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Cell resolved blood flow modeling with the Lattice Boltzmann method

Cell deformability and transport in diseases

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1

Introduction

The central motivation of this thesis is to understand the rheology of whole blood as a consequence of its cellular components across multiple scales. This is studied through the development and application of numerical blood flow models aimed at understanding the flow and transport of cells that make up blood. Four specific cases are explored, each probing the current understanding of the cellular nature of whole blood, and in some cases, how it may change when impinged by disease. The cases are: the rigidification of healthy deformable red blood cells, the flow and transport of cells into microaneurysms in the retina, the time dependence of blood flow and cell transportation in larger scale idealized aneurysms, and finally the exploration of the suspension nature of whole blood on vessel scales that have long been considered continuous.

The discovery and understanding of the phenomena associated with flowing blood have historically developed with technology. Therefore, paired with the central focus of this thesis is the development of numerical blood flow models. The correct, accurate, and efficient design of whole blood computational models is crucial for improving the understanding of hemorheology. Throughout this thesis cases are given which have elucidated and tested the limitations of contemporary blood flow models. This has led to an initial development of a new multiscale model for whole blood which may bring the cell nature of flowing whole blood up to previously unexplored scales.

1.1. Physiology of Blood

Blood performs three major functions in the human body: transportation, protection, and regulation [1]. Blood transports oxygen and carbon dioxide between the lungs and rest of the body, as well as providing nutrients to and collecting waste from the tissues of the body. It protects from invading micro-organisms and pathogens, as well as initiating normal coagulation function to minimize blood loss. Finally blood regulates the water and pH balance of the body.

Whole blood is made up of plasma (a watery solution of electrolytes, plasma proteins, carbohydrates, and lipids), red blood cells (erythrocytes), white blood cells (leuko-

cytes, i.e. granulocytes, lymphocytes, and monocytes), and platelets (thrombocytes) [2]. Human red blood cells (RBCs), have a bi-concave disk shape with a major diameter of approximately $8\ \mu\text{m}$ and a thickness of approximately $2\ \mu\text{m}$ [1], are by far the most numerous population of cells in blood with a normal volume fraction or hematocrit of 45% in adult men and 40% in adult women [1]. White blood cell (WBC) and platelet populations are much less in comparison to RBCs in whole blood. This is about 1000 RBCs to 1 WBC and 15 RBCs to every 1 platelet [3, 4]. Platelets have a disk like shape with a diameter of $2\text{-}3\ \mu\text{m}$ and a thickness of $\approx 0.5\ \mu\text{m}$ [5]. The size and relative volume fraction of each cell type is given in Figure 1.1. Note that leukocytes span a broad diameter range from as small as 9 microns in some lymphocytes to much larger diameters exhibited by monocytes. The average diameter of the most abundant white blood cell, the neutrophil, is reported in Figure 1.1.

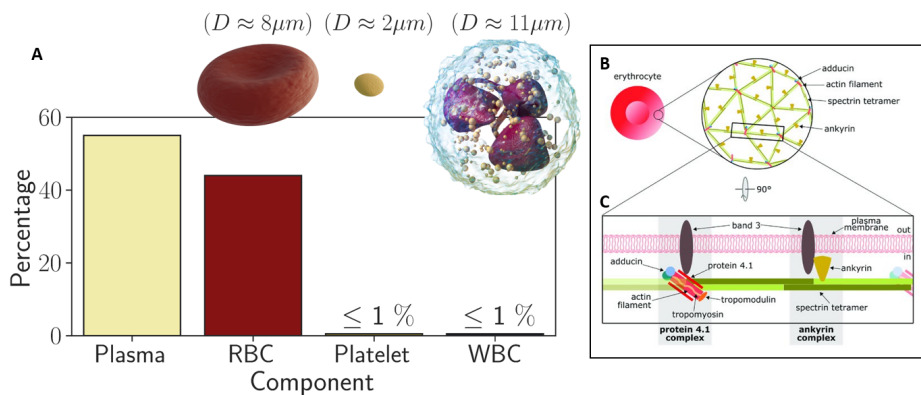


Figure 1.1: Components of whole blood and schematic of red blood cell membrane [6]. The left panel shows the relative volume fraction of each component of blood along with the average size of the most common blood cells. The right panel highlights the structure of the red blood cell membrane.

