therefore, by decreasing λ the number of RBCs in Hagen–Poiseuille flow undergoing tank-treading motion is increased. By comparing the results for multiple values of λ its importance in the margination process can be determined.

For φ=0.20, numerical experiments for λ= 0.5, 1, 5, and with rigid RBCs have been performed. Rigid RBCs are restricted to tumbling motion, i.e., cannot tank tread. The average trajectories of the platelets for the three values of λ are given in Fig. 64. This figure displays that λ is a major factor in the rate of margination. This figure emphasizes that lower viscosity ratios increase the rate of margination. Zhao *et al.* (2007) showed that a higher volume of platelets accumulated near the wall when the suspending fluid viscosity was increased. Many experiments are performed
in viscous solutions containing dextran where $\lambda \leq 1$. In these instances, more RBCs are tank treading and the present results imply that this will demonstrate enhanced margination than what would be observed in vivo and may not be representative of physiological conditions at comparable shear rates. The time evolution of the platelet concentration distributions are given in Fig. 65. The simulations with $\lambda = 0.5$ and 1 clearly exhibit margination more rapidly than the $\lambda = 5$ case. The case with rigid RBCs shows some spreading of the initial distribution, but the platelets cannot settle adjacent to the wall because, without RBC deformation, there lacks a clearly defined cell-depleted wall layer.

By decreasing the viscosity ratio, $\lambda$, the wall-normal diffusivity, $D_{rr}$, is increased significantly. Figure 66 demonstrates the time history of the average $D_{rr}$ values of the 40 platelets for the four simulations performed. The initial $D_{rr}$ values for $\lambda = 0.5$ and 1 are much greater than that for the rigid RBCs or for $\lambda = 5$. Peak values for $\lambda = 0.5$ and 1 reach $D_{rr}$ values of approximately $2.25 \times 10^{-7}$ cm$^2$ sec$^{-1}$ whereas $\lambda = 5$ reaches peak
Figure 65: Temporal evolution of platelet distributions for $\phi=0.20$ for (a) $\lambda=0.5$, (b) $\lambda=1$, (c) $\lambda=5$, and (d) rigid RBCs with platelet shaped particles. At $2\bar{u}t/D=200$ the platelet concentrations are labeled. The bin width for the concentration profiles is $w=1\ \mu m$. The end views of the tube are also given to display the distribution of platelets before, $t=0$, and after margination, $t = 100D/\bar{u}$.
values of approximately $1.25 \times 10^{-7}$ cm$^2$ sec$^{-1}$. The overall increase in the diffusivity values are due to the dramatic increase in the region of high shear within 10 µm from the tube wall as seen in Fig. 67. The tumbling to tank treading transition is extremely sensitive to $\lambda$. As an RBC is tank treading, it has a tendency to push a platelet downward (Crowl & Fogelson, 2011) or, in the present configuration, toward the wall. This tendency explains the dramatic increase in diffusivity in the high shear rate region that ultimately leads to an overall increased diffusivity value. Not only are the peak values larger for the reduced $\lambda$ values, but the width of the elevated diffusivity region is wider. This increase in width is due to a larger portion of the RBCs undergoing tank-treading motions, for the reduced $\lambda$ cases, near the wall.

Figure 66: Temporal evolution of the average $D_{rr}$ of 40 platelets for $\phi=0.20$ with rigid RBCs, $\lambda=5$, 1, and 0.5 in the 41.3 µm diameter vessel.

