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Transport of blood cells studied with fully resolved models

Lampros Mountrakis

University of Amsterdam
Transport of blood cells studied with fully resolved models

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Summary

Transport of blood cells studied with fully resolved models

Blood is an important fluid for the human body. It exhibits a complex behavior in terms of rheology and cell transport, that arises mainly from the high concentration of the deformable red blood cells (RBCs). Due to this property, blood can be approximated as a dense suspension of RBCs, immersed in a Newtonian fluid, the blood plasma.

The distribution and transport of cells in vessels is non-trivial. In the simple case of channel flow, RBCs migrate towards the center leaving a cell-free layer (CFL) near the walls. Platelets, one of the key ingredients of thrombus, are pushed towards this CFL due to the motion of RBCs. This ensures a more effective homeostatic response against vessel and tissue damages. This motion of platelets towards the walls is also known as margination. Models that explicitly represent RBCs and platelets can inherently capture the aforementioned phenomena, aiding in the understanding of the fundamental mechanisms and the role of the dominant parameters.

The present work focuses on the transport of blood cells with fully resolved models. This has a dual nature: on the one hand to look into the methods used for blood modeling, and on the other to apply these models in the transport of RBCs and platelets. For this purpose, two models are employed, one in two-dimensions with reduced computational requirements for an initial intuition on the relevant phenomena, and one in three-dimensions, computationally demanding, for use in more realistic studies. Both models are based on the combined Immersed boundary-Lattice Boltzmann method (IB-LBM).

The 2D model is able to recover the shear thinning behavior and the formation of a CFL, as well as the margination of platelets. Following its initial validation, simulations in aneurysmal geometries were performed, focusing on the transport of platelets. The results highlighted a region of high hematocrit with trapped platelets very close to the aneurysmal wall. This indicates that the distribution of cells might be relevant to the formation of a thrombus, or to the wall weakening
and the rupture of an aneurysm. This model was also applied for measuring the shear-induced diffusion of RBC- and platelet-like particles in shear flow. The simulations revealed a departure from the linear scaling with respect to the shear-rate for the diffusivity.

Fully resolved simulations of blood suspension can be very demanding, especially in three-dimensions. The performance of such an implementation can define the limits of the explorations we would like to consider. For this reason, a parallel 3D code was developed and the implementation is described. The performance of the code presented for weak and strong scaling, demonstrates a close to linear scaling, for both scenarios. This model was subsequently used to investigate the effect of IB-LBM parameters on a number of seemingly simple but challenging benchmarks. This study uncovered non-physical behavior occurring in under-resolved cases, which is more pronounced when using interpolation kernels with a smaller support.

Modeling blood as a suspension of deformable particles is a reasonable simplification, which reproduces some of the important aspects of blood rheology and transport. It can be a source of interesting results and, eventually, knowledge. However, the range of validity for these models should be defined, and their results should be carefully interpreted. Methods also introduce their own side-effects, which are more complex than numerical accuracy.
Samenvatting

Transport van bloedcellen bestudeerd met volledig gedetailleerde modellen

Bloed is een belangrijke vloeistof van het menselijk lichaam. Het vertoont complex gedrag in de zin van reologie en celtransport, dat tot uiting komt door de hoge concentratie van vervormbare rode bloedcellen (RBC). Door deze eigenschap kan bloed benaderd worden als een geconcentreerde suspensie van RBC omgeven door een Newtoniaanse vloeistof, het bloed plasma.

De distributie en het transport van cellen in vaten is niet triviaal. In het triviale geval van een vloeistofstroom door een kanaal concentreren RBC zich in het midden van het kanaal waardoor er een cel-vrije laag ontstaat aan de wanden. Dit zorgt voor een effectieve homeostatische reactie tegen vat- en weefselschades. Deze beweging van bloedplaatjes richting de wand van het bloedvat wordt marginatie genoemd. Modellen voor RBC en bloedplaatjes kunnen dit fenomeen beschrijven en kunnen daarmee helpen bij het begrip van de fundamentele mechanica en de invloed van de dominante parameters.

Dit werk richt zich op het gedetailleerd modelleren van het transport van bloedcellen waarbij de aanwezigheid van RBC, bloedplaatjes en plasma expliciet meegenomen word. Dit heeft twee redenen: om een beter inzicht te krijgen in de methodes die gebruikt worden voor bloed simulatie en om de methodes toe te passen voor het transport van RBC en bloedplaatjes. Hiervoor zijn twee modellen gebruikt, een in twee dimensies om een eerste indruk te krijgen van de belangrijke factoren en een in de meer realistische drie dimensies. Voor dit hoger dimensionale model vormt zijn meer geavanceerde computertechnieken nodig. Beide modellen zijn gebaseerd op de zogenaamde Immersed Boundary-Lattice Boltzmann methode (IB-LBM).

Met het twee dimensionale model kunnen de lagere bloed viscositeit bij stroming, de formatie van de cel-vrije laag en de marginatie van bloedplaatjes worden aangetoond. Na deze initiale validatie is het transport van bloedplaatjes geïmuleerd in aneurysmatische geometrin. De resultaten laten een gebied zien met hoge hematocriet waardes waar bloedplaatjes zich hechten in de holte van het...
aneurysma. Dit is een teken dat de distributie van cellen invloed heeft op de formatie van een thrombus, of op het verzwakken en uiteindelijk scheuren van de wand van het aneurysma. Dit model is ook toegepast om de diffusie van RBC en bloedplaatjes, die wordt veroorzaakt door afschuifsnelheid in de bloedstroom, te meten. De simulaties laat een afwijking zien van de lineaire schaling tussen de diffusie en de schuifsnelheid.

Een volledig gedetailleerde simulatie van de bloed suspensie kan computационeel erg intensief zijn, in het bijzonder in drie dimensies. De prestatie van een dergelijke implementatie kan de grenzen bepalen van wat we kunnen onderzoeken. Hierom is een parallelle 3D code ontwikkeld en beschreven. De prestatie van de code schalen bijna lineair voor zwakke en sterke schalingscriteria. Dit model is achtereenvolgens gebruikt om het effect van de IB-LBM parameters te onderzoeken op een aantal op het oog eenvoudige, maar uitdagende referentiecriteria. Deze studie heeft ontdekt dat er natuurkundig onverklaarbaar gedrag ontstaat bij het gebruik van een grove representatie. Dit wordt versterkt door interpolatie met te weinig punten.

Het modelleren van bloed als een suspensie van vervormbare deeltjes is een redelijke vereenvoudiging en reproduceert sommige belangrijke aspecten van bloed reologie en transport. Het kan een bron zijn van interessante resultaten en uiteindelijk kennis. Echter moet de reikwijdte van de validiteit deze modellen gedefinieerd worden en hun resultaten moeten kritisch genterpreteerd worden. Methoden introduceren hun eigen bijwerkingen die complexer zijn dan numerieke nauwkeurigheid.
Part I

Introduction
Blood is a complex, very important fluid for the human body. Its main function is to deliver oxygen and nutrients and to transport away waste products. It also ensures that platelets will effectively be delivered at sites of injuries and leukocytes will protect the body against infectious diseases and foreign invaders. Many blood phenomena, like the Fähræus-Lindqvist effect and the margination of platelets, have a clear mechanical base and no chemical or biological function is necessary. However, climbing down the ladder one can find several regulatory mechanisms involving the sensing of abnormalities through cell signaling and chemical reactions, like platelet-activation or vasodilation, while further down lie genetics and gene-expressions, such as the mutation causing sickle-cell anemia or the hereditary Von Willebrand disease.

An example complicated with many of the aforementioned mechanisms is hemostasis, the process the body stops bleeding. In the unfortunate, yet very common event of an injured artery, depending on the blood vessel it constricts limiting the blood loss while releasing pro-coagulants to promote the activity of platelets. Platelets, as a first step for healing the wound, get activated and sticky, adhering to the surface. It is a complex response, carefully regulated with many
cascading steps until it reaches the desired outcome. However finely tuned this process is, there is a number of occasions where things can go wrong: deficiencies or genetic diseases in coagulation factors, platelet hyperactivity and even anemia – the lower than normal RBC percentage– can deregulate this process and lead to undesirable behavior.

Blood extends to many spatial and temporal scales, and the processes involved are non-linear. It is therefore important to isolate the key mechanisms in each phenomenon in order to understand it. Modeling blood is a process that helps identify key elements and understand the mechanisms behind each phenomenon.

Modeling as a vehicle

In 1960 the Hungarian-American physicist Eugen Wigner published an article with the title "The Unreasonable Effectiveness of Mathematics in the Natural Sciences" [214]. There, motivated by the success of mathematics in physics and engineering, he addressed the “miracle” of mathematics as an appropriate language to describe the laws of nature. Fortunately or unfortunately, this article has provoked numerous responses over the years for the unreasonable ineffectiveness of mathematics in other disciplines [84, 206, 199, 9]. Even though no one can really argue that there is no underlying mathematical structure in the formation of corals, in the transmission of meaning in natural languages or even in the dynamics of the stock market, an elegant set of equations with a quantitative predictive power is often unfeasible. Yet, the qualitative behavior of these phenomena is frequently been captured with mathematical models.

Mathematical models identify the key processes in a phenomenon and deduct knowledge on the principle of analogy [136, 44]:

If two different phenomena A and B are described by the same mathematical formulas, quantitative conclusions can be drawn about the phenomenon A by studying the phenomenon B.

So a “model” is the apparatus of B which is designed to investigate A by analogy. If any given part of reality is infinitely complex in its multiple scales and interactions, it is consequential to simplify it and break it down to its important constituents. The simplification or idealization of this part of reality, constrains its complexity and renders the extraction of information tractable.

Following the above definition, models are not necessarily mathematical constructs. Each discipline has its own established “idealization vehicles” acting as models [208]. In physics a model can be a mathematical law, in statistics a sub-population, and in biology or medicine it can be an organism. Examples of model-organism are the drosophila melanogaster, the heroic lab-mice, the immortal cell line of Henrietta Lacks. They are being used to studies ranging from
heart diseases and developmental biology to Parkinson’s disease and even social behavior. These organisms are regarded as models, under the assumption that they will provide knowledge of certain aspects of the studied system [208].

In blood-related research, in-vitro and in-vivo experiments are also simplifications based on assumptions. For instance, it is common to add anti-coagulants in in-vitro experiments to prevent blood from clotting. This is done under the assumption that the quantity of interest will not be affected. In-vivo observations follow a similar path, assuming for example that the patient’s heart-rate will behave similarly inside and outside the examination room.

While an experimentalist is making a part of nature a model, in computational science parts of reality have to be identified and recreated in the models. While in the real world it is often not straightforward to change only one parameter without affecting the rest of the environment, in computational modeling it is done easier. Nevertheless, the misconception that it is always possible is lurking.

Very important steps in realizing a model are the verification and the validation steps [176]. Verification is a process of determining whether the model accurately represents the conceptual description and specifications. Validation is a process of determining the degree to which a model is an accurate representation of the phenomena intended to represent [191]. In short, verification stands for “solving the equations right”, while validation for “solving the right equations”. A part of the verification process is to compare the calculated outcome of the model with analytic solutions, such as the channel flow. This renders presence of exact and analytical results important in computational science. If simulation results disagree greatly with a known law or an exact result, like the conservation of energy or the parabolic shape of channel flow, then there is something wrong with the simulation [74]. Validation is a far more complicated process and usually involves comparing the predictions of a model with experimental ones. In blood for example, recovering the shear thinning behavior of blood, or the margination of cells, is part of the validation process. It is part of checking that the substance in the computer has several similar attributes with the one flowing in our arteries. If the predictions are explicitly added, they constitute a part of the verification process.

Quoting G.P.E. Box, all models are wrong, since they encompass simplifications and their range of validity is constrained, but some are useful [29]. Counter-intuitively and despite the frustration it might cause, assuming they are well-grounded – models are logically stronger when they fail [136]. Rejecting a hypothesis is always stronger than providing evidence that something holds and computational models by idealizing segments of reality can provide evidence that certain assumptions do not recover the desired behavior, thus forcing new questions.
CHAPTER 1. INTRODUCTION

Outline of this thesis

This thesis copes with the modeling of blood, using models that explicitly consider its constituents – plasma and red blood cells (RBCs), and looks into the transport of RBCs and platelets in different environments: straight channels, shear flow and aneurysmal geometries. Modeling blood encompasses a wide range of challenges and steps, from understanding blood rheology, choosing the methods and validating the model, to translating it into software preferably capable of running in thousands of processors. In light of the previous section, the major part of the model used in this thesis is based on mechanics and biology is considered only at the point of introducing a model of primary hemostasis.

This thesis is divided in three general parts: Methods, Results and Outlook. The first part deals with the methods and the models used in the current thesis, the second with applications of the model and the third with work that has started, but has yet some steps to be finished.

Chapter 2 provides a brief introduction to hemodynamics, describing the constituents of blood, its behavior in the circulatory system and the transport of blood cells. An overview of fully resolved computational models is also presented, along with a view on the question “why to simulate blood”.

In chapter 3 a two-dimensional model for blood-like suspensions is presented. RBCs are modeled as closed deformable membranes, coupled to a lattice Boltzmann fluid, counting for plasma, using the immersed-boundary method (IBM). This model agrees with several experimental findings, like the Fåhræus-Lindqvist effect, the formation of a cell-free layer and the transition from tumbling to tank-treading for a single RBC.

Chapter 4 presents fiscion, a general-purpose 3D suspension solver, build on top of the open-source framework Palabos. The implementation is described and weak and strong scaling results for parallel simulations of dense red blood cell suspensions is presented, demonstrating a fairly good, close to linear scaling, for both scenarios.

In chapter 5 the focus is shifted towards the fluid-structure interaction method, IBM. The effects of several IBM-specific parameters are investigated on basic systems of spheres, like the flow of a single sphere in shear flow and the interaction of two spheres in the same environment. The effective hydrodynamic and interaction radii are measured, and the role of each parameter is studied.

Chapter 7 investigates the shear-induced diffusion (SID) of RBCs in the pure shear environment of a Lees-Edwards boundary conditions domain. In high volume fractions, a departure of SID from the linear scaling with the shear-rate is observed. A potential increase in the collisional cross-section is not sufficient to explain this, indicating that the nature of collisions is different in high volume fraction, in which collective effects are taking place. The diffusivity of platelets
is also measured and found to be significantly enhanced by the motion of RBCs.

Chapter 6 looks into the transport of platelets in small aneurysmal geometries. Two different aspect ratios under two different pressure gradients are considered. The distribution of cells in these geometries is non-trivial, with the main result being a high-hematocrit region with trapped platelets, close to the walls of the aneurysm. Since RBCs and platelets are not biologically passive, in a real-world scenario this high hematocrit region can give rise to several hypotheses on the formation of a thrombus, as well as to wall weakening and possible rupture of the aneurysm.

In the last chapter, 8, a model for thrombosis is presented, extending the fully-resolved model of chapter 3 with a biological ruleset. The focus is turned to the grouping of various cell receptors according to their function and binding strength.
A short introduction to hemodynamics

Blood is a very special juice.

Johann Wolfgang von Goethe (Faust)

Blood is a dense suspension of deformable red blood cells (RBCs) immersed in a Newtonian fluid, the blood plasma. Its complex behavior, in terms of rheology and cell transport, arises mainly from the high volume ratio of RBCs. To a first approximation, blood is very much like a dense suspension of RBCs or even of deformable particles, immersed in a Newtonian fluid, the blood plasma. Fully resolved cell-based blood models, simulating blood through its main constituents, can inherently capture relevant phenomena and aid in the understanding of the fundamental mechanisms that make blood so complex, as well as in the treatment of diseases.

2.1 Blood Constituents

Blood is composed primarily of plasma, red blood cells (RBCs), and in much lower numbers, white blood cells and platelets. It exhibits a complex behavior, with a viscosity that depends on the shear rate (blood is a shear-thinning fluid) and on the size of the vessel it flows. The current section describes the main constituents of blood and their functions.
2.1.1 Plasma

Plasma is the liquid component of blood, amounting to approximately 55% of the total blood volume. It is a Newtonian fluid, consisting mostly of water dissolving various proteins, primarily fibrinogen, and organic and inorganic substances. Plasma’s central role is to transport these dissolved substances, nutrients and wastes throughout the circulatory system and act as a protein reserve for the human body. It has a density of \(1025 \text{ kg/m}^3\) (water’s density is \(999.97 \text{ kg/m}^3\)) and a dynamic viscosity of 1.1 to 1.3 mPas at 37°C [110]. Viscosity is affected by its water-content and protein concentration. Lack of several plasma proteins, like the von Willebrand factor or fibrinogen –proteins that help blood clot– may result in disorders like hemophilia or hypercoagulation.