Since RBCs have the greatest volume fraction of any of the blood cells they greatly influence the resulting flow dynamics of whole blood [7] and provide the crucial transport of oxygen to and collection of waste products from the body tissues. The dynamics of a single RBC play an important role of the distribution of oxygen and the collection of waste in the small capillaries of the body. The deformability allows the red blood cell to squeeze into very small slits, $\approx 1.2\ \mu\text{m}$, in the circulatory system like those found in the spleen [8]. The membrane of a RBC is composed of an outer lipid bilayer that is lined by a spectrin mesh-like network of cytoskeleton proteins [9, 10], both face and side views of the schematic of the RBC membrane is shown in panels (b) and (c) of Figure 1.1. The mechanics of the RBC are largely determined by the compression response of cytoskeletal spectrin network parallel to the membrane surface [11]. The perpendicular interaction of cytoskeleton and integral trans-membrane complexes which is accomplished by ankyrin, in turn provides bending rigidity [12]. Other effects such as the hydration state, surface to volume interactions, and metabolic processes also contribute, to a lesser ex-

tent, to the overall RBC mechanics. The interior of the RBC contains hemoglobin at high concentration which is essential for transferring oxygen, and additionally behaves mechanically as an incompressible fluid with a viscosity of 0.07 Pa [13, 14]. As the interior viscosity of the RBC is significantly more viscous than the suspending plasma, which has ≈ 0.012 Pa, this viscosity contrast contributes to the overall mechanical response to perturbations to the RBC [15]. The highly deformable membrane allows the RBC to change its shape due to external forces, and return to its biconcave shape after relaxation [16]. The deformability of the RBC allows it to squeeze through the smallest capillaries of the body to successfully deliver oxygen to the tissues of the body [17].

1.2. Rheology of Blood

A Newtonian fluid, for instance water, is a fluid that displays a linear relationship between shear stress and shear rate. In other words the viscosity of a Newtonian fluid is independent of shear rate [18]. The rheology of whole blood, which is a complex suspension of cells, is highly dependent on its cellular components, mostly on the RBCs. The high deformability and unique bi-concave shape of RBCs gives rise to many hallmark, non-Newtonian effects of whole blood. For example the decrease of viscosity with an increase in shear [19], and the decrease in apparent viscosity with decreasing vessel radius, the so called the Fåhræus-Lindqvist effect [20].

The dynamics of a single RBC is important because the motion and deformability give rise to the bulk flow properties of whole blood. It is generally known that three separate dynamical regimes exist when a single RBC is in a uniform shear flow environment. At low shear rates the RBC tumbles, maintaining its bi-concave shape flipping end over end in shear flow with a tumbling [21, 22] motion. As shear rates increase, the dynamics of the RBC enters an intermediate regime that is a swinging state [23]. And above a shear rate threshold [24, 25] the RBC membrane deforms and crosses over into a tank treading [26, 27] motion. Here the cell is no longer bi-concave but maintains a consistent shape with the cytoskeleton rotating like the treads of a tank.

Bulk blood viscosity is dependent on five major physiological properties; fibrinogen concentration in plasma [28], the volume fraction of RBCs also called the hematocrit [29], vessel radius [30], flow velocity [31], and temperature [32]. In the larger arteries, the human vasculature spans sizes from millimeters to centimeters and blood viscosity in these ranges has been found to be independent of vessel diameter [1]. Shear thinning, in the absence of vessel wall effects, was famously observed by Chien in 1966 [33], where whole blood viscosity increased at shear rates lower than $10s^{-1}$, which has since been attributed to the viscoelasticity of whole blood [34, 35]. This is caused primarily by the congregation of columns of RBCs forming rouleux structures [36–39], which has been shown to be induced by the plasma proteins like fibrinogen [40]. When shear rate increases the aggregates break up and additionally align in flow [41, 42] which results in the decrease of the bulk viscosity [43]. The experimental finding from Chien [13] along with a numerical fit to the data [44] is shown in panel (a) of Figure 1.2.

Shear thinning also comes in a different variety which was observed by Fåhræus and Lindqvist who, in 1931, passed human blood through narrow glass tubes and observed that the apparent relative viscosity decreases with decreasing tube diameter [20].