The RMS wall-normal velocities, $\sqrt{\bar{u}_\perp^2 / \dot{\gamma}_w a}$ are given in Fig. 68. The case with rigid RBCs exhibits elevated levels of $\sqrt{\bar{u}_\perp^2}$ which is not surprising due to the increased rigidity of RBCs resulting in stiffer inter-particle forces. However, the cases with $\lambda=0.5$ and 1 have a peak in $\sqrt{\bar{u}_\perp^2}$ at $r/R \approx 0.65$ and an increase from the $\lambda=5$ case.
Figure 67: Wall-normal diffusivity, $D_{rr}$, profiles plotted as a function of radius for $\phi=0.20$ with platelets with rigid RBCs, $\lambda=5$, 1, and 0.5 in the 41.3 $\mu$m diameter vessel.

at all $r/R$ values. This indicates the difference in interactions between RBCs and platelets due to changes in $\lambda$ is a determining factor in the margination process. When RBCs are tumbling, the interactions are less likely to have a preferred direction due to their random nature as opposed to the wall-normal direction during tank treading.

The average shear stress and maximum average shear stress profiles for the three viscosity ratios and with rigid RBCs are given in Fig. 69. Again, the hydrodynamic interactions drive the average shear stress profile, but the difference in dynamics of the RBCs alters the average maximum shear stress experienced by the platelets which is indicated by the rigid RBC case demonstrating larger magnitudes for nearly the entire range of $r/R$. Near the vessel center, the difference between all the simulations is less evident as RBCs will be tumbling due to the low shear rates at those locations. The rigid RBCs increase the maximum shear stress due to their lack of deformability, but the difference in shear stress due to different viscosity ratios is inconclusive.

The ensemble-averaged hematocrit, $\langle \phi \rangle$, profile in Fig. 70 reveals a slight inward
Figure 68: RMS wall normal velocities, $\sqrt{\frac{\overline{u^2}}{\gamma_w a}}$, for platelets in Hagen–Poiseuille flow for $\lambda = 0.5, 1, 5$ and with rigid RBCs. The tube diameter is 41.3 µm, $\lambda = 5$, and $Re_D = 7.32$ compared to the Poiseuille flow simulations of Zhao & Shaqfeh (2011).

Figure 69: Averaged platelet (a) shear stress, $\overline{\tau}/\mu \dot{\gamma}_w$, and (b) average maximum shear stress, $\overline{\tau}_{max}/\mu \dot{\gamma}_w$, profiles for three viscosity ratios in Hagen–Poiseuille flow. The tube diameter is 41.3 µm, $\phi = 0.20$, and $\lambda = 0.5, 5$, and with rigid RBCs.
shift in the peak hematocrit location for $\lambda=0.5$ from the location for $\lambda=5$, but the $\langle u_x \rangle/U$, profile seems unaffected by viscosity ratio for $\phi=0.20$. The shift in peak hematocrit corresponds to a larger cell-depleted layer. This phenomenon was observed for changes in $\lambda$ for dilute flows of RBCs in the experiments of Sakai et al. (2009).

**Figure 70:** Ensemble averaged (a) hematocrit and (b) axial velocity profiles for three viscosity ratios in Hagen–Poiseuille flow. The tube diameter is $41.3 \mu m$, $\phi=0.20$, and $\lambda=0.5, 5$, and with rigid RBCs.

### 5.4 Discussion

Using the LB-SL method a demonstration of the ability to simulate flows through microvessel-sized tubes at realistic hematocrit levels has been presented. A demonstration of the ability to monitor cell-depleted wall layer thickness values in agreement with Freund & Orescanin (2011) for a $11.3 \mu m$ diameter vessel was presented. The viscosity dependence on tube diameter was presented for $\phi=0.30$ in tubes ranging from $11.3-41.3 \mu m$ diameters demonstrating the Fåhraeus–Linqvist effect.

Numerical investigations of platelet margination are in their infancy. Those that have been performed previously are either two-dimensional in nature or focus on the effect of shear rate. This work is the first to quantify the effects of platelet morphology and viscosity ratio on the margination process in a rigid $41.3 \mu m$ vessel. The shape of
the particle was determined to be an influential factor in the margination process with spherical particles, platelets, and thin disks of the same volume. The wall-normal velocity fluctuations and diffusivity were notably larger for the spherical particles than for the disk- and platelet-shaped particles. The average rate of margination increases with the increase of hematocrit for the \( \phi = 0.20, 0.30 \) and \( 0.40 \) values simulated. The orientation of marginated platelets is determined by the thickness of the cell-depleted wall layer. The effects of the viscosity ratio are also extremely apparent in studies of RBC dynamics in shear and it has been shown that these dynamics are also paramount in characterizing the process of margination. The tendency for platelets to be forced in the wall-normal direction when interacting with tank-treading RBCs led to a dramatic increase in wall-normal velocity fluctuations and diffusivity for \( \lambda = 0.5 \) and 1.