2.1.2 Red blood cells

Red blood cells or erythrocytes, are in terms of rheology the most interesting constituent of blood. They are anucleated cells, disk-shaped, biconcave, and deformable with a diameter of about 8µm and a thickness of 2µm. The main role of the erythrocytes is to transport oxygen and waste products to and away from the body tissues. Under physiological conditions they account for 40 to 45% of the total volume of blood. These numbers add up to 4 to 6 \(\times 10^6\) RBCs/mm\(^3\) [177]. Their volume ratio is also known as “hematocrit” and is one of the integral parts of a person’s complete blood count results, indicating the amount of oxygen transferred from the lungs. An abnormally low hematocrit is commonly referred to as anemia and can be classified based on either an impaired production of
2.1. **BLOOD CONSTITUENTS**

RBCs, or an increased destruction.

Their high numbers and innate deformability (necessary to allow RBCs to enter the microcirculation) endow blood with its rich behavior in terms of rheology and cell transport. Blood’s shear-thinning behavior is due to high volume fraction of the suspended RBCs and their aggregation. Under low shear rates the erythrocytes form three-dimensional stack-like microstructures, called rouleaux, increasing the viscosity of blood. The size of these stacks depends on the shear rate in a decreasing fashion and experiments have shown that it almost halves upon each doubling of the shear rate in the range of 5.6 to 46/s [179].

The aggregation of RBCs is necessary to attain a strong shear thinning effect as indicated by Chien in his experiments in 1970 [37]. Chien compared the viscosities of blood with and without the plasma proteins fibrinogen and globulin, known to be responsible for RBC aggregation and even though an almost unchanged picture was found at higher shear rates, a clear decrease of viscosity was obvious in shear rates under 5/s.

RBCs are interesting cells in their own right. Their surface is a composite material formed by an outer lipid bilayer and an inner, two-dimensional, cytoskeleton network attached to the lipid bilayer [22, 80, 79]. They encapsulate a Newtonian solution of hemoglobin, an oxygen carrier protein responsible for the red color of blood. The density of an RBC is 1125 kg/m³, approximately 10% higher than that of plasma, while the viscosity of the hemoglobin solution is 5 times higher than that of plasma. It is common however, in in-vitro studies to use ghost RBCs: model RBCs with several parameters manipulated, like the viscosity or density ratio.

Under shear flow a single RBC engages in types of motion different from that of its rigid counterpart, due to its deformability. At low shear rates a RBC may act as a rigid body, performing a tumbling motion, flipping like a coin, yet as shear rates increase the cell’s membrane and the interior liquid undergo a steady rotary motion maintaining a fixed orientation, known as tank-treading motion [69, 67, 68, 10]. Swinging, an intermediate type of motion, was also noticed in the transition of tumbling to tank-treading, in which the inclination angle was oscillating with a period equal to half the tank-treading period [10, 157, 222, 70].

### 2.1.3 White blood cells

White blood cells (WBCs), or leukocytes, are nucleated cells of the immune system involved in protecting the body against infectious disease and foreign invaders. They vary morphologically and in function, while together with platelets they constitute less than 1% of blood’s total volume. There are five types of WBCs: basophils, eosinophils and neutrophils (collectively called granulocytes due to the presence of granules in their cytoplasm) and monocytes and lympho-
cytes. They are usually spherical with diameters ranging from 10 to 15\( \mu \)m with only small lymphocytes have diameters of approximately 7 to 8\( \mu \)m.

### 2.1.4 Platelets

Platelets, or “thrombocytes”, are small blood cells, whose main function is to contribute to the prevention of blood-loss. They are disk- or oval-shaped, with a mean diameter of 1 to 2\( \mu \)m [104] and amount to 250–500\( \times 10^3 \) PLT\( \text{mm}^{-3} \) [177]. Platelets play a central role in the formation of a thrombus during the normal haemostatic response to a vessel wall injury, by adhering to the site of injury while changing their shape from discoid to spherical with the extrusion of pseudopod, forming a mechanical plug by platelet-aggregation (primary hemostasis). Depending on a series of parameters, platelets can release granular contents and trigger the coagulation-cascade, a complex series of activities leading to the strengthening of the platelet plug with fibrin strands and the formation of a thrombus [215, 104, 204, 177].

Thrombogenesis is also related to some non-invasive treatments of intracranial aneurysms, like coiling and stenting [33, 23]. Intracranial aneurysms are a pathological dilatation (or ballooning) of a cerebral blood vessel, caused by the weakening of the vessel wall. A potential rupture of an aneurysm can be lethal for the patient, and the formation of a thrombus inside the aneurysm may significantly lower the risk of rupture. The transport of platelets, in the sense of their distribution inside the cavity of an aneurysm, along with their dynamics can aid in the understanding and the combat against this pathology.

### 2.2 Circulatory system

Discussing about blood, without taking into account the medium in which it flows, is incomplete. The human vasculature spatially spans several orders of magnitude. Vessel diameters range from the \( \sim 20\text{mm} \) diameter of the ascending aorta to the smallest capillaries and venules of \( \sim 0.005 – 0.01\text{mm} \). The human body contains approximately 5 liters of blood, flowing in an approximate laid end-to-end length of about 100.000km. Capillaries accounting for the 80\% of this number [130] and their size is comparable to the diameter of an RBC, which significantly deforms during its crossing, releasing its oxygen through the walls and into the surrounding tissue.

In the larger vessels, those with an internal diameter > 0.5mm, blood behaves as a homogeneous Newtonian fluid with a constant viscosity. In vessels smaller than that, blood behaves as a non-Newtonian fluid. Its viscosity depends not only on the applied shear rate, but also on the vessel diameter with the apparent viscosity decreasing as the vessel’s diameter decreases. The minimum value is
reached at approximately the size of a single RBC, 8µm, in which further decrease leads to a rapid increase of the apparent viscosity, as shown in Fig. 2.2.

This effect is known as the Fähræus-Lindqvist effect [73, 171] and is attributed to the motion of RBCs towards the center of the vessel, leaving a red blood cell-free layer near the walls, which acts as a lubrication layer. The relative thickness of this cell-free layer depends on vessel size and hematocrit and appears to be increased in smaller vessels [34, 111, 162]

### 2.2.1 Transport of cells

As stated earlier, transport is one of the principal functions of blood: transport of oxygen, nutrients, wastes and of course cells. The distribution of WBCs and platelets under physiological conditions is not homogeneous, due to the complex motion of red blood cells. A rather segregated behavior is observed, in which the different components are differentially distributed in the cross-stream [118].

The previously described migration of RBCs away from the wall, leaves a several micron thick cell-free layer, in which both platelets and white blood cells are preferentially found. This tendency of cells to exhibit an increased concentration near the walls, has come to be called margination [198, 194, 8]. From a biological perspective this location makes perfect sense: injuries happen in the vessel wall with WBC and platelets functioning more efficiently there. Platelets aid in the wound healing and WBCs against infections. However, an important distinction
between platelets and WBCs is the rate of margination with respect to the shear rate: increasing the shear rate increases the rate of margination for platelets, while the opposite holds for WBCs [118].

The effect of margination may arise purely from the hydrodynamic interactions between RBCs and WBCs/platelets, with the cell-size being enough to reproduce it. The literature of the computational studies investigating margination for a series of parameters and their importance is increasing [42, 41, 117, 118, 94, 64, 147]. More discussion on the transport of platelets is done in subsequent chapters of this thesis.

Simulations studying the transport of smaller particles in the blood stream, like nano/micro particles (NMPs) usually employed for the delivery of a drug, have shown that size (and shape) does matter. Lee et al. [123] observed via simulation that small NMPs (<100nm) move with RBCs and present a uniform radial distribution with a limited near-wall accumulation. Larger NMPs preferentially accumulate in a size-dependent manner next to the vessel walls. A similar observation was made by Müller et al. [152] studying the margination for a wide range of hematocrits, vessel sizes, and flow rates. In addition, they found that spherical particles marginate slightly better than ellipsoidal, however ellipsoidal particles have a reduced rotational activity near a wall, favoring their adhesion.

Because of the functions of the blood cells and other substances, their distribution and position is important in assessing the outcome of a pathology, like the formation of a thrombus or an atherosclerotic plaque, or the delivery of a drug. While in a tube the qualitative distribution of cells is known, in more complex geometries their transport and function is an active field of research. With complex geometries we refer to arterial stenosis, aneurysms and bifurcations. Both computational [103, 226, 147, 91] and experimental [154, 196, 167] studies are employed to understand these phenomena.

2.3 Blood models

As mentioned earlier, blood flow spans across many temporal and spatial scales and so do the computational models. It is therefore very useful to determine the question a model is supposed to answer. Computational blood models differ greatly, ranging from 0D solving the vascular network by applying a hydraulic-electrical analogue to the ones explicitly modeling RBCs, either as rigid particles [189, 168] or with a very fine RBC mesh taking into account the interactions of the RBC lipid bilayer with the cytoskeleton [164, 163]. In between one can find the common 2D/3D continuum models with constant or pulsatile flow using Newtonian or non-Newtonian models. It is not only an issue of computational resources, but also an issue of validity, with finer models not necessarily producing more valid results. For instance, one can study the importance of RBCs in plug
2.3. **BLOOD MODELS**

formation by explicitly approximating and modeling RBCs as hard spheres, as done in two studies by Mori et al. [145] and Pivkin et al. [168], yielding valid qualitative conclusions. However, on a larger scale spherical rigid RBCs would shear-thicken and jam at high hematocrits, essentially killing the virtual patient.

Blood flowing in vessels with a diameter of 1mm, can usually be approximated by a continuum Newtonian fluid due to the high shear rates present in that vessel, while smaller vessels would likely require the use of a non-Newtonian model. Nevertheless, this also depends on the question we need to answer and the quantities we are interested in. In cardiovascular diseases the wall shear rate is of particular importance and the differences between the use of Newtonian and non-Newtonian model is still subject of debate [77, 98, 25]. Resolving the blood flow in smaller vessels though, in the range of a few hundreds of µm, would require the explicit modeling of RBCs, due to the reasons described in paragraph (2.2).

Deformability endows RBCs with the ability to squeeze through vessels smaller than their diameter, to pack in higher volume fractions, and to perform an extra motion, that of tank-treading [108]. However, in the context of modeling, deformability in combination with the large numbers of RBCs also increases the computational cost. The spatial dimensions should be sufficiently small to resolve the deformation undergone by a single RBC, rendering simulations of large vessels, like an aneurysm, computationally very expensive.

Two-dimensional models of deformable particles constitute a valid simplification and have two main advantages: on the one hand their simplicity renders the understanding of a concept easier, and on the other they are much faster and cheaper in terms of computational cost than their three-dimensional counterparts. Prosenjit Bagchi [17] in 2007 was able to simulate 2500 elastic capsules in 2D, recovering the Fähræus-Lindqvist effect and the cell-free layer. Kaoui et al. [106], wondering why RBCs have asymmetrical shapes in symmetrical flows, found that a slipper shape of an RBC causes a significant decrease in the velocity difference between the cell and the imposed flow, providing higher flow efficiency for RBCs. Crowl & Fogelson [41] attempted to analyze the mechanisms for platelet near-wall excess, while Fedosov et al. [64] investigated the dependence of white blood cell margination on their interactions with RBCs and the vessel walls. Recently, Thiébaut et al. [192] demonstrated in 2D that in confined flows the nontrivial spatiotemporal organization of RBCs can result in anomalous blood viscosity, contributing to the fundamental understanding of rheology in confined complex fluids.

In three dimensions, there have been attempts to model RBCs with reduced models, still capable of accurately resolving viscosity and transport. Janoschek et al. [96] introduced in 2010 a coarse-grained particulate model for hemodynamics, using the Lattice Boltzmann method (LBM) and the momentum exchange
method, where RBCs are approximated as ellipsoids interacting on empiric potentials. The model was fitted to reproduce the macroscopic viscosity of blood and several other features known from experiments, yet a critical analysis revealed several inconsistencies, like unrealistically low viscosities in high hematocrits and an unphysical migration of particles in shear flow [95]. In 2011, Melchionna [139] introduced a model of RBCs for large-scale blood flows, using a combination of LBM and a modified molecular dynamics scheme for motion of RBCs. This model, used in a variety of geometries [139, 140, 26], considers oblate ellipsoids as RBCs interacting hydrodynamically with a far-field potential, while viscosity raises with hematocrit and with many-body collisional contributions.

On the other end of the spectrum, lies the approach of Li et al. [127], who introduced a three-dimensional random network model for the RBC equilibrium shape and evolution, down to the spectrin-level. Spectrin is the building block of an RBC’s cytoskeleton and in their study, they considered ~ 23867 points, each one representing a junction complex in the RBC spectrin network. However computationally expensive this study was, it revealed important aspects of RBC’s membrane energetics and its equilibrium shape, while laying the foundation for the coarse grained approach of Pivkin & Karniadakis [169], which is used in a multitude of studies. Pivkin & Karniadakis managed to reduce the huge number of discretization points used by Li et al. to 100 points or to 500 points, depending on the desired accuracy and stability. Later on, Fedosov, Caswell & Karniadakis [59] presented a rigorous procedure to derive coarse-grained RBCs from the above model, subjecting it afterwards to an extensive set of validation tests including mechanics, dynamics, membrane fluctuations and rheology [60, 63].

Earlier than the coarse graining though, in 2006, Dupin et al. [53] employed multi-component lattice Boltzmann to simulate RBCs as immiscible, deformable, and viscous drops. This creative use of LBM was able to recover Goldsmith’s observations on the flow properties of RBCs [78]. One year later, Dupin et al. [54] presented one of the first 3D models for the flow of deformable particles. A coarse mesh of 500 points accounted for one RBC and was coupled with a variant of the immersed boundary method to the LBM fluid. This model was later applied to the blood flow of malaria and sickled RBCs [55].

Two other RBC modeling approaches worth noting are the low dimensional RBC (LD-RBC) [162] and the two-component RBC model [164]. An LD-RBC is constructed as a closed-torus-like ring of 10 colloidal particles connected by wormlike chain springs and a bending resistance and is able to accurately predict blood’s behavior for vessels larger than the diameter of the cell [63]. The two-component model treats the lipid bilayer and the cytoskeleton of an RBC as two distinct components and recovers a large numbers of experiments regarding the single cell, like the thermal fluctuations of the membrane, measurements of twisting torque cytometry and the tank-treading motion of a RBC in a shear flow.
Hematological disorders also constitute a relevant subject for modeling, with sickle-cell anemia and malaria being high on the list due to their purely mechanical consequences (and not causes) [128]. In malaria, RBCs are infected by a Plasmodium parasite, which causes a decreased membrane deformability, stiffening more than ten-fold in comparison with healthy RBCs. Sickle cell anemia (SCA) is a hereditary blood disorder in which the oxygen-carrying haemoglobin is abnormal and forms strands, leading to a rigid, sickle-like RBC shape. Many studies using dissipative particle dynamics (DPD) based on the spectrin-link model investigate the flow of malaria infected RBCs in the micro-vasculature [62, 92] and their margination [93], while with the help of simulations the fabrication of micro-devices for cell-separation is also explored [28]. Computational studies have also explored the vasoocclusion phenomena in SCA [125] and aided in the understanding of the morphology of sickled-RBCs [124].

2.4 Why simulate?

A simulation is an experiment performed on a model for a system, in order to answer questions about that system [36]. Simulations are conceptually also an important cognitive function, where humans “simulate” the outcome of an action before actually performing it, thus evaluating the outcome and re-adjusting their strategy. Assuming a well-grounded model, trying to answer the question in a virtual environment can in principle save time, effort and money (and potentially several mouse-lives).