This decrease in relative apparent viscosity seems to begin at vessels of 500 to 600 μm in diameter [45], and becomes more apparent as the vessel diameter decreases. This vessel diameter dependent shear thinning phenomena is, as a result, called the Fåhræus and Lindqvist effect (FLE). This effect can be attributed to a tendency of RBCs to migrate away from the vessel walls, creating a red blood cell free layer (CFL) at the vessel wall [14, 46, 47]. This migration has since been observed in multiple *in vitro* studies to create two phases over the cross section of a tube; a central region of mainly RBCs, and an on average cell depleted region close to the wall [48] where RBCs experience a wall induced lift force [49]. The CFL has a local viscosity that is lower than the central RBC rich region of the flow, which provides a lubrication layer that gives rise to the shear thinning behavior observed in small diameter vessels [14, 48, 50]. A compilation of the experimental evidence for the FLE is shown in panel (b) of Figure 1.2. The experimental data [51] for the relationship between the CFL and vessel diameter is shown in panel (e) of Figure 1.2. The FLE has also been observed *in vivo*, but exhibited a higher apparent viscosity as compared to measurements taken in glass tubes [29, 52]. This may be attributed to the endothelial cells that line real vessels [1], and thus are much more complex in geometry than straight glass tubes.

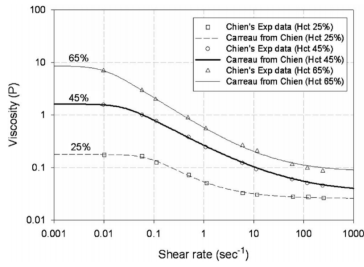
Another departure from the Newtonian fluid description of blood flow is the existence of a plug-flow profile [54, 57]. This is a unique pattern of laminar blood flow that is flattened in the middle of the channel, and therefore departs from the Hagen-Poiseuille Newtonian flow profile. The plug flow has been observed in larger vessels such as the aorta or common carotid artery [58], with an increased presence on smaller vessel scales of micro meters in diameter [54, 55].

The last hallmark of the cell nature of flowing blood that needs to be mentioned in this introduction is the margination of platelets. This phenomena is crucial for the normal coagulation function of blood, one of the processes which aids the bodies response to stop bleeding at damaged vessel sites. Margination is the transport of platelets during flow to and subsequent sequestration at the vessel wall. This allows blood to maintain higher populations of platelets at the vessel wall, which increases the likelihood of platelets repairing a damaged site. This is purely a rheologic process that depends on the collisions between RBCs and platelets and has further been identified to be subject to shear rate [59], hematocrit, and gradients in hematocrit [60]. Simulation evidence of platelet margination is shown in panel (f) of Figure 1.2.

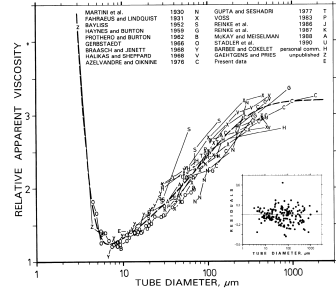
The descriptions given here on the hallmarks of the cell nature of blood flow should serve as the contemporary understanding of blood flow, though the full extent of these phenomena are still not completely known. The suspension nature of whole blood therefore needs to be taken into consideration in order to properly study the processes, both physiological and rheological, that occur in blood flow.

1.3. Numerical Modeling of Blood

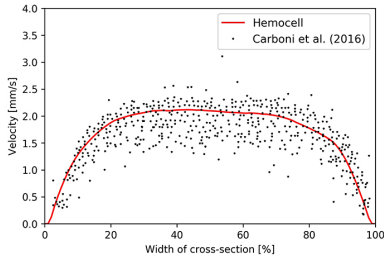
Resolving the physiology and rheology of flowing whole blood via *in vitro* or *in vivo* experiments has limitations. Such methods may be limited by the optical depth of either the surrounding tissue or the blood itself in order to completely resolve the cellular dynamics. This provides an area where computational modeling of blood flow can fit in and



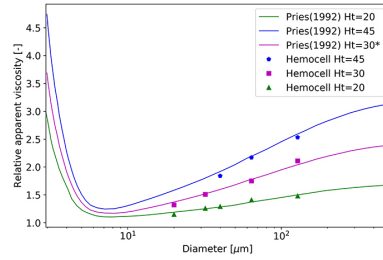
(a) Chien viscosity curves [13, 44].



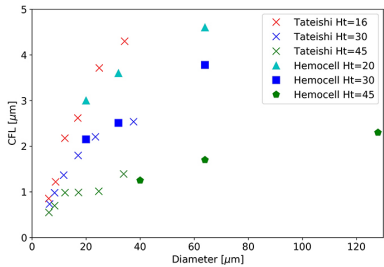
(b) Pries viscosity curves [53].