These simulations were performed for a fixed tube diameter, but the results could be extended for larger vessels. The diffusivity in the core region, where low shear rates are observed, should be similar for larger vessels and the rate of margination in high shear rate regions near the wall should also behave similarly. However, the distance needed for a platelet to marginate an average of 8 \( \mu \)m was roughly five seconds in the small vessels simulated here. For larger tubes, this would increase significantly due to the larger low shear regions and larger radial distances.
CHAPTER VI

CONCLUSIONS AND RECOMMENDATIONS

Understanding the physics of blood as it flows through small vessels has always been a goal of the scientific and medical communities. Even with the technology available today, the opaque nature of blood makes probing for certain flow properties difficult. Great strides have been made in the experimental field that allow for the monitoring of flow fields in complex geometries such as mechanical heart valves or for measuring the growth of thrombi due to the accumulation of platelets. As the use of artificial devices in medicine continues to grow, their impact on the blood needs to be better understood. The advancement of robust and high fidelity numerical tools will continue to aid experiments in the design and analysis phases of implant development.

The computational framework of the code used in this study began with the work of Robert MacMeccan (MacMeccan, 2007; MacMeccan et al., 2009) in which the LB method was coupled with a linear FE method for the simulation of hundreds of deformable capsules and RBCs in bounded and unbounded shear configurations. The methodology for computing fluid-structure interaction problems with the standard bounce-back operation was documented in MacMeccan (2007), MacMeccan et al. (2009), & Clausen (2010). Jonathan Clausen, who co-developed the implementation of MacMeccan et al. (2009), modularized the code so that additional fluid, particle, and contact models could be added without widespread modifications. Afterward, Clausen et al. (2010) extended the LB-FE method for use on distributed memory architectures and the performance was documented on the world-class IBM BG/P supercomputer (Intrepid) at Argonne National Laboratory. The distributed memory parallelization with MPI was urgently needed so that larger problems could be
simulated and to reduce the amount of lead time for sets of simulations analyzing specific parameter spaces, e.g., hematocrit and $Ca_G$. The implementation of checkpoint/restart capabilities was added so that simulations could be performed on supercomputing resources available on the National Science Foundation’s TeraGrid network where run times are limited to twenty-four hours or less.

The modular organization of the code allows for the implementation of additional deformable particle models with minimal rewriting or custom development. This work demonstrated that the LB-SL method is capable for simulating cellular blood in numerous configurations and at larger shear rates than the LB-FE method. The SL method has demonstrated the capability to capture tank-treading motions and parachuting deformations that the FE method failed to resolve. The SL membrane model was implemented alongside of the FE and rigid-body solver so that multiple particle models can be simulated simultaneously. The SL implementation leverages the MPI communication scheme originally developed for the LB-FE method with few additions for specific arrays needed for the SL membrane model and for post-processing. These additions did not significantly alter the MPI communication cost. Several versions of the code exist and are managed using Git (Hamano et al., 2011). Current research is underway on a separate branch of the code using the entropic lattice-Boltzmann method (Vahala et al., 2008) with the EBF fluid-solid coupling from Wu & Aidun (2009, 2010) to monitor the accumulation of shear stress on platelets through bileaflet mechanical heart valves as an extension of earlier work (Wu et al., 2010). This method, used in conjunction with the SL membrane model, could feasibly reduce the computational requirements while simultaneously increasing accuracy. The strides made in documentation via Doxygen (van Heesch, 2009), organization, and version control of this tool have shown to be extremely useful for the continuous development and improvement for multiple researchers studying numerous applications.
A detailed study of the rheology of blood has been presented for reduced and realistic hematocrit levels. The literature pertaining to the viscosity of blood in numerous flow conditions exists thanks to a century of experimental investigations, but numerical methods and computational resources have just recently reached the level to make direct numerical simulations feasible. The results presented in this work are in good agreement with rotational viscometer experimental measurements, at realistic hematocrit levels, for shear rates as high as 440 sec$^{-1}$. The shear-thinning characteristic, associated with the non-Newtonian behavior of blood, was also presented. Simulation results characterizing the strong dependence of blood viscosity on hematocrit were also presented. The inter-particle forces, that enforce a finite gap, lead to a slight under prediction in viscosity, but within 10% of experimental observations. The particle-phase normal stress tensor has been previously investigated for rigid and deformable spherical capsules. But until this work, has not been reported for cellular blood simulations at realistic hematocrit levels. The particle-phase pressure was observed to undergo a sign change as the normal stress contribution in the flow direction exceeded the applied shear stress in the suspending fluid.