With respect to blood-related research, lab-experiments can face several constraints: a limited amount of a specific blood sample and limited variability or long waiting times in obtaining material. These problems can be successfully tackled by computer simulations, where the definition of new blood cell types, like malaria and sickled RBCs, or new materials with a specific function is easier. Once they are defined and validated, these new substances can be stored and reused – the difficulty lies in the first steps.

Investigating the margination of NMPs of various sizes, as discussed in section 2.2.1, is tractable in a lab environment, and it would require the presence of NMPs, the measuring equipment and the occupation of a lab-member for several work-hours. Using a validated computational model (which its definition and implementation is an issue), the material is readily available, no specialized equipment is necessary and the setup of parametric studies requires a reduced amount of effort. The results of the simulations can guide the focus of the experiments, saving time, material and work hours.

Computer simulations act complementary to experiment and contribute in numerous fast-prototyping processes. In micro-devices for example, simulations
can screen the parameter space and/or estimate the efficacy of potential geometries, as performed for deformability-based cell-separation micro-devices for malaria cells [28]. Modeling blood through its constituents can also serve a meta-purpose of formulating and improving coarser or multiscale blood flow models. These fully resolved models can be used for validation purposes, parameter calibrations, uncertainty quantification and sensitivity analysis for other models [89].

An interesting question in this context would be when not to simulate. Establishing models in the interdisciplinary region of biomedical sciences has quite a few challenges and the answers provided by the simulations should be carefully transmitted. The overuse for example, of Computational Fluid Dynamics (CFD) in patient specific cases of aneurysms has sometimes been confounding to the medical community [102]. Solving the Navier-Stokes equations correctly is a necessary but not sufficient criterion to simulate blood flow on a physiological or clinical point of view [185]. The correct boundary conditions and input data is a prerequisite, while minor details like the flow rate regulation from the heart may be of importance in a clinical environment. However, the interpretation of the results and the limitation of the models may lie in the experience of the user (the medical personnel), using simulations as a tool, or an indication, like an X-ray or blood test.

The process of exploring the range of validity for a given model is also an important reason to simulate, aiding in the definition of a model. In principle, investing time, money, and gray matter in modeling, namely in the process of organizing knowledge about a given system [36], is an investment which, in due time, saves time, money, and gray matter.
Part II

Numerical methods
Validation of an efficient two-dimensional model for blood-like suspensions

Many rheological properties of blood, along with transport properties of blood cells can be captured by means of modeling blood through its main constituents, red blood cells (RBCs) and plasma. In the current chapter, we present a fully resolved two-dimensional model for the flow of blood-like suspensions, employing a discrete element model (DEM) for RBCs and coupling it to a lattice Boltzmann method (LBM) fluid solver using the immersed boundary method (IBM). We identify an efficient computationally reduced mesoscopic representation of cells and flow, still able to recover essential physics and physiological phenomena. This model is found to recover experimental findings, like the Fähræus-Lindqvist and shear thinning effects, while the thickness of the cell-free layer (CFL) matches the observations. In addition, we investigate the tank-treading frequency of a single RBC in shear flow along with the transition from tumbling to tank-treading, also matching experimental data.

The contents of this chapter are based on: L. Mountrakis, E. Lorenz, and A. G. Hoekstra. Validation of an efficient two-dimensional model for dense suspensions of red blood cells. *Int. J. Mod. Phys. C*, pages 1441005+, Mar. 2014. doi: 10.1142/s0129183114410058
CHAPTER 3. VALIDATION A 2D BLOOD-LIKE MODEL

3.1 Introduction

The high concentration of red blood cells (RBCs) gives rise to the complex non-Newtonian rheology of blood. Modeling blood as a suspension of RBCs allows to inherently capture important rheological and transport properties of blood. Two-dimensional models for blood simulations have been extensively used for this purpose [17, 145, 42, 41, 147].

Due to their reduced computational requirements, 2D models are preferable as a method for delivering an initial intuition, measurements and to fast-prototype an idea, regarding several relevant phenomena which can later be explored experimentally. One of the first blood models capable of performing dense suspensions in two-dimensions was presented by Bagchi in 2007 [17], simultaneously considering a large ensemble of red blood cells along with their deformation. The significance of RBCs on primary thrombus formation was studied in 2D by Mori et al. [145], while Crowl & Fogelson [41] used a lattice Boltzmann-immersed boundary method to simulate the motion of dense red blood cell suspensions and their effect on platelet-sized particles. Mountrakis et al. [147] studied the flow of RBCs and platelets through aneurysm vessels.

Modeling RBC suspension flow coping with high volume fractions, high shear rates and, consequently, large cell deformations and frequent cell-cell interactions, remains challenging while at these conditions the employed methods introduce their own restrictions.

In the current work we present a two-dimensional model for blood flow, using a lattice Boltzmann model (LBM) for the fluid flow, coupled to a discrete element model (DEM) for RBCs with the immersed boundary method (IBM). We define a comparably coarse mesoscopic representation of cells and flow that is still able to recover essential physics and physiological phenomena. The model is compared against experimental data for the tank-treading frequency of a single RBC in shear flow, the thickness of the cell-free layer in channel flows and the shear-thinning behaviour.

3.2 Numerical models and methods

A suspension of neutrally buoyant RBCs, immersed in a fluid with the viscosity of plasma represents blood in our simulations. Fluid is simulated with LBM using the D2Q9 LBGK scheme [188] and RBCs are closed deformable membranes, represented by Lagrangian surface points (LSPs). They have a biconcave shape and a diameter of 8\(\mu\)m. The lattice constant is \(\Delta x = 1\mu m\), proven sufficient to resolve the flow field around the cells. IBM couples RBCs and fluid [166].
3.2. NUMERICAL MODELS AND METHODS

3.2.1 Membrane Model

The membrane of an RBC consists of 26 neighboring LSPs connected by Hookean springs, enhanced with bending resistance. Furthermore, forces that ensure the conservation of area (2D equivalent of volume) and that consider the cell-cell interactions are specified. Similar approaches can be found in [17, 181].

The Hookean spring force between the membrane points is defined as

\[ F_{spr} = -C_{spr}(|r_{i+1} - r_i| - r_0)e_{i,i+1} \]

where \( r_0 \) is the equilibrium length, \( e_{i,i+1} \) the unit vector connecting the two membrane points and \( C_{spr} \) the spring constant. \( C_{spr} \) is chosen as large as numerical stability allows, to ensure the conservation of RBC’s area (perimeter in 2D). The damping of this interaction is omitted, owing to the immersed boundary coupling with the dissipative fluid.

A bending (torsion) force associated with a damper is incorporated to the model in the form of:

\[ F_{trs}(r_i) = -f_{trs}n_i \quad \text{with} \quad f_{trs} = -C_{trs}\angle(r_i - r_{i-1}, r_{i+1} - r_i) - D_{trs}\partial_t \angle(r_i - r_{i-1}, r_{i+1} - r_i) \]

where \( n_i \) indicates the normal vector of point \( r_i \), \( f_{trs} \) the magnitude of the force, \( \angle(\cdot, \cdot) \) the angle between the two vectors, \( C_{trs} \) the bending constant and \( D_{trs} \) the bending "viscosity". A similar and opposite force is applied to the neighboring points of \( r_i \):

\[ F_{trs}(r_{i-1}) = f_{trs}n_{i-\frac{1}{2}}, \quad F_{trs}(r_{i+1}) = f_{trs}n_{i+\frac{1}{2}} \]

with \( n_{i\pm\frac{1}{2}} \) being the normal vector of the segment \((r_i, r_{i\pm1})\). Note that \( n_l = n_{l+\frac{1}{2}} + n_{l-\frac{1}{2}} \) results in zero total force on this 3-point system.

To ensure that the area of the 2D-RBC will be conserved, we employ a simple relaxation mechanism:

\[ F_{area}(r_i) = -C_{area}(A - A_0)n_i \]

where \( A_0 \) represents the equilibrium area of a cell and \( C_{area} \) the area constant. Due to the discretization of the cell, the total force may not be equal to zero and therefore a force correction must be applied.

The repulsive force has the form:

\[ F_{rep} = \begin{cases} -C_{rep}h^{-2}e_{ij}, & h \leq h_{cutoff} \\ 0 & h > h_{cutoff} \end{cases} \]

where \( h = |r_i - r_j| \), \( C_{rep} \) a constant and \( h_{cutoff} \) the cutoff distance within which the force is applied. The existence of this force serves two purposes: on the
one hand it prevents cells from sticking (see 3.2.2) and on the other it assists in tuning the rheology of the suspension. However, it also contributes in increasing the effective cell area.

RBCs are initialized as discs followed by a deflation to a surface ratio of $S_{\text{RBC}}/S_{\text{sphere}} = 0.45$. The biconcave shape emerges as a combination of the constitutive model and the surface ratio. The viscosity ratio between the fluid inside and outside of the RBC is 1.0, similar to [181, 114], but IBM seems to introduce additional damping contributions, influencing the effective viscosity of the membrane and the surrounding fluid. For $\Delta x = 1\mu m$, the complete inner fluid of the RBC is affected.

The parameter values listed in Table 3.1 were used in all the following simulations. Deviations from experimental values found in the literature, can be attributed to the presence of the interpolation kernel, which affects the properties of the RBC’s membrane, due to the numerical thickness it introduces [115].

The spatial discretization, $\Delta x = 1\mu m$, is from 3 to 5 times larger than similar models, while the number of LSPs, $N_{\text{LSP}} = 26$, is likewise reduced [181, 226, 17]. For a 2D-LBM alone this yields a reduction of a factor up to $5^4$ in the computational effort, due to the diffusive scaling. The complexity of the DEM scales linearly with $\Delta x$, however the $O(N^2)$ part resulting from the repulsive force significantly benefits from the coarsening.

### 3.2.2 Immersed Boundary Method

The Immersed Boundary Method (IBM) [166] is a pure coupling method, tackling the problem of fluid-structure interaction and is widely used in blood flow.
applications [17, 181, 41, 181, 226, 116]. The key principle behind IBM is the no-slip condition at the interface of the membrane and the fluid. The Langrangian point $x_i(t)$ on the boundary of the membrane exerts a force $F_i(t)$ on the fluid, which is distributed among the closest Eulerian points $X$ of the fluid:

$$f(X, t) = \sum_i F_i(t) \delta(X - x_i(t))$$  \hspace{1cm} (3.8)

where $\delta(X - x_i(t))$ is a discrete Dirac delta function.

Subsequent to the LBM update, the velocity of the membrane point $i$ is updated based on the local flow field and advected according to the Euler scheme:

$$x_i(t + \Delta t) = x_i(t) + u_i(t + \Delta t) \Delta t$$ \hspace{1cm} (3.9)

where $$u_i(t + \Delta t) = \sum_i u(X, t + \Delta t) \delta(X - x_i(t)),$$ \hspace{1cm} (3.10)

The $\delta(r)$ function of eqs. 3.8 and 3.10 is used for the numerical spreading of forces (Eq. 3.8) and the interpolation velocities (Eq. 3.10). It is constructed by multiplying 1D interpolation kernel functions $\phi_n$, as $\delta(r) = \phi_n(x)\phi_n(y)$, where $n$ denotes the extent of the support in both directions. In the present work we used the following kernels:

$$\phi_2(r) = \begin{cases} 
1 - |r| & |r| \leq 1, \\
0 & |r| \geq 1
\end{cases} \hspace{1cm} (3.11)$$

$$\phi_4^2(r) = \begin{cases} 
\frac{1}{4}(1 + \cos \frac{2\pi}{r}) & |r| \leq 2 \\
0 & |r| \geq 2
\end{cases} \hspace{1cm} (3.12)$$

$$\phi_4^4(r) = \begin{cases} 
1 - r^2 & |r| \leq 1 \\
2 - 3|r| + r^2 & 1 \leq |r| \leq 2 \\
0 & |r| \geq 2
\end{cases} \hspace{1cm} (3.13)$$

The implications of the choice of kernels are investigated in Sec. 3.3.1. For the suspension simulations of this work $\phi_2(r)$ is used.

**Restrictions of IBM**

IBM’s simplicity comes with a cost and the restrictions of the method are prevalent in dense suspensions with high shear rates [114]. The major shortcoming of IBM in dense suspensions appears when the distance of two or more LSPs is small compared to the lattice constant $\Delta x$. Adjacent LSPs interpolate similar velocities and are advected to adjacent positions anew. Under normal conditions this induces a form of ”correlation” between the LSPs (different from lubrication interactions), thus affecting the rheology. In worse cases LSPs ”stick” to
each other, preventing their further separation. In dense suspensions with high velocity gradients this can be a frequent event.

Two types of LSP interaction can be distinguished: LSPs of the same cell in need of an optimal distance to ensure separation and LSPs of different cells that have to be kept apart by an additional repulsive force. The repulsive force, introduced in sec. 3.2.1, has to be carefully tuned such that the correct rheological behavior of blood is recovered.

The distance in units of $\Delta x$ between adjacent membrane LSPs, plays an important role for the impermeability of the membrane. Krüger [115], studying 3D capsules, suggests that an average point distance $\bar{l}$ between 0.5 and 1.5 $\Delta x$ does not compromise the impermeability of the capsule, but a similar analysis for our 2D model revealed that an average point distance of $\bar{l} = 0.33\Delta x$ is adequate (data not shown). The difference could be attributed to the coarseness of our model and the disparities between 2D and 3D.

The interaction of solid and IBM-type boundaries deserves also some attention, in the case which a solid node is within the reach of the interpolation kernel. In this work we remove a layer of the boundary domain extending $1\Delta x$, placing a spatially fixed membrane governed by IBM, similar to the cell membranes. This approach overcomes a number of difficulties that arise from the combination of IBM and LBM bounce-back boundaries [17, 114], allowing smoother boundary representations.

### 3.3 Results and Discussion

One of the main goals of a blood-like model, is for it to reproduce important blood and cell phenomena. For this reason we compare our simulations with experiments of single RBC in shear flow and RBC-suspensions in shear and channel flow.

#### 3.3.1 Single red blood cell in shear flow

Three types of motion have been observed for a single RBC in shear flow: tumbling (T), tank-treading (TT) and swinging motion (S). In tumbling the cell flips like a solid body, in tank-treading the cell maintains a fixed orientation angle while the membrane and the interior fluid undergo a steady rotary motion and in swinging the inclination angle of the cell is oscillating [17, 10, 70].

A single RBC was positioned in the center of a domain with Lees-Edwards boundary conditions (LEbc) [134] and the T and TT frequencies were measured with different interpolation kernels. The simulation results shown in Fig. 3.1a are in good agreement with experimental data [197, 18]. The different types of motion that can be distinguished in Fig. 3.1b are: the plateau in low shear rates for T,
3.3. RESULTS AND DISCUSSION

Figure 3.1: (a) Tank-treading frequency normalized by the shear rate $\dot{\gamma}$ (Experimental data from Tran-Son-Tay et al. [197] and Basu et al. [18]) and (b) tumbling frequency as a function of the shear rate for different interpolation kernels. Simulations are represented with open symbols and experiments with filled.

zero tumbling frequency in higher shear rates for a TT cell and the existence of intermediate values qualitatively corresponding to S. Figure 3.1b reveals that the choice of an IBM interpolation kernel affects the transition from T to TT and the magnitude of T frequency but not the TT frequency. This is likely a consequence of the coarsened model, since the mean LSP distance is comparatively small and kernels with large support introduce larger spatial correlation. When $\phi^c_4$ was used, the RBC was stopping its motion after a number of iterations, possibly due to these large spatial correlations. Kernel $\phi^h_4$, having negative parts for $r > \Delta x$, does result in a steady tumbling motion however. This behavior requires further investigation.

3.3.2 Blood suspension flow

Blood is a shear thinning fluid and its viscosity depends on the shear rate. Viscosity measurements from channel flow are not accurate enough, due the exposure of blood to a range of shear rates and the presence of a cell-free layer (CFL). A shear flow “viscometer” has to be employed and a LEbc domain can serve this purpose. The periodic boundaries of LE allow more realistic computational setups than a bounded Couette flow, which can bias typical flow structures of the suspension [134].