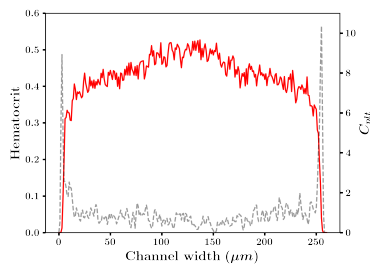
(c) Plug-Flow profile [54, 55].



(d) HemoCell fit to FLE [55].



(e) Cell Free Layer [51, 55].



(f) Platelet margination [56].

Figure 1.2: The hallmarks of cellular blood flow.

contribute to the research concerning blood flow [4] where experimental disciplines are limited. Simulating blood has recently aided the understanding of blood flow throughout the body such as in the aorta and coronary arteries [61, 62], in the brain [63, 64], and even in the small capillaries of the body [57, 65, 66]. Numerical models have also been developed for a variety of biomedical applications ranging from simulating the deployment of flow diverting stents into patient vessels as a treatment for brain aneurysms [67], to simulating cell sorting in microfluidic devices [68–70].

There are two basic regimes when it comes to blood simulation; a continuous fluid regime and a cell-resolved regime. In the continuous regime whole blood is treated as a homogeneous Newtonian fluid. This is largely applied in regions of the circulatory system with vessel diameters that are $\geq 600 \mu\text{m}$. Here boundary layers and inertial effects, though not limited to this scale, are important [71], and blood flow is largely assumed to follow the Newtonian description. The continuous regime is significantly less computationally expensive as there is no need to include the individual cells and cell mechanics. There are many flavors of numerical methods used to simulate continuum blood flow, such as dissipative particle dynamics (DPD) [72–74], finite volume methods [75], smoothed particle hydrodynamics (SPH) [76, 77] and the Lattice Boltzmann method (LBM) [78, 79]. Each numerical method has its own advantages, for instance the proven widespread usability of Navier-Stokes methods like the finite volume method, the Galilean in-variance of particle based methods like SPH and DPD, and the ability to easily incorporate complex geometries and scalability of LBM.

Adaptations to continuum models have been constructed to account for the non-Newtonian behavior of whole blood. Traditionally, such models have been developed to reproduce the relationship between viscosity and shear rate of blood thus replicating shear-thinning behavior. There are a large variety of continuous non-Newtonian models [80] and can be categorized into either time dependent or time independent models. Most time independent models are obtained by fitting a function to experimental viscosity data [81–84], and are able to reproduce Newtonian behavior at low and high shear rates, while accounting viscosity changes in an intermediate shear rate regime. Time independent models commonly use a power law to describe the relationship between viscosity and shear. Such examples of power law fluids are the Casson [85] and Carreau-Yasuda [86] models. Time dependent models are commonly developed to reproduce the viscoelastic behavior of blood [87, 88].

It may be obvious from the prior section that in order to correctly recover the full picture of cell nature of whole blood cell resolution should be a requirement in numerical models. Cell-resolved models generally are built upon continuum fluid models, with additional models handling the mechanical structure of the suspended blood cells. There are many well rooted attempts to model whole blood as a suspension of cells and have been able to reproduce the emerging rheology of blood as a suspension of cells [57, 89–94]. The significant limitation with cell-resolved modeling is by far the computational expense, and as a result such models are currently limited to simulate micro scale vessels on very short timescales.

It is the position of this thesis that though there may be good continuum approximations for the non-Newtonian behavior of whole blood, all non-Newtonian continuum models are empirically fitted models based on strongly simplified experimental settings.

It is not completely understood for instance how the rheology of blood behaves in a vessel bifurcation. Therefore a numerical model should be chosen in such a way to recover the cell nature of whole blood as an emergent property rather than an imposed property.

The Lattice Boltzmann Method

The scaling capability and efficient handling of complex geometries of LBM serves as an interesting choice for cell-resolved modeling, since it could be able to handle the flow between suspended RBCs as well as be scaled up to reach larger vessels in the vasculature. In LBM, the Boltzmann transport equation is solved on a discretized Eulerian lattice. Here the statistical distribution functions that describe particle locations and momentum are solved in a discretized velocity space. The single relaxation time LBM formulation can be written as

$$f_i(x + c_i \delta t, t + \delta t) = f_i(x, t) + \Omega_i(x, t). \quad (1.1)$$

This describes the density of particles $f_i(x, t)$ that move with velocity c_i , in a direction i , to a neighboring point $x + c_i \delta t$ over a time step $t + \delta t$. Solving the Boltzmann equation numerically requires the correct treatment of the discretized collisions between velocity populations on the lattice, and is achieved through an appropriate choice of a collision operator. The most used and simple to implement is the Bhatnagar, Gross, and Krook (BGK) collision operator Ω_i [95], as it requires a single relaxation parameter that ensures that the lattice always develops towards local equilibrium.