High blood viscosity is a common characteristic in patients with cardiovascular disease. The alignment of RBCs with the flow direction was shown to cause a reduction in viscosity in the unbounded shear simulations presented in this work. By increasing the bending energy of RBCs, alignment was enhanced at low shear rates. The LB-SL method can be used quantify the reduction in viscosity due to RBC alignment in specific geometries by using different initial orientations of RBCs and platelets. In cases (Tao & Huang, 2011) where RBCs are manipulated into short “chains” of aggregates, aligned with the flow, blood viscosity can be reduced as much as 20% for several minutes in small vessels like those simulated in this work. The development of experimental methods and clinical procedures, that exploit this phenomenon, could improve the treatment of patients with disorders like hyperviscosity syndrome.
The capability to simulate different RBC interior and suspending fluid viscosities can be leveraged to quantify the effects of adding substances, such as dextran or compound sodium lactate, to blood plasma. Reductions in blood flow rates, due to increased suspending fluid viscosities, can be studied using the LB-SL to quantify its influence in the hemostatic system. Increased plasma viscosities have been observed (Lowe et al., 1991) in patients with high blood pressure and high cholesterol which typically experience reduced circulation. Furthermore, patients with unstable angina pectoris with plasma viscosities greater than 1.38 cP were at significant risk for myocardial infarctions (Neumann et al., 1991). The shear-stress environment of RBCs and platelets, immersed in fluids with larger suspending viscosities than normal plasma, can be quantified through numerical simulations. More specifically, increases in shear stress on individual platelets can be monitored in LB-SL simulations to determine if activation is more likely in viscous solutions at realistic hematocrit levels.

Three critical factors in the platelet margination process were revealed to be hematocrit, platelet shape, and the viscosity ratio between the internal fluid of the RBC to the suspending fluid. Experimental studies in margination have focused on determining these factors and the computation community has recently shown increased interest in this area. An increase in platelet margination rate with increasing hematocrit was observed which was expected from experimental observations. The investigation of platelet shape demonstrates that spherical particles marginate more rapidly to the vessel wall than ellipsoidal-shaped particles and thin disks, and has not been demonstrated previously. Also, by reducing the viscosity ratio, and therefore changing the dynamics of the RBCs at identical shear rates, the rate of margination was increased when comparing to the physiological ratio of $\lambda=5$. The experimental study of Zhao et al. (2007) showed that a higher volume of platelets accumulated near the wall, consistent with the observations of this work, but the rate of margination was not monitored due to the lack of appropriate methods for tracking platelet trajectories in
whole blood.