RBCs were randomly positioned in the LEbc domain and the relative apparent viscosity was computed using Batchelor’s method [114, 19]. The results are shown
in Fig. 3.2b. The behavior of the viscosity is highly affected from the interactions between RBCs, constituting Eq. (3.6) and IBM’s “stickiness” crucial. Shear thinning in blood is seen as the breakdown of the rouleaux-like RBC structures which are formed in low shear rates.

The apparent viscosity of blood changes depending on the diameter of the vessel it flows, an effect known as the Fåhræus-Lindqvist effect [73]. This is observed in small vessels (< 500µm) and is caused by the migration of RBCs towards the center, leaving a cell-free layer near the walls. The viscosity of the CFL, much smaller than that of the core region, effectively leads to a boundary slip [126].

RBCs were again positioned randomly and the fluid, initially set at rest, was driven by a constant body force chosen to matched experimental values in a way similar to Bagchi [17]. The simulation measurements of the relative apparent viscosity (Fig. 3.3a) agreed with the empirical relation proposed by Pries et al. [171] based on in vitro blood flow. The thickness of the CFL becomes more pronounced for vessels with smaller diameters, thus resulting in smaller relative apparent viscosities, in contrast to larger vessels where δ/(D/2) becomes negligible (Fig. 3.3b) [126]. CFL thickness δ was measured as the distance from the wall that first reaches half of the value of the channel hematocrit. It was found to be close to experimental results from [34] and [111] (Fig. 3.3c).
3.4. CONCLUSIONS

Figure 3.3: (a) Relative apparent viscosity of blood as a function of the vessel size and hematocrit (data from Pries et al. [171], dashed line), (b) hematocrit distribution along the with respect to the vessel position, normalized by its diameter for $H = 40\%$ and (c) CFL thickness $\delta$ normalized with the radius of the vessel $D/2$ (experimental data from Bugliarello and Sevilla [34]) and Kim et al. [111]. Open symbols represent simulation results and filled symbols experimental data.

3.4 Conclusions

In the current work we have presented a two-dimensional model for blood-like flow, which explicitly simulates RBCs immersed in a plasma-like fluid. The model constitutes a coarse representation of cells and flow that is still able to recover essential physics and physiological phenomena. It can reproduce the Fåhraeus-Lindqvist effect, the formation of a CFL and shear thinning, showing that the model captures essential rheological and transport effects. Furthermore, a single RBC in shear flow tumbles and tank-treads, while the tank-treading frequency was in good agreement with experiments.

IBM is an effective method, but care has to be taken when the spatial resolution is reduced. Simulations revealed that the choice of an interpolation kernel affected the transition from T to TT and the magnitude of T frequency. Additionally, IBM introduces an artificial interaction between LSPs, necessitating an adaptation of the cell-cell interactions in order to adequately recover blood’s apparent viscosity.
ficson: A parallel framework for immersed cell suspensions

Dynamics classes are (relatively) easy, because lattice Boltzmann is easy, as long as there are no boundaries, refined grids, parallel programs, or any other advanced structural ingredients.

Palabos User Guide v1.0 r1

We present performance results from ficson, a general purpose parallel suspension solver, employing the Immersed-Boundary lattice-Boltzmann method (IB-LBM). ficson is built on top of the open-source LBM framework Palabos, making use of its data structures and inherent parallelism. We describe the implementation and present weak and strong scaling results for simulations of dense red blood cell suspensions. Despite its complexity the simulations demonstrate a close to linear scaling, both in the weak and strong scaling scenarios.

4.1 Introduction

Blood is a substance where the microstructure plays an important role in understanding the rheology and transport properties of this dense suspension. Approximately 5 million deformable red blood cells (RBCs) per cubic millimeter account for 40 to 45% of the total blood volume. They bring out many biologically interesting phenomena like the Fähræus and Fähræus-Lindqvist effects [72, 73], the margination of platelets [8] and the non-Newtonian nature of blood [76]. Blood flow models can give insights to studies of cell diseases, such as malaria or sickle-cell anemia [223, 128] and also in cardiovascular diseases like the formation of atherosclerotic plaques or thrombosis in aneurysms [39, 232, 147, 140].

Simulations of dense suspensions, like blood, demand considerable computational resources. Software, in terms of algorithms, data structures and parallelism, is becoming more and more crucial in extracting knowledge from such systems. Implementing basic algorithms is relatively straightforward, yet complexity steeply increases by incorporating parallelism, elaborate boundary conditions, or other advanced elements, such as thermal and multiphase flows, moving objects, and suspended particles. A number of lattice-Boltzmann solvers already have several of the aforementioned capabilities implemented and tested and are released under an open-source license. Some examples of such established frameworks are, e.g. Palabos [6], LB3D [5], Sailfish [97], HemeLB [138], LUDWIG [46] and Musubi [85].

In this work we present the parallel performance of ficsion, a general purpose parallel IB-LBM solver with a focus on suspensions of deformable particles, like blood. ficsion is build on top of the open-source C++ framework Palabos [6], making use of its data structures, parallelism and well-tested modules. The development of a fully parallelized suspension code implemented on top of a third-party framework is a challenging task, especially when the developer has no direct control over parallelization, and the existing parallel data structures have to be employed creatively. In this chapter we describe ficsion and present weak and strong scaling results for its application to the simulation of fully resolved blood flow.

4.2 Methods

Our approach is based on the immersed boundary-lattice Boltzmann method (IB-LBM), a combination frequently used in modeling blood suspensions [116, 227, 148]. Suspensions of deformable cells are the focus of ficsion, yet methods for hard-objects, like the Noble-Torczynski [156] or Ladd’s method [120], could be incorporated and parallelism would be retained.

RBCs are represented as a mesh of Langrangian surface points, interacting
4.2. METHODS

Figure 4.1: Snapshot of channel flow between two parallel plates, placed on the top and bottom of the channel. The domain is periodic in the other dimensions. Size of the domain is $128 \times 64 \times 64 \mu m^2$ with $\approx 1530$ RBCs (hematocrit $H \approx 30\%$). The simulation was performed in 16 cores and color denotes the MPI rank.

via a spectrin link model. LBM is used for the fluid phase and is coupled to the suspended RBCs with the immersed boundary method. Fig. 4.1 depicts a snapshot from a representative simulation of blood flow between two parallel plates with fission using $N_p = 16$ processors. Periodic boundary conditions were used for this simulation, with a body force acting as a pressure gradient.

4.2.1 Lattice Boltzmann method

The lattice Boltzmann methods (LBMs) [188] are a class of mesoscopic particle-based approaches simulating fluid-flow. LBM’s local kinetic scheme allows for an intrinsic parallelization, rendering it a good candidate for parallel computing [15, 187].

The main quantity of a lattice Boltzmann model is the population density $f_i(x,t)$, which corresponds to the discretized probability distribution of finding fluid particles at site $x$ and time $t$, moving with a discrete velocity $c_i$. The general form of a LBM is:

$$f_i(x + c_i \Delta t, t + \Delta t) = f_i(x, t) + \Omega_i(f_i(x, t))$$  \hspace{1cm} (4.1)

where $\Omega_i(f_i(x,t))$ is the collision operator, which re-shuffles densities $f_i$ according to the kinetic theory of gases and $\Delta t$ is the time step.

A wide range of models for a variety of applications has been developed starting from the general description. A simple and widely used form of $\Omega_i(f_i(x,t))$ is the linearized single relaxation time collision operator, or LBGK model. In LBGK the collision operator takes the form:

$$\Omega_i(f_i(x,t)) = -\frac{1}{\tau}(f_i(x,t) - f_i^{eq}(x,t)),$$  \hspace{1cm} (4.2)
where \( \tau \) is the relaxation parameter and \( f_{\text{eq}}^i(x,t) \) the equilibrium population corresponding to an expansion of the Maxwell-Boltzmann distribution for small Mach numbers. The zeroth and first moment of the population densities recover the fluid density \( \rho \) and velocity \( u \) according to \( \rho = \sum_i f_i \) and \( \rho u = \sum_i f_i c_i \). Kinematic viscosity \( \nu \) for the LBGK collision operator is given by \( \nu = (\tau - \frac{1}{2})c_s^2 \Delta t \) in which \( c_s = \frac{1}{\sqrt{3}} \Delta x/\Delta t \) is the lattice speed of sound.

### 4.2.2 Immersed boundary method

The immersed boundary method (IBM) \[166\] is a pure coupling method used in fluid structure interaction. One of the main advantages of IBM, is that the fluid and the immersed structure do not need to conform. This alleviates the need for remeshing and renders complex configurations like dense suspensions easier to handle. With IBM the cell \(^1\) follows the Lagrangian description.

The basic concept of IBM is the no-slip condition at the interface of the membrane and the fluid. This is realized as the Langrangian surface points (or surface particles) which constitute the membrane mesh, exert a force to the fluid, while they are advected by interpolating the fluid velocity.

The surface particle \( x_i(t) \) spreads a force \( F_i(t) \) to the closest Eulerian points \( X \) of the fluid according to

\[
\begin{align*}
  f(X,t) &= \sum_i F_i(t) \delta(X - x_i(t))
\end{align*}
\]  

(4.3)

where \( \delta(X - x_i(t)) \) is a discrete Dirac delta function. Following this step, the position of the particle is updated according to the Eulerian scheme

\[
\begin{align*}
  x_i(t + \Delta t) &= x_i(t) + u_i(t + \Delta t)\Delta t \\
  \text{where} \quad u_i(t + \Delta t) &= \sum_X u(X,t + \Delta t)\delta(X - x_i(t)),
\end{align*}
\]  

(4.4) (4.5)

and uses the same discrete Dirac delta function \( \delta(X - x_i(t)) \) as in Eq. 4.3.

\( \delta(r) \) is constructed by multiplying 1D interpolation kernel functions \( \phi \), as \( \delta(r) = \phi(x)\phi(y)\phi(z) \). It is possible to find many discretized delta functions with varying interpolation ranges, yet a number of restrictions should be fulfilled \[166\]. In the present work we used the kernel \( \phi_2(r) : \)

\[
\phi_2(r) = \begin{cases} 
  1 - |r| & |r| \leq 1, \\
  0 & |r| \geq 1
\end{cases}
\]  

(4.6)

\(^1\)The term particle is typically used in the literature of hard objects for what we here define as a cell. As cell we define the network of surface particles (or simply particles) that constitute the surface of the object and interact via a constitutive model.
4.2. METHODS

<table>
<thead>
<tr>
<th>parameter</th>
<th>value</th>
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<tbody>
<tr>
<td>plasma density, ( \rho )</td>
<td>1025 kg/m(^3)</td>
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<tr>
<td>kinematic viscosity, ( \nu )</td>
<td>( 1.7 \times 10^{-6} ) m(^2)/s[105]</td>
</tr>
<tr>
<td>shear modulus, ( \mu_0 )</td>
<td>5.5 ( \mu )N/m[59]</td>
</tr>
<tr>
<td>bending constant, ( k_{bend} )</td>
<td>100 ( k_B T )[59]</td>
</tr>
<tr>
<td>volume constant, ( k_{volume} )</td>
<td>6 ( \times ) 10(^4)</td>
</tr>
<tr>
<td>surface constant, ( k_{surface} )</td>
<td>6 ( \times ) 10(^4)</td>
</tr>
<tr>
<td>local area constant, ( k_{shear} )</td>
<td>100[59]</td>
</tr>
<tr>
<td>maximum length, ( L_{max} )</td>
<td>2.5 ( \times ) ( L_0 )</td>
</tr>
<tr>
<td>viscosity ratio, ( \lambda )</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Table 4.1: Model parameter and constants. Most of the values were taken from modeling studies using a similar model, while others like volume and surface constants resulted from simulations of stretching RBC (data not shown).

for its simplicity and compact support. The subscript of \( \phi \) describes the support width of the kernel. More kernels are available and we have performed some benchmarks in 2D [148].

4.2.3 Membrane model of a single RBC

As discussed, a typical case of a highly demanding dense suspension, is the one of blood. Blood consists of a vast number of red blood cells, which are biconcave disk-shaped membranes with a diameter of 6 – 8\( \mu \)m and a thickness of approximately 2 – 2.5\( \mu \)m. The membrane of an RBC is composed of an incompressible lipid bilayer underlined by an elastic spectrin cytoskeleton, encapsulating a Newtonian solution of hemoglobin and may undergo severe deformation in narrow capillaries [75, 143].

In the current work we employ the spectrin-link model to represent an RBC [169, 59, 60, 175], in which a systematic coarse-graining procedure has been developed [169] allowing for an RBC to be described with arbitrary number of vertices.

The 3D membrane model takes into account the in-plane shear energy, the bending energy, a fixed surface and local area and a fixed enclosed volume. The Helmholtz free-energy of the system is given by

\[
F(\{x_n\}) = F_{\text{in-plane}} + F_{\text{bending}} + F_{\text{volume}} + F_{\text{area}}
\] (4.7)
The in-plane free energy term is written as

\[ F_{\text{in-plane}} = \sum_{l \in \text{edges}} V_{\text{WLC}}(L_l) + \sum_{l \in \text{edges}} \frac{k_{\text{rep}}}{L_l}, \quad (4.8) \]

with

\[ V_{\text{WLC}}(L_l) = k_B T L_{\text{max}} \frac{3x_l^2 - 2x_l^3}{4p} \frac{1}{1 - x_l}. \quad (4.9) \]

where \( V_{\text{WLC}} \) stands for the worm-like chain potential, referring to the total entropic free energy stored in the spectrin proteins [127]. \( L_l \), \( L_{\text{max}} \) and \( p \), denote the length of edge \( l \), the maximum allowed extension length and the persistence length respectively, \( k_{\text{rep}} \) is a constant chosen so that the in-plane force is zero for the equilibrium length \( L_0 \), \( x_l \) is defined as \( x_l = L_l / L_{\text{max}} \), \( k_B \) is Boltzmann’s constant and \( T = 300^\circ \text{K} \) the temperature.

The bending energy is defined as

\[ F_{\text{bending}} = \sum_{\alpha, \beta \text{pair}} k_{\text{bend}} [1 - \cos \{ \theta_{\alpha \beta} - \theta_0 \}] \quad (4.10) \]

where \( k_{\text{bend}} \) is the bending constant, \( \theta_{\alpha \beta} \) and \( \theta_0 \) are the instantaneous and equilibrium angles between two adjacent triangles respectively.

Micropipette aspiration experiments [88] have revealed that RBCs elongate and bend rather easily, yet it is very difficult to increase their volume. This is incorporated as a set of volume and surface constraints:

\[ F_{\text{volume}} = k_{\text{volume}} \frac{k_B T ( \Omega - \Omega_0)^2}{2L_0^3 \Omega_0} \quad (4.11) \]

\[ F_{\text{area}} = k_{\text{surface}} \frac{k_B T (S - S_0)^2}{2L_0^2 S_0} + \sum_{k=1}^{N_1} k_{\text{shear}} \frac{k_B T (A_k - A_0)^2}{2L_0^2 A_0} \quad (4.12) \]

in which \( k_{\text{volume}}, k_{\text{surface}} \) and \( k_{\text{shear}} \) are the volume, surface and local triangle area constants, while \( k_{\text{volume}} \) and \( k_{\text{surface}} \) can be chosen arbitrarily high, to ensure the conservation of volume and surface. \( \Omega, S \) and \( A_k \) are the volume, surface and triangle area of the cell, while \( \Omega_0, S_0 \) and \( A_0 \) are their corresponding equilibrium values. The values of the simulation parameters, including those of the fluid, are shown in Table 4.1.

The force acting on vertex \( i \) is derived as \( f_i = -\frac{\partial F(x_i)}{\partial x_i} \) and as Reasor et al. [175] pointed out, each contribution is an extensive exercise in chain-rule differentiation. An analytic derivation of the forces from free energy, can be found in [114].

The shear modulus of the membrane can be calculated from [60] as:

\[ \mu_0 = \frac{\sqrt{3} k_B T}{4p L_{\text{max}} x_0} \left( \frac{x_0}{2(1 - x_0)^3} - \frac{1}{4(1 - x_0)^2} + \frac{1}{4} \right) + \frac{3\sqrt{3}k_{\text{rep}}}{4L_0^3}, \quad (4.13) \]
while area-compression and Young’s moduli are given from:

\[ K = 2\mu_0 + k_{\text{shear}} + k_{\text{surface}} \]  
\[ Y = \frac{4K\mu_0}{K + \mu_0}. \]  \hspace{1cm} (4.14, 4.15)

### 4.2.4 Parallel Implementation

ficsion is built on top of Palabos [6], one of the parallel open-source CFD solvers based on the lattice Boltzmann method. Palabos offers a wide range of modules and data-structures, in which the parallelization schemes are fully hidden in the API.