$$\Omega_i(f) = -\frac{f_i - f_i^{eq}}{\tau} \delta t \quad (1.2)$$

The collision operator will relax the populations towards an equilibrium f_{eq} at a rate which is determined by the relaxation time τ . The equilibrium distributions are given by

$$f_i^{eq}(x, t) = w_i \rho \left(1 + \frac{u \cdot c_i}{c_s^2} + \frac{(u \cdot c_i)^2}{c_s^4} - \frac{u \cdot u}{2c_s^2} \right). \quad (1.3)$$

Here u is the velocity of the fluid and w_i are the weights specific to the chosen velocity set. LBM needs special treatment at the boundary nodes in order to properly model correct macroscopic boundary conditions and ensure numerical stability in the simulation. Two most widely used boundary conditions in LBM are the bounce back boundary condition [96] and the Zou-He boundary condition [97].

LBM reproduces the Navier-Stokes equation with second order accuracy [98], depending on the boundary conditions. Since LBM is solved using a Eulerian grid it becomes relatively straightforward to implement in parallel, operations on the lattice are local and therefore can be spatially partitioned to many different compute cores. Of course the LBM described so far can only reproduce the continuum description of the fluid. This means that for blood flow simulations it will model the blood plasma. To include cells into LBM requires the proper handling of the fluid-structure interaction between the blood cell membranes and the blood plasma, as well as correctly modeling the mechanical structure of the blood cells.

HemoCell

With the purpose to accurately resolve the suspension nature of blood the choice is made in this thesis to employ the high performance library HemoCell (High performance Microscopic CELLular Library). HemoCell implements a validated, constitutive force, mechanical model of an RBC which is capable of reproducing the emergent transport phenomena and non-Newtonian characteristics of a cellular suspension of blood cells [91, 93]. The fluid structure interaction between the discrete element method of the RBC membrane and the LBM fluid is handled through the immersed boundary method [99]. Each RBC is composed of many Lagrangian surface points (LSP) that serve as a nodes where momentum can be communicated between the RBC material and the underlying LBM plasma.

The HemoCell RBC mechanical model is a superposition of four discrete forces, equation 1.4, that give rise to the natural responses of an RBC membrane to environmental perturbations. A schematic of the entire model is highlighted in Figure 1.3 where the LSPs are represented as white spheres, the force represented through a triangulated mesh of links between LSPs are shown as a black wireframe, and the suspending LBM fluid is shown as yellow cubes. A general outline of the forces is given in this introduction. For a complete detail of the parameters of the HemoCell model please refer to appendix A.1

$$F_{total} = F_{link} + F_{bend} + F_{area} + F_{volume} \quad (1.4)$$

The first force (F_{link}) models the in plane stretching and compression of the underlying spectrin-network, which is implemented along the edges of the surface triangles that represent the cumulative behavior of the local spectrin links. The second force accounting for the bending response (F_{bend}) of the membrane which arises from the non-zero thickness of the spectrin-network, is implemented by pointing in the normal direction on each triangle surface element. The bending force then acts via the angle between two neighboring surface elements. The third force (F_{area}) represents the combined surface response of the supporting spectrin-network and the lipid bilayer of the membrane to stretching and compression, is applied to all three vertices of each triangle face and points in the direction of the centroid. Finally the fourth force (F_{volume}) is a global volume conservation force which maintains the quasi-incompressibility of the cell and is applied at each LSP pointing towards the normal of the membrane surface. The RBC model has been further developed to include the viscosity contrast between the internal fluid of a RBC and the surrounding blood plasma [15], and is implemented by identifying and increasing the relaxation time of the LBM nodes that lie within the RBC membrane. The choice of lattice resolution ($0.5 \mu\text{m}$) allows the suspending fluid to accurately and sufficiently capture the momentum communication from the cell membrane to the fluid. HemoCell relies on a D3Q19 LBM lattice, where the velocity space is discretized into 19 directions which is shown in the schematic of Figure 1.3.