Based on the results obtained for the 41.3 µm diameter vessel simulations, and assuming the rate of margination is similar in large vessels, the required distance for the majority of platelets to migrate to the vessel wall can be estimated. Assuming the rate of margination is consistent for a wall shear rate of approximately 350 sec$^{-1}$, the estimated distance required for the majority of platelets to marginate in a 1 mm diameter tube with $\phi=0.40$ would be approximately 100 mm. A reduced hematocrit value of $\phi=0.20$ would yield a longer distance of approximately 250 mm. These estimates can be used to approximate the length of tube needed for experimental studies that want to determine the effect of stents on platelets that have already reached a marginated state. Using higher viscosity suspending fluids or spherical latex beads will reduce these length estimates while disk-shaped particles would increase them.

The platelet shaped particles were observed to migrate to the high-shear, low-velocity regions of the vessel near the wall. In more complex geometries, such as implants with geometry in the center of the vessel, high concentrations are not likely to be found in the center due to their tendency to marginate to the lower velocity regions near walls. However, complex geometries near the vessel walls, such as the hinge regions in a bileaflet mechanical valve, would likely encounter large concentrations of platelets. Since these areas also experience large shear stresses, platelets would likely activate and accumulate on those surfaces. This is observed clinically and the major complications from this accumulation are commonly associated with hemolysis, platelet destruction, and thromboembolic events arising from clot formation and detachment. Currently, anticoagulation therapy is required to counteract these events, but further knowledge of the margination process, describing how platelets reach these locations, is of great value. Modification of the flow via placement of small vortex generator arrays (Murphy et al., 2010) on leaflet surfaces reduce thrombin-antithrombin
III levels that are used to quantify thrombus formation. While not scalable to the full geometry of a bileaflet valve, the LB-SL method can be used to determine if wall geometry modifications are an effective means in preventing margination and, in the case of the valve hinge regions, the formation of clots.

Using the LB-SL method to model an exact experimental apparatus for measuring platelet margination for specific analogue shapes, flow rates, and hematocrit values would be a natural transition from the current work. The parameter space in the process of platelet margination is vast and continued research in this field will allow for better understanding of the processes that lead to the formation of thrombi. The addition of platelet adhesion, similar to the Morse potential contact, could be implemented easily and used to model the formation and growth of thrombi. The effect of implants, such as stents, on margination could also be analyzed in detail using the LB-SL method. Due to the computational requirements of a vessel large enough for stent implantation, a clear definition of the problem would be needed. Simulations in these vessels, those with a 500 μm diameter or larger, would require in excess of 300,000 RBCs and a minimum of 8,192 computational cores.

The implementation of the SL RBC membrane model into the distributed memory parallelization scheme developed by Clausen et al. (2010) demonstrates that the method is not only robust and capable of capturing continuum-level physics, but can scale to thousands of computational cores. As the availability of large computing resources becomes more readily available, this method has the capability to scale to problems of more applied significance such as the flow through hinge regions in mechanical heart valves or the formation of thrombi. In 2007, when the LB-FE code was in its infancy, a suspension containing 100 deformable particles was considered state-of-the-art. The parallelization study of the Aidun group (Clausen et al., 2010) stood as the largest simulation of deformable particles with approximately 200,000 capsules until the recent work of Rahimian et al. (2010). The parallelization scheme for the
LB fluid phase is in a nearly optimal state from a scaling standpoint, but core-level optimization to better manage the memory hierarchy could reduce cache misses and improve FLOPS performance. Developing a tool capable of performing simulations on thousands of cores is a daunting task that has been tackled to a great extent, but managing the output from such simulations is just as important. Future work in the development of robust and adjustable parallel input/output schemes will increase the capability for running larger simulations as resources become available. The EBF method for fluid-solid coupling shows promise for reducing the largest computational expense in the method. If trends in computing resources continue to emphasize multi-core CPUs and with installations currently growing to petaFLOP capabilities, the continuous development of this method will soon allow for simulations mimicking the larger geometries investigated in clinical studies. The relationship formed by the Aidun group with the National Science Foundation’s TeraGrid network will allow for future improvements and continuous development on world-class supercomputing resources.
REFERENCES