The class ParticleField is one of the main Palabos modules employed in ficsion: a container of Lagrangian particles in a structure analogous to the so-called cell-list\(^2\) in Molecular Dynamics algorithms [12]. Finding neighboring particles for cell-cell forces can be a time consuming task and cell-lists can reduce the potentially \(O(N^2)\) complexity to \(O(N)\), which is crucial when the number of particles \(N\) becomes large[187, 12]. The parallelism of a ParticleField follows the domain-decomposition of the fluid field and allows to directly identify the particles that belong to the envelopes and communicate them to the neighboring subdomains. Envelopes are the boundary nodes communicated in the domain-decomposition approach, also commonly referred to as ghost nodes.

Two instances of ParticleField are utilized for the simulation of a cell-type: one where particles represent the vertices of the cell’s surface and interact according to the constitutive model – they are coined SurfaceParticles – and one for the cell as a whole carrying essential cell information like volume or surface – coined CellParticles. Since ParticleFields are fully parallelized, the field of CellParticles is taking care of all the necessary communication of information between the neighboring subdomains. The position of CellParticles is defined as the centroid of the SurfaceParticles belonging to the actual subdomain (envelopes excluded) and have only a small memory and communication footprint. The drawback of this approach is that it introduces an additional overhead of frequently instantiating and organizing SurfaceParticles into CellParticles, due to the motion of cells across the subdomains.

Optimizing communication is an important aspect of the implementation, since the different fields (fluid, SurfaceParticles, and CellParticles) have different needs for spatial information over the neighboring subdomains. In that respect, the widths of the envelopes differ for each field, to minimize the amount of data transferred. For the fluid this width is determined by the support width of the IBM kernel \(\phi\), for the SurfaceParticles by the maximum

\(^2\)Not to be confused with the definition of a cell used here.
Figure 4.2: Schematic representation of the domain decomposition of ficsion. Blue crosses represent the actual domain and the blue, red, and black lines the extent of the envelopes for the fluid, the SurfaceParticles, and the CellParticles respectively. The position of CellParticles is defined as the centroid of the SurfaceParticles belonging to the domain and not in the envelopes. SurfaceParticles have different color depending if they are inside or outside of the domain (in the envelopes), and CellParticles depending on the domain they belong.
4.2. METHODS

distance between two neighboring surface particles of a single cell\(^3\) and for the CellParticles by the maximum stretch a cell can have. Typically for blood suspensions, CellParticles have envelopes that are larger than SurfaceParticles, which in their turn have larger envelopes than the fluid. A schematic of the domain decomposition is shown in Fig. 4.2, and the main data structures are depicted in Fig. 4.3.

With these central structures a cell can freely move between domains and is created upon entrance and destroyed on exit. Additionally, a wide range of cell types can be incorporated within one simulation. The price for this modularity is an overhead created by the bookkeeping and updating of the corresponding data structures.

\(^3\)Owing to the bending force in which two neighboring triangles must be present for the computation, a safe choice would be two time the maximum distance.
Parallel workflow

An outline for the parallel workflow for our IB-LBM implementation is depicted in Fig. 4.4. Each task can contribute to a different “group of actions”, used for profiling reasons. The workflow is as follows:

**Force computations.** In this step the forces are calculated via the constitutive model, and subsequently cell-cell interactions. At the end, a synchronization step is performed for the surface-particles.

**IBM force spreading.** After the LBM force-field has been reset to zero, the surface-particle forces are spread to it.

**LBM step.** The fluid-flow step is performed, with a synchronization step at the end.

**Position update for surface-particles.** The velocity of the surface particles is interpolated from the fluid and they are advected accordingly. A synchronization step is performed for the surface-particles.

**Book-keeping** The Cell3D structures are updated.

**Collective cell quantity computations.** Volume, surface and other potentially useful cell quantities are computed and communicated via cell-particles.
4.3 Results

In this section we report on the performance of `ficsion`. We perform an analysis of weak and strong scaling and examine the behavior with respect to hematocrit \( H \), i.e. the cell number density. We are in the process of obtaining more detailed profiling measurements and additional parallel performance results.

The results of this study were obtained on Cartesius, SURFsara in The Netherlands [1], while the code has also been ported on FERMI BG/Q, CINECA in Italy [4] The part of Cartesius we used consists of 3 thin node islands with 360 thin nodes each, with 2×12-core 2.6 GHz Intel Xeon E5-2690 v3 (Haswell) CPUs/node with hyper-threading technology. Each node has 64 GB/node and a Mellanox ConnectX-3 InfiniBand adapter.

### 4.3.1 Weak and strong scaling

A fully periodic unbounded domain was used for the simulations and an initial velocity of \((0.02, 0.02, 0.02)\) lattice units was applied to the fluid. Essentially, this setup is a Galilean invariant case, forcing cells to move only with respect to the reference frame. For the weak-scaling case, cells were initialized randomly at a fraction of their initial volume, while for the strong-scaling case, cells were
initialized with their full volume in ordered columns. Load balancing issues and specifically deviations in the number of cells, were one of the main reasons for the poor scaling performance of Clausen et al. [40] on the IBM Blue Gene/P architecture. Our initialization setup ensures a high degree of load-balance, expecting the same amount of SurfaceParticles and CellParticles in each subdomain.

The quantity we measure is the wallclock-time per iteration taken from the last 100 iterations of a 200 iteration simulation and one iteration is one LBM timestep. In these 200 iterations all cells moved 4 lattice units from their initial position. Initialization and I/O operations were not taken into account. The parameters of the simulations are shown in Table 4.2.

For strong scaling the size of the whole domain is fixed and the number of processes varies. Strong scaling Speedup and Efficiency read:

\[ \text{Speedup}_{\text{strong}} = \frac{t_{N_0}}{t_N} \]  
\[ \text{Efficiency}_{\text{strong}} = \frac{t_{N_0} N_0}{t_N N} \times 100\%. \]  

with \( t_{N_0} \) being the time spend in \( N_0 \) processes and \( t_N \) in \( N \) processes.

In weak scaling the size of the subdomain per process is fixed, and parallel Speedup and Efficiency are defined as:

\[ \text{Speedup}_{\text{weak}} = \frac{t_{N_0}}{t_N} \frac{N}{N_0} \]  
\[ \text{Efficiency}_{\text{weak}} = \frac{t_{N_0}}{t_N} \times 100\%. \]
4.3. RESULTS

Figs. 4.5a and 4.6b reveal a fairly good strong and weak scaling. This can be attributed to two points: (a) the computation to communication ratio is in favor of computation due to the low spatial resolution, and (b) the cases we ran are almost perfectly load balanced, with insignificant deviations in the number of cells and without deviations in the number of LBM nodes. With the low resolution employed, when compared for example to Clausen et al. [40], more RBCs can fit per cubic lattice unit increasing the amount of computation per subdomain. The influence of the load imbalance, for example created by the presence of solid walls inducing cell free layers close to the surface, is part of our future work.

In weak scaling, a unit-subdomain of $32 \times 32 \times 32$ is used for each processor. For $N_p = 16$ a grid of $4 \times 2 \times 2$ subdomains is created, while $N_p = 32$ yields a $4 \times 4 \times 2$. The first case where a central subdomain exists, i.e. it has different neighboring subdomains on all sides all residing on different processors, is observed for $N_p = 32$ and in combination with the fact that each thin node in Cartesius has 24 cores so that all subdomains run in a shared-memory space, it could explain the drop from 16 to 32 cores in Fig. 4.6.

4.3.2 Profiling with respect to hematocrit

In Fig. 4.7a we observe that the constitutive model (with the identifier CellModel) consumes most of the computational time, followed by IBM and routines related to book-keeping and data structures (identifier Helper). LBM takes up only a small fraction of the computational time. This is a trait of the low resolution ($dx = 1 \mu m$), resulting in more RBCs per cubic lattice unit, and consequently per subdomain, which as mentioned earlier, leads to a good computation to communication ratio.
Fig. 4.7b shows that all modules scale linearly with hematocrit, except LBM, which is expected to remain constant and independent of hematocrit, given a small increase due to the increased number of nodes performing the LBM force-collision step.

4.4 Discussion and conclusions

We have presented ficsion, a suspension framework build on top of the open-source LBM solver Palabos. We have analyzed the issues resulting from the suspension of deformable cells and presented our parallelization strategy. It was shown that the execution time of ficsion scales linearly with the hematocrit and exhibits satisfactory weak and strong scaling results, as a consequence of the favorable computation to communication ratio and the good load-balance of the simulation setup.

Perfectly load-balanced cases are not representative for suspensions [187]. In blood for example, it is known that RBC distributions are inhomogeneous with a red blood cell-free layer near the walls of the vessel, while having an elevated hematocrit in the center [61, 153]. For a static regular decomposition based on a lattice, this would result in load-imbalance, since some subdomains would have less or no RBCs at all. We currently study the effect of such vessel wall-induced imbalance.
Revisiting the use of Immersed Boundary-Lattice Boltzmann method for simulations of suspended particles

The Immersed boundary-Lattice Boltzmann method (IB-LBM) is increasingly being used in simulations of dense suspensions. These systems are computationally very expensive and can benefit from lower, yet accurate, resolutions. IB-LBM has a number of free parameters, such as the lattice constant \( \Delta x \), the number of vertices \( N_v \), the interpolation kernel \( \phi \) and the LBM relaxation time \( \tau \), and their behavior in low resolutions is not well understood.

We investigate the effect of these IB-LBM parameters on a number of seemingly simple but challenging benchmarks. The systems considered are (a) the flow of a single sphere in shear flow, (b) the collision of two spheres in shear flow, and (c) the lubrication interaction of two spheres. The first two systems are used for determining two effective radii, the hydrodynamic radius \( r_{\text{hyd}} \) and the particle interaction radius \( r_{\text{int}} \), while the last system is used to establish the robustness of

---

the lubrication forces.

In the parameter space we investigated the hydrodynamic radius is independent of the interpolation kernel for adequately resolved spheres. The results reveal an interpolation kernel-dependent interaction radius, which is systematically larger than the hydrodynamic. The vertex density seems to be important: under-resolved spheres lead to non-physical particle behavior. This effect is more pronounced in interpolation kernels with shorter support.

5.1 Introduction

The Immersed boundary method (IBM) is a pure fluid-structure interaction method which has been used in a wide range of applications [58, 193, 229, 41, 147, 148, 116]. Since its original introduction in 1972 by Charles S. Peskin [165, 166], many variations of IBM have been presented. An improved IBM with a direct formulation of the fluid-solid interaction force was proposed by Uhlmann [200], using the regularized delta function to associate arbitrary Lagrangian with discrete Eulerian positions. Yang et al. [219] developed a smoothing technique for the discrete delta functions of IBM to suppress the non-physical oscillations in the volume forces, while Wu and Shu [216] presented a model which accurately satisfies the non-slip boundary condition at boundary points. Kempe and Fröhlich [109] proposed several enhancements to Uhlmann’s approach [200] for improving the range of stability of the method and for dealing with approaching interfaces.

The role of some key IBM parameters and their effect on the interactions between the fluid and the immersed structure, or between the immersed structures, is not fully understood. Krüger et al. [115] investigated the impact of some of these relevant parameters by looking into the deformation of an initially spherical capsule, freely suspended in simple shear flow. The tessellation method and resolution of the membrane mesh were found to play only a minor role, while the width of the discrete delta function significantly affected the results of their simulations.

To understand the role of IB-LBM parameters in particle-particle interactions, we performed an extensive study of their impact on the accuracy of the method. The parameters considered are the interpolation kernel $\phi_n$, the grid resolution $\Delta x$, the number of vertices $N_v$, and the LBM relaxation parameter $\tau$. The basic IBM implementation is used, along with stiff spheres while keeping track of any deviation from rigidity. The benchmark systems are (a) a single sphere in shear flow, determining its effective hydrodynamic volume by measuring Einstein’s viscosity, (b) the collision of two particles in shear flow and (c) the lubrication interaction of two spheres.
This chapter is organized as follows: section 5.2 introduces the methods employed for this study, section 5.3 presents the systems and the results obtained, and section 5.4 discusses the findings of the simulations.

5.2 Methods

A combined immersed boundary-lattice Boltzmann method is employed to couple the suspended spheres with the fluid. This method has been extensively used in blood suspension simulation [41, 147, 148, 116], and the constitutive model used here is the same as for red blood cell (RBC) simulations [151], yet much stiffer. Spheres are chosen for the simulations due to the existence of benchmark tests and some known analytical results. The departure from the spherical shape is being tracked and ensured to be within acceptable limits (less than 1% of the radius). More information can be found in appendix B.2.

5.2.1 Lattice Boltzmann Method

The Lattice Boltzmann method (LBM) is a well established mesoscopic approach, which solves asymptotically the incompressible Navier-Stokes equation [188]. LBM’s main quantity is the set of populations \( f_i(x,t) \), which corresponds to the discretized probability distribution of finding particles in site \( x \), at time \( t \), moving with velocity \( c_i \).

The time evolution of the distributions, when an external force is involved, is given by the forced single-relaxation time LBGK equation [188, 83],

\[
\frac{f_i(x + c_i \Delta t, t + \Delta t) - f_i(x, t)}{\tau} = f_i(x, t) - f_i^{eq}(x, t) + \Delta t F_i
\]

(5.1)

where \( \tau \) is the relaxation parameter, \( \Delta t \) is the time step, \( f_i^{eq}(x, t) \) the equilibrium population and \( F_i \) the forcing term.

The equilibrium populations are given by

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

(5.2)

where \( w_i \) is the weighting factor, \( \rho \) and \( u \) are the fluid density and velocity respectively and \( c_s = \frac{1}{\sqrt{3}} \Delta x / \Delta t \) is the lattice speed of sound.

The zeroth and first moment of the populations recover the fluid density \( \rho = \sum_i f_i \) and velocity \( \rho u = \sum_i f_i c_i + \frac{\Delta t}{2} f \), while the kinematic viscosity \( \nu \) of the fluid is given by \( \nu = (\tau - \frac{1}{2}) c_s^2 \Delta t \). The forcing term \( F_i \) of Eq. 5.1 is in form of

\[
F_i = \left( 1 - \frac{1}{2\tau} \right) w_i \left( \frac{c_i - u}{c_s^2} + \frac{(c_i \cdot u)}{c_s^4} c_i \right) \cdot f,
\]

(5.3)
where $f$ is the external body force density.

We used the so-called D3Q19 model (3-dimensional with 19 velocity components) as implemented in the open-source LBM-solver Palabos [6, 151] and built IBM and the constitutive model on top of it.

5.2.2 Constitutive Model of cell membrane

We employ the spectrin-link model [169, 175], widely used in red blood cell simulations and carefully parameterized in this study to correspond to a near-rigid sphere. Each sphere consists of a network of vertices, forming a triangular mesh.

The Helmholtz free-energy of the system is given by

$$F(\{x_n\}) = F_{\text{in-plane}} + F_{\text{bending}} + F_{\text{volume}} + F_{\text{area}},$$

(5.4)

where $x_n$, $n \in 1 \ldots N_v$ are the vertices of a two-dimensional triangulated network describing the surface of a sphere.

The in-plane free energy term is written as

$$F_{\text{in-plane}} = k_{\text{WLC}} \left( \sum_{l\in \text{edges}} V_{\text{WLC}}(L_l) + \sum_{l\in \text{edges}} \frac{k_{\text{rep}}}{L_l} \right),$$

(5.5)

with

$$V_{\text{WLC}}(L_l) = \frac{k_B T L_{\text{max}}}{4p} \frac{3x_l^2 - 2x_l^3}{1 - x_l},$$

(5.6)

$V_{\text{WLC}}$ is the worm-like chain potential, $L_l$ is the length of edge $l$, $L_{\text{max}}$ is the maximum allowed extension length, $x_l$ is defined as $x_l = \frac{L_l}{L_{\text{max}}}$, $p$ is the persistence length and $k_{\text{rep}}$ is a constant chosen so that the corresponding in-plane force is zero for the equilibrium length $L_0$. $k_B$ is Boltzmann’s constant and $T = 300^\circ K$ the temperature.