HemoCell has been validated to reproduce the experimental evidence of mechanical responses of an individual, healthy, RBC induced by uniform sheared flow and optical tweezers [91]. The correct implementation on the single cell level leads to emerging accurate behavior on the bulk flow level. The Fåhræus-Lindqvist effect has been reproduced in HemoCell across multiple hematocrits shown in panel (d) of Figure 1.2. This of

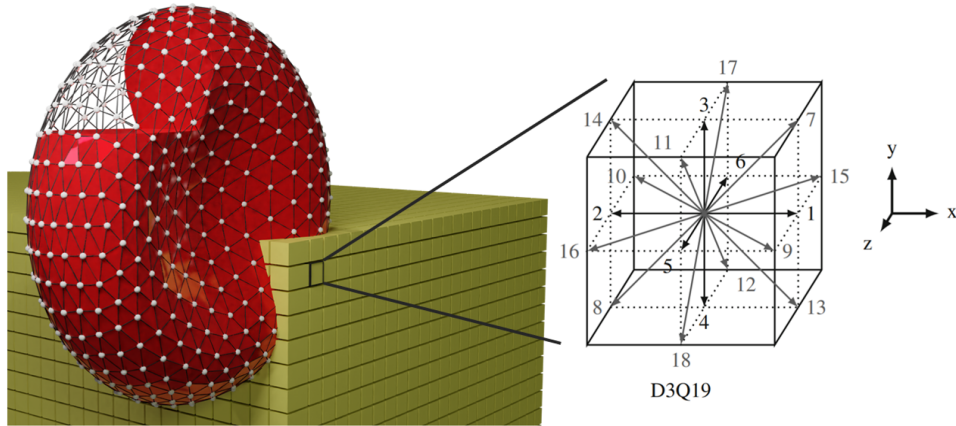


Figure 1.3: Schematic of the HemoCell red blood cell model suspended in a 3Q19 lattice. The Lagrangian surface points of the RBC mechanical model are shown as white spheres. The spatial resolution of the lattice is $dx = 0.5 \mu\text{m}$, and the average diameter of a RBC in HemoCell is $8 \mu\text{m}$.

course relies on the existence of a red blood cell free layer, which has been matched with HemoCell shown in panel (e). And additionally HemoCell has reproduced the plug flow profile and platelet margination, panels (e) and (f) respectively in Figure 1.2.

The spatial scales currently achievable by HemoCell, as well as other cell-resolved models, are typical focused in the sub $100 \mu\text{m}$ range and limited to a timescale of second. This has opened up a rich environment to study the rheologic properties of blood and how they occur within these scales. Recently HemoCell has been used to study the effects of RBC cytoplasmic viscosity contrasts in bulk flow [15], the role of hematocrit profiles on cell diffusivities in straight vessel flow [60], as well as identifying the start of a platelet aggregate [100]. The stage provided by HemoCell allow for the investigation into the effects of RBC mechanics on bulk flow, and even cell transport into diseased vessels like aneurysms.

Throughout the course of development and use of such models to investigate such topics, it becomes apparent that the physical processes begin to outgrow the current achievable spacial-temporal timescales of such cell-resolved models. Such as the proper account of the rheology and transport of blood cells on larger vessel scales. Biological process, like blood clot formation, also start to push the boundaries of what is currently achievable by models like HemoCell. Therefore numerical modeling techniques should be developed to start to bridge the scale and temporal gaps between cell-resolved and continuum blood flow models, in order to accurately resolve the processes that occur on the multiple scales of the vascular system.

1.4. Multiscale Modeling

The circulatory system spans multiple scales ranging from vessel diameters of micrometers to centimeters. Shown in Figure 1.4 is a spatial-temporal scale separation map