The bending energy is defined as

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

(5.7)

where $k_{\text{bend}}$ is the bending constant, $\theta_{\alpha\beta}$ and $\theta_0$ are the instantaneous and equilibrium angles between two adjacent triangles respectively.

The volume and surface conservation constraints are written as

$$F_{\text{volume}} = k_{\text{volume}} \frac{k_B T (\Omega - \Omega_0)^2}{2L_0^3 \Omega_0}$$

(5.8)

$$F_{\text{area}} = k_{\text{surface}} \frac{k_B T (S - S_0)^2}{2L_0^2 S_0} + \sum_{k \in 1 \ldots N_t} k_{\text{shear}} \frac{k_B T (A_k - A_0)^2}{2L_0^2 A_0}$$

(5.9)
5.2. METHODS

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<tbody>
<tr>
<td>fluid density, $\rho$</td>
<td>$1025 \text{kg/m}^3$</td>
</tr>
<tr>
<td>kinematic viscosity, $\nu$</td>
<td>$1.7 \times 10^{-6} \text{m}^2/\text{s}$</td>
</tr>
<tr>
<td>bending constant, $k_{\text{bend}}$</td>
<td>$2 \times 10^5 k_B T$</td>
</tr>
<tr>
<td>volume constant, $k_{\text{volume}}$</td>
<td>$6 \times 10^5$</td>
</tr>
<tr>
<td>surface constant, $k_{\text{surface}}$</td>
<td>$6 \times 10^5$</td>
</tr>
<tr>
<td>local area constant, $k_{\text{shear}}$</td>
<td>$5 \times 10^4$</td>
</tr>
<tr>
<td>maximum edge length, $L_{\text{max}}$</td>
<td>$1.1 \times L_0$</td>
</tr>
<tr>
<td>WLC coefficient, $k_{\text{WLC}}$</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 5.1: Model parameters and constants.

in which $k_{\text{volume}}$, $k_{\text{surface}}$ and $k_{\text{shear}}$ are volume, surface and local triangle area constants. $\Omega$, $S$ and $A_k$ are the volume, surface and triangle area of the cell, while $\Omega_0$, $S_0$ and $A_0$ are the corresponding equilibrium values.

The force acting on vertex $i$ is derived from $f_i = -\frac{\partial F(\{x_i\})}{\partial x_i}$ and was calculated analytically.

The equilibrium quantities in the above equations are obtained from the initial shape and may differ per vertex and triangle. This ensures the absence of residual stresses in a similar fashion to the stress-free membrane model followed by Fedosov et al. [59]. The remaining simulation parameters, including those of the fluid, are shown in Table 5.1. The density and viscosity ratio between the inner and the outer fluid is set to 1.

The mesh is obtained by subdividing a regular icosahedron or octahedron and mapping the points of the surface to a sphere, similar to [115]. Applying a stretch force of 250pN in the two poles of the sphere, similar to the stretching of an RBC, yields a deviation of less than 0.08% from the initial radius.

Considering the low particle Reynolds numbers used in this study, the spheres are rendered near-rigid; however, the departure from the spherical shape is tracked for every experiment. Particle Reynolds number is defined as $Re_p = \frac{4\nu r^2}{\dot{\nu}}$ where $\nu$ is the kinematic viscosity of the fluid, $\dot{\nu}$ the applied shear rate and $r$ the radius of the sphere.

5.2.3 Immersed Boundary Method

The Immersed Boundary Method (IBM) [166] is a pure coupling method used in fluid-structure interaction problems. The major advantage of IBM, apart from its simplicity, is that the discretized representations of the fluid and the immersed structure do not need to conform. This alleviates the need for remeshing, rendering complex configurations like dense suspensions easier to handle.
The key principle behind IBM is the no-slip condition at the interface of the membrane and the fluid. This is attained as the fluid velocity is interpolated at the Lagrangian surface points and the computed forces are exerted to the fluid. The force $F_i(t)$ computed at the surface point $x_i(t)$ is distributed among the closest Eulerian points $X$ of the fluid according to

$$f(X,t) = \sum_i F_i(t)\delta(X - x_i(t))$$  \hspace{1cm} (5.10)

where $\delta(X - x_i(t))$ is a discrete Dirac delta function. $f(X,t)$ is coupled to LBM via the forcing term as described in Eq. 5.3.

Subsequently, the velocity of the membrane point $i$ is updated based on the local flow field and advected according to the Euler scheme

$$x_i(t + \Delta t) = x_i(t) + u_i(t + \Delta t)\Delta t$$  \hspace{1cm} (5.11)

or to the Adams-Bashforth scheme

$$x_i(t + \Delta t) = x_i(t) + \left(\frac{3}{2}u_i(t + \Delta t) - \frac{1}{2}u_i(t)\right)\Delta t$$  \hspace{1cm} (5.12)

where

$$u_i(t + \Delta t) = \sum_i u(X, t + \Delta t)\delta(X - x_i(t)),$$  \hspace{1cm} (5.13)

Function $\delta(r)$ of eqs. 5.10 and 5.13, used for the velocity interpolation and force spreading, is replaced by 1D interpolation kernel functions $\phi_n$, where $n$ denotes the support of the kernel in both directions, as $\delta(r) = \phi_n(x)\phi_n(y)\phi_n(z)$. 

---

**Figure 5.1:** Support functions for IBM kernels $\phi_2$, $\phi_3$ and $\phi_4$ (eqs. 5.14, 5.15, and 5.16 respectively).
5.2. METHODS

In the present work we make use the following kernels:

\[
\phi_2(r) = \begin{cases} 
1 - |r|, & |r| \leq 1, \\
0, & 1 \leq |r|
\end{cases} \quad (5.14)
\]

\[
\phi_3(r) = \begin{cases} 
\frac{1}{3}(1 + \sqrt{1 - 3r^2}), & |r| \leq \frac{1}{\sqrt{3}} \\
\frac{1}{6}(5 - 3|r| - \sqrt{-2 + 6|r| - 3r^2}), & \frac{1}{\sqrt{3}} \leq |r| \leq \frac{1}{2} \\
0, & \frac{1}{2} \leq |r|
\end{cases} \quad (5.15)
\]

\[
\phi_4(r) = \begin{cases} 
\frac{1}{8}(3 - 2|r| + \sqrt{1 + 4|r| - 4r^2}), & |r| \leq 1 \\
\frac{1}{8}(5 - 2|r| - \sqrt{-7 + 12|r| - 4r^2}), & 1 \leq |r| \leq 2 \\
0, & 2 \leq |r|
\end{cases} \quad (5.16)
\]

The support of each kernel is plotted in Fig. 5.1.

**Free parameters of IBM**

IBM comes with a number of free parameters. The ones examined in this study are the interpolation kernel \( \phi \), the number of surface vertices \( N_v \), the lattice discretization \( \Delta x \), the update scheme (Eq. 5.12 and 5.11) and the LBM relaxation time \( \tau \). While it is implied that a finer resolution would yield more accurate results, the computationally demanding case of dense suspensions can significantly benefit from identifying the limits and the artefacts of each parameter.

The interpolation kernel \( \phi \) is the core of IBM. It introduces an artificial length scale effectively changing the thickness of the membrane. It is known that kernel \( \phi_2 \) (Eq. 5.14) does not satisfy certain moment conditions and violates the translational invariance and it has been found to introduce non-physical oscillations [166, 219]. Yet, \( \phi_2 \) is considered to capture the relevant physics and is still preferred due to its compact support (1 \( \Delta x \) in each direction), small numerical thickness, and reduced amount of computations [115, 148].

In other works the number of surface vertices \( N_v \) has been found to play only a minor role [200, 115], and a suggested mean vertex distance varies between 0.5 and 1.5\( \Delta x \) [115] (3D simulations) or 0.33\( \Delta x \) [148] (2D simulations) without compromising the impermeability of the particle membrane. The Euler update scheme is used more often in the literature, while Krüger [115] argues that higher order schemes, like the Adams-Bashforth scheme, will not change the outcome of short simulations, yet it might provide additional accuracy for longer-time simulations. The effect of the LBM relaxation time \( \tau \) on the other hand, has been found to be considerable on the IB-LBM simulations, in both simulations of capsules [115] and when acting as velocity boundaries [122]. It is also worth noting that \( \tau \) has a similarly considerable effect on bounce-back boundaries.
5.3 Simulation results

In this section we present the results obtained from our simulations. We consider three representative cases, accounting for the interactions of IBM membranes with the fluid and with other IBM membranes. All the simulations correspond to the same system in SI units: a domain of \( 80 \times 80 \times 80 \mu m^3 \) with one or two spheres of radius 4\( \mu m \). These length-scales have been chosen for their relevance to red blood cell suspensions.

We use stiff spherical particles without additional interparticle forces, like explicit lubrication or penetration correction. Finite size effects were not considerable, less than 6% in all of the examined cases. The results of this analysis are presented in appendix B.1.

The default parameter set is shown in Table 5.2 with each figure that follows explicitly denoting the parameters varied. In the cases where LBM relaxation parameter \( \tau \) is changed, the timestep changes according to the diffusive scaling relation \( \Delta t = \frac{\nu_{LB}}{\Delta x^2} \), where \( \nu_{LB} \) is the lattice viscosity. The parameters of the membrane model have been scaled accordingly to correspond to the same dimensional system. Results are presented in two forms, dimensional and dimensionless, always denoting the unit: \( \mu m \) for dimensional and LU for lattice units.

At first we look into the behavior of the effective hydrodynamic radius \( r_{hyd} \) of a sphere with radius \( r \) in a sheared environment, by measuring the viscosity of this single-sphered suspension with respect to the IBM parameters. Next, we investigate the interaction between two particles, in a sheared environment. A direct collision is used as our final case, where two spheres are forced to collide, examining the gap \( h \) where lubrication forces breakdown.

### 5.3.1 Hydrodynamic radius of a sphere

Einstein’s well-known relation \( \nu_{rel} = 1 + 2.5\phi_V \) connecting the relative apparent viscosity \( \nu_{rel} \) of a dilute suspension with the volume fraction \( \phi_V \) is a convenient
5.3. SIMULATION RESULTS

Figure 5.2: Imposed radius \( r \) (solid lines) and effective hydrodynamic radius \( r_{hyd} \) (dashed lines). Their difference \( \Delta r_{hyd} = r_{hyd} - r \) defines the deviation of the imposed from the measured.

Figure 5.3: Schematic for case described in section 5.3.1. A sphere is positioned in a shear flow environment at rest. The bottom plate is fixed and measuring the suspension stress via the momentum exchange algorithm.

A way to measure the effective hydrodynamic radius of a sphere, by measuring its volume. The effective hydrodynamic radius of a sphere is measured as

\[
r_{hyd} = \sqrt[3]{\frac{3}{4\pi} \phi V},
\]  

(5.18)

where \( V \) is the volume of the domain, equal to \((20r)^3\). A schematic of the hydrodynamic radius and the relevant measures is shown in Fig. 5.2. The maximum extent of \( r_{hyd} \) is defined by the reach of IBM: the support of the kernel. For \( \phi_4 \) this extent is \( \pm 2LU \). Parameters like the radius \( r \) of the sphere, the relaxation time \( \tau \), and the surface density of the vertices \( N_v/S_LU \) control the actual extent of the radius.

A sphere is placed between two plates in a shear-flow type of environment, as depicted in Fig. 5.3, and the fluid is initialized at rest. From the two parallel plates, only the top one is moving and the bottom measures the shear-stress of the suspension via the momentum exchange method. Measurements using Batchelor’s method [19] would already imply the knowledge of the sphere’s radius. The location of the bottom boundary wall is considered to be in the center of the bounce-back node, since \( \tau = 1.0 \) [86]. Fluid-only measurements of the relative apparent viscosity were performed to verify this approach, obtaining relative viscosity \( \nu_{rel} = 1.0 \). The applied shear-rate is \( \dot{\gamma} = 1000/\text{s} \) and the particle Reynolds number of \( Re_p = 0.038 \).
Figure 5.4: (a) Evolution of the hydrodynamic radius $r_{\text{hyd}}$, as calculated from Eq.(5.18) with respect to the lattice unit $\Delta x$. Finer lattice resolution results in lower effective hydrodynamic radii. (b) Dimensional hydrodynamic versus imposed radius measured in Lattice Units, varying the number of surface vertices $N_s$. Inset figure: same data where the increase $\Delta r_{\text{hyd}}$ is now measured in lattice units. (c) Increase in hydrodynamic radius $\Delta r_{\text{hyd}}$ measured in LU with respect to the surface density of the vertices $S_{\text{LU}}/N_s$, $(S_{\text{LU}} = 4\pi r^2)$. A slight increase of $\Delta r_{\text{hyd}}$ is observed, yet it seems that surface densities $S_{\text{LU}}/N_s \leq 2$ are not sufficiently resolved, resulting in significantly lower $r_{\text{hyd}}$. Radius $r = 2.7\text{LU}$ is a very coarse case with a radius comparable to the length-scale of the interpolation kernel $\phi_n$. (d) Increase in hydrodynamic radius $\Delta r_{\text{hyd}}$ with respect to the interpolation kernel $\phi_n$, for $r = 4.0\text{LU}$. Vertex numbers of $N_s = 162, 258$ have a low surface density resulting in smaller $r_{\text{hyd}}$, an effect less prevalent in larger interpolation kernels. Adequately resolved spheres produce similar $r_{\text{hyd}}$ for all kernels.

Results

The time evolution of the effective hydrodynamic radius $r_{\text{hyd}}(t)$ is shown in Fig. 5.4a. $r_{\text{hyd}}$ is measured as the time average of $r_{\text{hyd}}(t)$ from $\dot{t} = 10$ to 25, and the
standard deviation of this time period defines the error of our measurements.

The hydrodynamic radii are shown in Figs. 5.4a and 5.4b for dimensional and dimensionless units respectively. \( r_{\text{hyd}} \) is increased in coarser resolutions, as expected, since an increase by 1LU is uneven in \( \mu \text{m} \) for each case. For a radius of 8LU the increase compared to the actual is \( \sim 10\% \), while for 2.7LU it is in the order of 35\%. These numbers indicate that \( r = 2.7 \)LU is pretty coarse resolution. However, there is an uneven increase of \( \Delta r_{\text{hyd}} \) in terms of LU as well for coarser resolutions (inset of Fig. 5.4b) and it can be seen as an effect of the surface density. For the surface densities with radii \( r = 2 \)LU an increase is observed above a threshold of approximately 2 vertices per LU\(^2\) (Fig. 5.4c), with \( \Delta r_{\text{hyd}} \) for \( r = 4 \) and 5LU having similar values above that threshold and \( r = 5 \) and 8LU returning a steeper increase.

The default value of the radius is \( r = 4 \) and it is useful to remember that \( N \nu = 162 \) and 258 are below the aforementioned threshold, while \( N \nu = 642 \) and 1026 are not. Cases below this threshold will be referred to as under-resolved. Figure 5.4d indicates that the effect of the under-resolved spheres is more intense in kernels with smaller support. Under-resolved triangulations produce significantly smaller radii, an effect less seen in \( \phi_4 \). The dependence on the surface density supports the view that the interpolation kernel causes vertices to behave as volume sources, rather than points [52].

All kernels, regardless of support, seem to produce comparable values for sufficient surface vertex densities (Fig. 5.4d). Under-resolved cases returned a noticeably lower hydrodynamic radius for \( \phi_2 \) and \( \phi_3 \). It is also worth noting that the use of a higher order scheme, like the Adams-Bashforth (Eq. 5.12), had no impact in the results we obtained (data not shown).

### 5.3.2 Interaction between nearby membranes

#### Two spheres in shear-flow

The simple interaction of two spheres in a simple shear-flow environment is important for studies related to the transport properties of particles in a suspension. Analytical solutions for this system have been derived by Batchelor & Green in 1972 [20] for systems without inertia. Depending on the initial distance of the two spheres, their trajectories can either extend to infinity or not, characterized as open or closed trajectories respectively. In open trajectories of an infinite domain two smooth spheres return to their original streamlines after a collision. A potential asymmetry between the pre- and post- collision positions leads to a shear-induced dispersion [43, 132]. Also, in bounded cases of Couette flow a neutrally buoyant sphere migrates towards the center of the domain [205].

We place two identical spheres in a linear shear-flow domain of size \((20r \times 20r \times 20r)\) and apply a shear-rate of \( \dot{\gamma} = 132.8/\text{s} \), resulting in a particle Reynolds
number of $Re_p = 0.005$, using the input radius. The initial distance between the two spheres is $(\Delta X_0, \Delta Y_0, \Delta Z_0) = (10r, 1.5r, 0)$, where the $y$-direction is the shear-gradient direction. The setup is shown in Fig. 5.5.

We are interested in the collision distance in the $y$-direction, $\Delta Y_{\text{max}} = \Delta Y_{AX=0}$ which occurs when $\Delta X = 0$, and from that we define the interaction radius $r_{\text{int}} = \Delta Y_{\text{max}}/2$. Under the assumption of smoothness and low $Re_p$ two spheres of equal size pass very close to each other, so that $\Delta Y_{\text{max}} \rightarrow 2r$, while having symmetric pre- and post-collisional trajectories [20]. The increase in the interaction radius is measured as $\Delta r_{\text{int}} = r_{\text{int}} - r$. It is worth noting that $\Delta r_{\text{int}}$ is used as a reference to study deviations and is not a particle property but can be simulation-specific ($\dot{y}, \Delta X_0, \Delta Y_0$).

Results

Figs. 5.7a, 5.7b and 5.7c show that the interaction radius $r_{\text{int}}$ appears systematically larger than the hydrodynamic radius $r_{\text{hyd}}$ measured in the previous section. Contrary to $\Delta r_{\text{hyd}}$, $\Delta r_{\text{int}}$ seems from to be leveling off above $\sim 1LU$ for adequately resolved triangulation (inset of Fig. 5.7a). When plotted against the surface density, an increase is observed up to a $Ne/S_{LU} = 2$, after which the value roughly flattens (Fig. 5.7b). This however is not a conclusive picture, and more values from the parameter space should be sampled in future works.
5.3. SIMULATION RESULTS

Figure 5.7: (a) Dimensional interaction radius versus imposed. Transparent symbols correspond to the values measured in section 5.3.1. Finer resolutions mitigate the increase in the effective interaction (and hydrodynamic) radius of a sphere. Inset figure: same data where the increase $\Delta r_{\text{hyd}}$ is now measured in lattice units. (b) Increase in dimensional interaction radius, $\Delta r_{\text{int}}$, with respect to the vertex surface density $N_{v}/S_{LU}$. Transparent symbols correspond to the values measured in section 5.3.1. (c) Increase in interaction radius, $\Delta r_{\text{int}}$, with respect to the interpolation kernel $\phi_n$, for $r = 4.0LU$. Transparent symbols correspond to the values measured in section 5.3.1. Interpolation kernels with larger support increase the interaction radius, while $N_{v} = 162, 258$ still appear to be result in lower $r_{\text{int}}$ due to the low surface resolution. (d) Increase in interaction radius, $\Delta r_{\text{int}}$, with respect to the relaxation time $\tau$, for $r = 4.0LU$. Increasing $\tau$, decreased the interaction radius $r_{\text{int}}$.

The interpolation kernel $\phi_n$ also affects $r_{\text{int}}$ in an increasing fashion, as opposed to $r_{\text{hyd}}$ which was found to be independent for adequately resolved spheres (Fig.
While \( r_{\text{hyd}} \) is constant with respect to the support of the IBM kernel, and increasing for the under-resolved cases, \( r_{\text{int}} \) is increasing for both cases. However, their distinction is observable here as well. These results are important, because they show that there is a difference between the radius “felt” by the fluid (via the stress exerted and measured by \( r_{\text{hyd}} \)) and the radius “felt” by the suspended spheres.

The interaction radius is decreasing with an increasing relaxation time \( \tau \) (Fig. 5.7d). A similar behavior was also observed by Nguyen & Ladd [155] for the momentum exchange algorithm [120, 121]. A deviation from the expected is observed in Fig. 5.7d for \( N_\nu = 1026 \): the value of \( \Delta r_{\text{int}} \) for \( N_\nu = 1026 \) lies between the one values for 642 and 258. In order to understand this better, the trajectories of the spheres before the collision have to be examined.

Before the collision a shift is evident in Fig. 5.6 for \( N_\nu = 1026 \). This shift corresponds to the migration of neutrally buoyant spherical particles in a Couette flow towards the center of the domain [205] and depends on the ratio of the diameter of the particle to the distance between the walls and on the particle Reynolds number. Kromkamp et al. [113] also noticed an increase in migration with increasing \( Re_p \) in their simulations. The system was checked for finite size effect and returned the same behavior, while simulating each sphere individually also produced a migration towards the center (data not shown). This pre-collision shift is measured as \( \Delta Y_{\text{shift}} \equiv \min(\Delta Y_{AX/r<0}) - \Delta Y_0 \).

With respect to the migration, as Fig. 5.8a suggests, there is no migration for spheres using \( \phi_2 \), and in comparison to \( \phi_4 \) and \( N_\nu = 1026 \), \( \phi_3 \) and the under-resolved cases of \( \phi_4 \) migration is reduced. This migration is independent of the relaxation time \( \tau \), (Fig. 5.8b) and has a strong dependence on the vertex surface density (Fig. 5.8c) Above a threshold of approximately 1 vertex/LU\(^2\), there is a clear increase of \( \Delta Y_{\text{shift}}/r \) in absolute value. The Adams-Bashforth produced the same results, having no effect in the course of the simulation (data not shown).

Lubrication forces between two spheres

Motivated by the results of the previous section, we study the lubrication interaction of two spheres. When two spheres are in proximity, IBM kernels overlap and the fluid flow in their gap cannot be accurately resolved, causing the breakdown of the lubrication force. For particles coupled with the Momentum Exchange Algorithm (MEA), Nguyen & Ladd [155] proposed a correction for the lubrication force between two spheres with radii \( r_1 \) and \( r_2 \) when they are closer than a cutoff distance of \( h_N \):
5.3. SIMULATION RESULTS

Figure 5.8: Normalized pre-collision shift, $\Delta Y_{\text{shl}}/r$: (a) with respect to the interpolation kernel $\phi_n$. (b) With respect to the relaxation time $\tau$. (c) With respect to the vertex surface density $N_v/S_{LU}$.

\[
F_{\text{hub}} = -6\pi \rho \nu \frac{r_1^2 r_2^2}{(r_1 + r_2)^2} \left( \frac{1}{h} - \frac{1}{h_N} \right) U_{12} \cdot \hat{R}_{12}, \quad h < h_N
\]
\[
=0, \quad h > h_N, \quad (5.19)
\]

$U_{12} = U_1 - U_2$ refers to the velocity difference between the two spheres, $h = |R_{12}| - r_1 - r_2$ to the gap between the two surfaces, and $\hat{R}_{12} = R_{12}/|R_{12}|$ is the unit vector connecting the centers of the two spheres.

The purpose of these simulations is not to propose a lubrication correction scheme for IBM, but rather to indicate the range in which lubrication forces are correctly resolved for IBM surfaces. To measure this, the domain of section 5.3.2
with \( \dot{y} = 0/\text{s} \) and dimensions \((20r \times 20r \times 20r)\) is considered. The two spheres are separated by an initial distance of \((\Delta X_0, \Delta Y_0, \Delta Z_0) = (10r, 0, 0)\).

Subsequently, a constant and opposite force of \( F_0 = 125\text{pN} \) in the \( x \)-direction is applied on each sphere and their relative position is measured. This force introduces an artificial density difference between the inner and the outer fluid, yet due to the simplicity of the system, potential side-effects similar to \([133]\), are considered to be minor and to not considerably change the outcome. Due to anisotropies in the discretization of the membrane, spheres that are forced may roll over each other and diverge from the head-on collision. To ensure this will not happen, an additional spring force is considered, keeping the centers of the two spheres aligned with the direction of the force. The force is defined as

\[
F_{\text{corr}} = (0, -F_0 \frac{(Y-Y_0)}{1\mu\text{m}}, -F_0 \frac{(Z-Z_0)}{1\mu\text{m}}).
\]

### Results

The quantity we are interested in, is the gap \( h \) between the two spheres and in particular \( h_{\text{fail}} \), the gap in which lubrication forces breakdown. In Fig. 5.9b the evolution of the gap, with respect to time is shown. A point is evident, in which the course of the trajectories changes, indicating that lubrication force is not accurately resolved. The gap distance \( h \) this happens, defines \( h_{\text{fail}} \). The way \( h_{\text{fail}} \) is determined is presented in appendix B.3.
5.4. DISCUSSION

As is shown in Fig. 5.9b, smaller effective radii (measured in the previous sections) reach further before they fail. These simulations are pretty demanding in terms of computational time, since the gap decays exponentially over time. The latter causes simulations with low effective radii (mainly of $\phi_2$), to terminate within the designated simulation time without having failed. This by no means implies that they will not fail on longer simulations, or with an imposed force with larger magnitude.

As with the previous case, $h_{\text{fail}}$ seems to be independent of $\tau$, while it is obvious from Figs. 5.10a and 5.10b that the gap in which lubrication fails, increases with the vertex surface density. The use of the Adams-Bashforth scheme had no impact in the results we obtained (data not shown).

5.4 Discussion

We have presented a parametric study for the combined IB-LBM method applied in simulations of one or two suspended particles. In principle finer resolutions, in both lattice and mesh, might be more accurate, yet this accuracy comes with a computational cost, which can be too expensive in dense suspensions. In a 3D-LBM solver, doubling the lattice resolution would imply an increase by a factor of 32 in computational time ($\times8$ in space and $\times4$ in time, due to the diffusive scaling). Not all parameters yield the same reduction in cost or accuracy and efficiently choosing parameters is useful.
The number of vertices for each of the suspended particles has to increase accordingly when adjusting the resolution, in order to compensate for the loss in vertex density, as our results suggest. Using a higher order kernel can balance an increase in vertex density, however, higher order kernels also increase the interaction radius between the IBM surfaces and, when in close contact, can fail to accurately resolve lubrication forces.

One important finding is that the radius of an IBM sphere is discerned differently from the fluid and from other IBM objects. This on the one hand leads to an effective increase in the suspension volume, and on the other warns on potential artifacts related to the transport of IBM objects. Asymmetries between the pre- and post- collision positions in shear flow, lead to a shear-induced dispersion which affect the diffusion of the substance [43, 132]. The effect of this interaction needs to be further addressed.

It is very important for an IBM particle to be adequately resolved. Under-resolved spheres were also unsuccessful in capturing the migration towards the center of the vessel in a bounded shear flow, failing to capture essential physics. This was observed in all cases of kernel \( \varphi_2 \) we considered, raising some concerns if it indeed captures the relevant physics. A single set of parameters for which all benchmarks were passed sufficiently could not be identified. The parameter space we explored was sufficient to catch the role and the tendencies for each parameter, yet it is not exhaustive and further analysis could help identify and understand the drawbacks of this method.
Part III

Results
Where do the platelets go?
A simulation study of fully resolved blood flow through aneurysmal vessels

Despite the importance of platelets in the formation of a thrombus, their transport in complex flows has not yet been studied in detail. In this chapter we simulated red blood cells and platelets to explore their transport behavior in aneurysmal geometries. We considered two aneurysms with different aspect ratios (AR = 1.0, 2.0) in the presence of slow and fast blood flows (Re = 10, 100) and examine the distributions of the cells. Low velocities in the parent vessel resulted in a large stagnation zone inside the cavity, leaving the initial distribution almost unchanged. In fast flows though, an influx of platelets into the aneurysm was observed, leading to an elevated concentration. The connection of the platelet-rich cell free layer (CFL) with the outer regions of the observed recirculation zones, leads to an increased platelet concentration. These platelet-enhanced recirculation zones produced a very different distribution of cells inside the aneurysm, for the different aspect ratios. A thin layer of platelets was observed on the top of the wide necked aneurysm, while a high hematocrit region very close to the vessel wall was present in the narrow necked case. The simulations revealed that non-trivial distributions of red blood cells and platelets are possible inside aneurysmal geometries, giving rise to several hypotheses on the formation of a thrombus, as well as to the wall weakening and the

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0The contents of this chapter are based on: L. Mountrakis, E. Lorenz, and A. G. Hoekstra. Where do the platelets go? a simulation study of fully resolved blood flow through aneurysmal vessels. Interface Focus, 3(2), Apr. 2013. ISSN 2042-8901. doi: 10.1098/rsfs.2012.0089
possible rupture of an aneurysm.

6.1 Introduction

Intracranial aneurysms are pathological dilatations of the cerebral blood vessels with a high mortality and morbidity rates associated to their possible rupture. One repair mechanism is the formation of a thrombus inside the aneurysm, significantly lowering the risk of rupture [213, 211]. This formation can also be induced by positioning a flow diverting stent in the orifice of the aneurysm. Quantitative models of thrombosis in intracranial aneurysms are now in need and the EU funded project THROMBUS aims to validate such models and translate them to clinical practice [2].

Platelets, or thrombocytes, are the main component of thrombus. They exhibit an excess in the concentration near the walls of the vessel [194, 8, 231], ensuring a more effective response to wounds and tissue damages. This margination is amplified by the shape and the dynamics of red blood cells (RBCs) [194, 8, 231, 201], observing similar behavior for the white blood cells [64]. Based on computational studies, the presence of RBCs is also important in the adhesion and aggregation of platelets [145, 168]. Almost all thrombosis models that have been developed [87, 27, 218, 66] and applied to aneurysm geometries [38, 39, 21, 207] treat platelets on a mean field level, by modeling them as tracer particles in a homogeneous fluid.

The methods that have been proposed and used to describe the transport of platelets in blood flow vary. A simple approach for the transport is by using an advection diffusion model, with a simple scalar diffusion term as used in [27, 39]. Modeling the transport of platelets with scalar diffusion in an incompressible fluid without sources and sinks will eventually lead to a homogeneous distribution [90]. Eckstein and Belgacem [56] proposed an additional drift term to mimic red blood cell enhanced motion, while more sophisticated approaches involving the explicit dependence of the diffusion coefficient on the local hematocrit and shear rate have also been proposed [233, 183]. The dependence on these quantities has been recognized already in early experimental work [194, 198]. Although such methods may provide adequate results in simple channel flows, little is known about the behavior of platelets in more complex flow geometries, where most of these models lack in validity [99]. The research on the modeling of thrombosis to date mainly uses advection-diffusion descriptions at the macroscopic scale for the transport of platelets, without taking full account of the non-trivial nature of the presence of RBCs in the transport, especially in more complex geometries.

Simulations with fully resolved red blood cells and platelets suspensions are challenging, due to the computational cost of considering thousands or even millions of particles. Smaller scale studies of blood flow are preferred for qualitative
6.2 Methods and model

Blood is a multiphase non-Newtonian fluid consisting of red blood cells, platelets and white blood cells suspended in plasma, a protein-rich Newtonian fluid. The complex behavior of blood mainly arises from the high concentration of red blood cells, which constitute up to 45% of the total blood volume. Our approach fully resolves deformable red blood cells (RBCs) and platelet-shaped particles, suspended in the plasma. A two-dimensional approach was employed, using the Lattice Boltzmann method [188] as a fluid solver and coupled to a discrete-element representation of the cells using the immersed-boundary method [166].

The Lattice Boltzmann method (LBM) is a well established mesoscopic approach, solving the incompressible Navier-Stokes equation and has demonstrated capabilities in many studies of biomedical interest, e.g. [27, 190, 161, 13, 16].

The immersed boundary method (IBM) is a fluid structure interaction method in which a membrane is immersed in the fluid. The idea behind IBM is to advect the elements of the membrane with the fluid, based on the no-slip condition. The forces between the membrane elements are applied back to the fluid. IBM is a pure coupling method with a small numerical overhead and is one of the most widely used methods to couple red blood cell-like structures with fluid flow in 2D [42, 17, 228, 181] and in 3D [107, 49].

6.2.1 Blood model

Modeling blood through its constituents allows to capture important rheological and transport properties, without the simplifications that would be necessary for a macroscopic approximation for the diffusion of platelets.