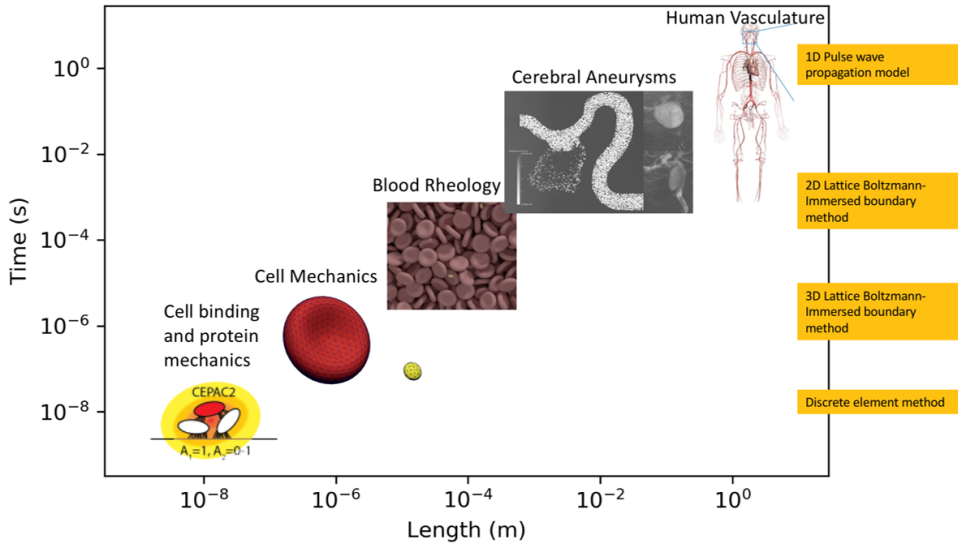


Figure 1.4: Scale separation map highlighting the physical length and time scales of blood flow through the circulatory system and the common numerical methods employed at each scale.

highlighting the different scales for just a few physiological processes of blood flow that occur within the arterial system, along with the typical numerical methods used to solve them. On the largest scales it is typical to use relatively inexpensive models like 1D models that propagate pulse waves in the human arterial tree [101–103] as they can simulate large space-timescales efficiently. 3D continuum models can be employed in large scale vessel segments to further resolve the flow of blood in tortuous geometries. If it is needed to resolve smaller scales, where cell mechanics are important while still being able to sweep a large parameter space efficiently 2D cell-resolved models are typically used [57, 92, 93]. If the full three dimensional mechanics of blood are required then 3D cell-resolved models [11, 91, 104] are employed. Finally to resolve the diffusion of chemicals within the blood stream, complete molecular dynamic simulations may be required. Coupling such different models together to create a multiscale model for say, a virtual human [105], presents a great challenge for computational blood flow modeling. Successfully resolving the physical processes on all scales in the circulatory system presents an interesting challenge to adapt and develop new computational methods that resolve blood flow on multiple scales at the same time.

Multiscale modeling is a methodology that uses combinations of separate models, that are stitched together, with each model working on different scales focusing a certain physiological process of interest [106]. Such modeling techniques are being developed for the vasculature to bridge time scale gap between the cardiac cycle and the longer period of vascular adaptations from wall remodeling [107]. Some are even being developed to resolve the multiple scale levels of blood flow that occurs in the brain [108].

Multiscale techniques could be borrowed from other research disciplines that bridge the gap between fluid and particle dynamics. Examples of this may be the techniques

used in molecular dynamics simulations. Here multi-domain methods have been developed [109–112] to subdivide a simulation domain into a particle resolved sub-domain coupled to a continuum sub-domain. Particle dynamics are then run only where required, and run less expensive continuum models are run where the particle nature is not needed. An example application may be fluid flow around a nano tube, where the particle nature is only needed for the immediate volume surrounding the tube, where the peripheral flow field may be modeled using a continuum solver. Techniques in this field however seem to rely heavily on symmetric cases, and as a result are very sensitive to anti-symmetric geometries, like vessel walls. Multiscale blood flow frameworks are being developed using such decomposition (multi-domain) schemes [108], but do not seem to have a clear answer for the in-homogeneous particle distributions, as is the case with platelet margination, one of the hallmarks of cellular blood flow.

An interesting novel multiscale technique, in regards to blood flow modeling, is the so called Heterogeneous Multiscale method (HMM). HMM has been developed to solve multiscale problems that are a result of many different (heterogenous) processes all working together.

The Heterogeneous Multiscale Method

The Heterogeneous Multiscale Method [113] is a modeling technique used to numerically solve multiscale problems by coupling multiple sub-models ϕ together that each solve a component separately, but by combining each separate sub-model together an overall macromodel Φ emerges. Heterogeneous here suggests the problem is multi-physics in nature [114]. HMM relies on efficient coupling between macro- and micro-models [115]. A macro scale model can be either limited or too computational expensive to numerical solve an entire problem on its own; therefore micromodels are employed to resolve each component of the problem separately and return the result to the macro-model.

Scale separation is a common exploitation in HMM as many numerical problems are difficult to capture solely with one single model. Such multiscale and multi-physics problems are for instance, in molecular dynamics. On the micro scale molecules follow the laws of statistical mechanics, but as a result together can be described on the macro scale through continuum mechanics. A general methodology for applying HMM has been laid out by [116]. Compared to existing multiscale modeling methods for example the multi-domain methods [117, 118], HMM actually simulates the micro scale phenomena with the sub-models. Where multi-domain or multi-grid modeling the micro scales are often approximated and not directly simulated.

HMM is a relatively new multiscale method and in regards to blood flow may be more relevant as physiological problems often cross scientific domains. In the case of thrombus formation, platelet margination (physics) and activation (biochemistry) are occurring in the same process. A HMM model for blood flow could therefore offer a rich environment to capture the many processes behind the physical, chemical and biological processes of blood. In this thesis a HMM model is proposed to first capture the rheological nature of cellular flow and apply it on scales that are currently unreachable by contemporary cell-resolved blood flow models.

1.5. Outline

The organization of the content of this thesis begins on the cell level and gradually ascends in spatial-temporal scale to eventually study blood flow in vessel sizes of multiple millimeters in size. The core motivation is to understand the cell based rheology at each respective scale in the human vasculature.

In chapter two, the thesis begins with the development a stiffened red blood cell membrane model. This is achieved by computing RBC deformations induced by uniform shear flow. The numerical RBC model is matched to experimental ektacytometry data, which was obtained from RBCs that were chemically stiffened through oxidative stress. The central question probed in this chapter is the direct impact of red blood cell deformability in flowing blood. *In vitro* and *in silico* experiments are carried out together which identified a decrease in platelet margination with increasing fractions of rigid RBCs present in blood flow. The decrease of the CFL with increasing fractions of stiffened RBCs is identified to be a significant contributor to the reduction of platelet margination.

In chapter three, blood flow and the transport of blood cells was studied through a segmented retinal microaneurysm. Blood flow within the vasculature of the retina has been found to be influenced by the progression of the condition called diabetic retinopathy, and has never been studied before with cell-resolved blood flow models. One interesting aspect of this study is the availability of full 3D information on patient specific microaneurysm geometries, as opposed to typical 2D projections. Images of a microaneurysm were obtained using adaptive optics optical coherence tomography of the retina of a patient with diabetic retinopathy. A sidewall (sacciform) microaneurysm was segmented from the resulting volumetric data. Wall shear stress was calculated throughout the multiple segmented aneurysm domains, and the quantification of the influence of the RBCs is presented. Average wall shear stress patterns increased due to the increase of RBC membrane stiffness. Stiffened RBCs were also found to induce higher local wall shear stress as they passed through the leading and draining parental vessels. Stiffened RBCs were found to penetrate the aneurysm sac more than healthy RBCs, as well as decreasing the margination of platelets to the vessel walls of the parental vessel, which caused a decrease in platelet penetration into the aneurysm sac.

In chapter four, the effect of pulsatile flow on the transport of red blood cells and platelets into larger scale cerebral aneurysm geometries with varying dome-to-neck aspect ratios is studied. A two dimensional cell-resolved blood flow model is used to probe time and spacial scales previously un-reached by such models before. Flow velocities and vessel diameters were matched with magnetic resonance imaging measurements of cerebral perforating arteries and flow was driven by a synthetic heartbeat curve typical for such vessel sizes. We observe a flow regime change, in the aneurysms, as aspect ratio increases from a momentum driven regime in small aspect ratio to a shear driven regime in the larger aspect ratios. In all cases we observe aneurysms that are platelet rich and red blood cell poor when compared to their respective parental vessel populations. Pulsatility also plays a role in the small aspect ratio case as we observe a smaller population of older trapped cells along the aneurysm wall in the pulsatile case as compared to a steady flow case. Pulsatility does not have a significant effect in shear driven regime

aspect ratios.

Chapter five ties the previous chapters together by developing a heterogeneous multiscale model for blood flow. The physical intuition gained from the different scale levels in each of the prior chapters provides a base understanding of what information should be represented on each of the levels of the HMM. The HMM model is developed to solve blood flow in vessels that are millimeters in diameter or larger. This HMM operates as a collection of two separate blood flow models. One a continuous macro scale blood flow model coupled to an advection diffusion solver that together solves for the flow and transportation of red blood cells on larger vessel scales. The macro scale models receive local RBC diffusion coefficients and bulk viscosities from micro scale models. On the micro scale cell-resolved simulations are carried out for each shear rate and hematocrit combination, passed down from the macro scale. The micromodels are used to compute the bulk viscosity and cell diffusions. The non-Newtonian hallmark shear thinning Chien curves are reproduced on the micro scale and the relationship with hematocrit is further investigated. The proposed model in this chapter tries to accurately solve cell informed blood flow and cell transportation on macro scale vessel.

Finally a conclusion, discussion, and outlook concerning the results and proposals found in throughout this thesis are given in chapter six.