The D2Q9 LBGK scheme is used to simulate the fluid flow [188], while the viscosity is chosen to match blood plasma [105]. Red blood cells are represented as a closed deformable membrane with a biconcave shape and a diameter of 8µm.
**Figure 6.1:** Snapshot of a simulation of blood flow through the simplified aneurysm geometry Sa, explicitly tracking red blood cells and platelets. The small circular particles represent the platelets. Dotted blue lines denote the boundaries. The simulated case is Sa100 and details can be found in Table 6.1. Inset Fig. (I) depicts the shape of red blood cells when exposed to the high shear rates encountered close to the walls of the main vessel, as well as their proximity to the boundary inside the aneurysm. Inset Fig. (II) depicts parts of the recirculation zone, a boundary layer with low hematocrit and elevated platelet concentration, and a region with densely packed red blood cells. The time integrated concentration profiles are shown in Fig. 6.9. Flow runs from top to bottom.
Circular shaped cells with a diameter of 2 $\mu$m, slightly deformable, constitute the platelet sized particles. Our “platelets” are not reactive and do not adhere nor aggregate, but correspond to the platelet sized passive particles found in in-vitro studies [194, 231, 224].

The membrane of the cells is represented with neighboring surface points connected with Hookean springs and enhanced with bending resistance between the adjacent membrane springs. The viscous properties of the membrane derive from damper elements connecting surface points, while the conservation of volume and surface is ensured by applying forces in an equivalent way to the pressure differences between the inner and surrounding fluid of the membrane. Similar models and implementations can be found in [42, 17, 181].

The model is tuned such that the single cell dynamics are resolved sufficiently in the range of shear rates of interest [148]. A repulsion force is also included to overcome artificial correlation resulting from the IBM interaction and is tuned to the extent that the shear-thinning behavior is correctly recovered. Shear-thinning results naturally from the deformability of the RBC shape and the formation of rouleaux-like structures at lower shear rates [170].

A balance is necessary between resolving important aspects of the flow field around an RBC shaped particle and avoiding the heavy computations due to the diffusive scaling of LBM. Our approach is aiming for the simplest possible model that reproduces important aspects of rheology and single cell dynamics. It has been validated against various benchmarks, like tumbling and tank-treading transition of a single RBC in shear flow, the shear-thinning behavior and the hematocrit dependance of blood viscosity (data not shown, for details see [148]). Figure 6.1 illustrates a snapshot from a simulation of the flow through an aneurysm geometry, demonstrating the model representation of the cells along with two magnifications.

With the current model we investigate the three-dimensional process of cell transport in the blood flow, limited to two dimensions. The distributions of cells inside two-dimensional aneurysms may differ significantly from three-dimensional idealized cases, since no obvious symmetry exists. In many aspects however, the behavior of a two dimensional suspension system is similar to the one in a three dimensions, particularly in terms of the quantities and effects we are interested in this work [42, 174], maintaining this way the main advantage of a 2D simulation, which is the reduced computational requirements.

### 6.2.2 Simulations setup

The fluid was initially set at rest and then it was driven by a constant body force, mimicking a pressure gradient. The pulsatility of the flow was neglected due to the relatively small Womersley number $Wo = L \sqrt{\frac{\omega}{v}}$, $L$ being the characteristic
CHAPTER 6. WHERE DO THE PLATELETS GO?

Table 6.1: Geometrical parameters and setup of the aneurysm cases. $N_{RBC}$ is the number of red blood cells and $N_{plt}$ the number of platelets.

<table>
<thead>
<tr>
<th>Case ID</th>
<th>$Re$</th>
<th>Geometry</th>
<th>Aspect ratio</th>
<th>Neck size</th>
<th>$N_{RBC}$</th>
<th>$N_{plt}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>LLa100</td>
<td>$\approx 100$</td>
<td>![LLa]</td>
<td>1.0</td>
<td>0.2mm</td>
<td>4900</td>
<td>300</td>
</tr>
<tr>
<td>LLa010</td>
<td>$\approx 10$</td>
<td>![LLa]</td>
<td>1.0</td>
<td>0.2mm</td>
<td>4900</td>
<td>300</td>
</tr>
<tr>
<td>Sa100</td>
<td>$\approx 100$</td>
<td>![Sa]</td>
<td>2.0</td>
<td>0.1mm</td>
<td>4700</td>
<td>300</td>
</tr>
<tr>
<td>Sa010</td>
<td>$\approx 10$</td>
<td>![Sa]</td>
<td>2.0</td>
<td>0.1mm</td>
<td>4700</td>
<td>300</td>
</tr>
</tbody>
</table>

length scale, $\omega$ the angular frequency of the oscillations and $\nu$ the kinematic viscosity. For intracranial arteries typically $Wo \approx 3.2$. Instead, two different Reynolds number $Re = \frac{LU}{\nu} \approx 10$ and 100 were considered, in order to approximate two different situations within the cardiac cycle ($U$ is the characteristic velocity). The total simulated time is 0.2s. Reynolds numbers were calculated based on the size of the parent vessel, the plasma viscosity and the imposed pressure gradient, supposing a Poiseuille profile without red blood cells. Due to the suspension of RBCs and the aneurysm bulge, the final resulting velocity will be slightly different.

First we consider the case of a straight channel and compare our results to those of in-vitro experiments, recovering the transport properties of platelets in a tube in the presence of RBCs. Next we consider two aneurysmal geometries with different aspect ratios in order to study the cell transport in more complex flows, exposing the fluid to two different pressure gradients. The aspect ratio is defined as the ratio of the maximum perpendicular height to the average neck diameter [47]. The aspect ratio has been identified as an important parameter for the rupture and the formation of a thrombus in aneurysms [212].

We have chosen to use the geometries introduced in [87, 39] in order to compare our fully resolved model to simulations where blood was modeled as a continuous Newtonian fluid. The four cases are codenamed after the geometry acronym and the Reynolds number; LLa100, LLa010, Sa100 and Sa010 and details of the geometrical parameters can be found in Table 6.1. Similar flow patterns to the studies reported earlier were found by using the same Reynolds number, but the smaller size of the vessel caused higher absolute velocities and shear rates. The diameter of the main vessel is 0.1mm, close to 10 times smaller than those found in human cerebral arteries [14]. The dimensions of the domain were preferred in order to reduce the computational cost of each simulation, since a factor of 10 in diameter would yield a factor of 100 in number of lattice nodes and cells.

The initial positions of red blood cells and platelets were chosen at random without any overlaps, providing a homogeneous initial distribution. Both fluid and cells were subjected to periodic boundaries. The number of red blood cells corresponds to the hematocrit under physiological conditions (42%). Hematocrit
6.2. METHODS AND MODEL

Table 6.2: Simulation parameters. * refers to the channel simulations. See Table 6.1 for corresponding values for the aneurysm geometry

<table>
<thead>
<tr>
<th>parameter</th>
<th>value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinematic viscosity (v)</td>
<td>(1.7 \times 10^{-6} \text{ m}^2 \text{ s}^{-1})</td>
</tr>
<tr>
<td>Hematocrit (H)</td>
<td>42%</td>
</tr>
<tr>
<td>(N_{RBC})</td>
<td>850*</td>
</tr>
<tr>
<td>(N_{plt})</td>
<td>45*</td>
</tr>
<tr>
<td>Diameter (d) (main vessel)</td>
<td>100(\mu)m</td>
</tr>
<tr>
<td>Length (L) (main vessel)</td>
<td>600(\mu)m</td>
</tr>
<tr>
<td>Spatial resolution (dx)</td>
<td>1(\mu)m</td>
</tr>
<tr>
<td>Time step (dt)</td>
<td>(9.8 \times 10^{-8})\text{s}</td>
</tr>
<tr>
<td>(\bar{C}_{plt})</td>
<td>2.6 \times 10^{-3} \frac{\text{plt}}{\mu\text{m}^2}</td>
</tr>
</tbody>
</table>

is defined as the volume ratio of red blood cells to blood. The number of platelets was selected close to the physiological ratio of red blood cells to platelets 20/1, ranging from 16/1 to 19/1, providing a suspension slightly richer in platelets for better statistics.

6.2.3 Quantities of interest

Besides flow fields, velocity and shear rates, the concentration of RBCs and the local concentration of platelets \(C_{plt}\) are of particular interest in this study. As “normalized platelet concentration” we define the ratio of the local platelet concentration to the mean platelet concentration

\[
\hat{C}_{plt} = \frac{C_{plt}}{\bar{C}_{plt}}
\]  

(6.1)

where \(C_{plt}\) is the local concentration of platelets and \(\hat{C}_{plt}\) mean platelet concentration. A normalized platelet concentration equal to 1.0 corresponds to the mean concentration.

The results presented here are the outcome of 15 simulations with different initial conditions. The simulation results are time averaged over the last 0.08s of the total 0.2s. The parameters and the setting of the simulations are reported in Table 6.2.
6.3 Results

First, we present the results obtained on a straight channel with a hematocrit equal to 42% and a platelet only case. This provides a benchmark of the simulated transport. Next we investigate the transport of platelets and RBCs in two aneurysmal geometries under higher and lower pressure gradients.

6.3.1 Transport in a straight channel

Results from the straight channel with a hematocrit of 42% are shown in Fig. 6.2. The excess of platelets near the walls of the channel is evident, as well as the clearly visible RBC-free layer (CFL). The formation of a CFL is the microscopic phenomenon behind the Fahraeus-Lindqvist effect, which is characterized by a decrease in the apparent blood viscosity as the vessel diameter decreases below 500 µm [73].

The peak of the RBC concentration in the center of the channel is a result of the symmetry of the simulated channel, also observed by Zhao [230]. Such a peak is not observed under experimental conditions, where higher mixing is expected.

In the absence of red blood cells, the distribution of platelets is not homogeneous as would have been expected for Brownian point particles. Platelets tend to crowd around approximately 60% of the radius of the channel. This effect is known from dilute rigid sphere suspensions as the Segré - Silberberg [180] or tubular pinch effect [8] and is a balance of viscous drag and inertial lift forces [52]. Our obtained results are similar to the in-vitro profiles of Aarts [8] shown in Fig. 6.3. The in-vitro data by Aarts show a dependency on the wall shear rate,
6.3. RESULTS

Figure 6.3: Platelet distributions across a channel of \( d = 100 \mu m \) without red blood cells. Platelets crowd around the 60% of the radius \((0.6 \times 50 \mu m = 30 \mu m)\). In-vitro data from [8] shown in red \((d = 3 mm)\), the blue line is the simulation result.

probably due to the insufficient equilibration in the low shear rate cases. This is also true for the profiles obtained in our simulations 1.0s after the initialization with a homogeneous distribution (blue curve in Fig. 6.3).

6.3.2 Transport in aneurysmal geometries

We examined the transport of platelets in aneurysms with different aspect ratios, under high and low pressure gradients.

6.3.3 Lower velocities

The imposed pressure gradient yields a maximum velocity of \( u_{\text{max}} \approx 6 \, \text{cm/s} \) in the parent vessel. Significantly lower velocities are observed inside the aneurysm for both aspect ratios (Fig. 6.4). Examining the velocity field and the distribution of hematocrit and platelets from Figs. 6.4 and 6.5, we can distinguish three zones for Sa010: (i) the parent vessel, (ii) a circulation zone close to the entrance of the aneurysm and (iii) a large stagnation zone where cells move really slow. The stagnation zone occupies most of the aneurysm.

Two zones are clearly visible in LLa010: (i) the region of the flow entering the aneurysm and (ii) a large stagnation zone. Close to the entrance of the aneurysm, we observe a region with a depletion of red blood cells and occupied by platelets (fig 6.5II and IV). A recirculation zone is absent from this case.

Two cross-sections are examined closer for each of the cases. Cross-section (a) corresponds to the main vessel flow, and cross-section (b) for the rest. Detailed profiles are shown in Figs. 6.6 and 6.7.
Figure 6.4: (I) Velocity profiles for the Sa010 and (II) LLa010. (a) and (b) refer to the positions of the two chosen cross-sections. Note the logarithmic color scale, reflecting the considerably lower velocities inside the aneurysm.
6.3. RESULTS

Figure 6.5: (I) Hematocrit $H$ for Sa010 and (II) for LLa010, (III) normalized platelet concentration $\hat{C}_{plt}$ for Sa010 and (IV) for LLa010. Sa010 possesses a recirculation zone, along with a large stagnation zone. LLa010 exhibits a large stagnation zone as well, with a platelet rich area close to the entrance of the fluid. Values larger than 3.0 for $\hat{C}_{plt}$ and 60 for $H$ are colored with dark red.

Figure 6.6: Hematocrit and normalized platelet concentration for Sa010 cross-sections marked in Fig. 6.4III. Shown are (a) the distributions in the parent vessel with a clearly visible margination of platelets, and (b) the cross-section containing parts in the recirculation and the stagnation zones. The green line refers to the mean platelet concentration ($\hat{C}_{plt} = 1$).
Figure 6.7: Similar to Fig. 6.6, but now for LLa010, shown are (a) the distributions in the parent vessel with a clearly visible margination of platelets, and (b) the cross-section containing parts in the flow entering the aneurysm and the stagnation zone.
6.3. RESULTS

Figure 6.8: (I) Velocity profiles for Sa100 and (II) LLa100. (a), (b) and (c) refer to the positions of the three chosen cross-sections. Note the logarithmic color scale, reflecting the considerably lower velocities inside the aneurysm.

The lateral position of platelets is visible for LLa010A and Sa010A in Figs. 6.7a and 6.6a respectively. Both cases have a noticeable lower peak in the platelet concentration, closer to the neck of the aneurysm. This may yield an influx of platelets into the aneurysm, yet no significant increase in the aneurysm concentration is evident (Figs. 6.5III, 6.7b and 6.6b), possibly due to the slow transport resulting from low velocities and small shear rates.

The initial distribution of platelets can be recognized in the stagnation zones of Fig. 6.5, as an effect of their slow movement compared to the simulated time (Figs. 6.5III, IV and 6.7a).

6.3.4 Higher velocities

The Reynolds number for these two cases is \( Re \approx 100 \) and corresponds to a parent vessel velocity of \( u_{\text{max}} \approx 1 \text{ m/s} \). Lower velocities are found inside the aneurysm cavity (Fig. 6.8).

Three zones can be distinguished in the hematocrit and platelet distributions in the cases Sa100 shown in Figs. 6.9I and III: (i) the main vessel flow, (ii) a region with high red blood cell density and (iii) a recirculation zone in the center of the aneurysm. Three zones are noticeable for LLa100 as well: (i) the main vessel flow with a part entering the aneurysm, (ii) a region with slightly
higher hematocrit and (iii) a recirculation zone. For each of the three zones, one cross-section is examined closer, (a), (b) and (c), respectively.

The lateral motion of platelets is present in the parent vessels of LLa100 and Sa100 as well. The concentrations are similar to those of the straight channel flow (Figs. 6.11a and 6.10a), but a considerably lower concentration of platelets is observed on the right side of the wall, the side of the aneurysm orifice. Platelets flowing close to the wall are transported into the cavity and due to the periodic boundaries the number of platelets is decreased in the channel.

This can be confirmed by the increased platelet concentration inside the cavity (Figs. 6.11b and c, 6.10b and c), providing evidence for an influx of platelets into the aneurysm, mainly increasing the outer layers of the recirculation zones.

A large area of high hematocrit is present in zone Sa100(b), shown in Figs. 6.9 and 6.10b. The transport of RBCs there, has formed a cell free layer on the top of the aneurysm, close to zone Sa100(c). Platelets from the homogeneous initialization are trapped between red blood cells in region Sa100(b) and are visible as the steep peaks in Fig. 6.10b. A snapshot of this interesting situation
6.4 Discussion

In the current work we studied the transport of platelets and red blood cells in fast and slow flows, in two aneurysmal geometries with different aspect ratios. The distributions of cells inside the cavity are far from trivial.

Platelets flow closer to the vessel walls, remaining close to flow boundaries, like walls or separation zones, where their function is beneficial. The connection of the platelet-rich cell free layer (CFL) with the outer regions of the recirculation zones in the simulated fast flows, enhances the transport of platelets inside the aneurysm and leads to an increased platelet concentration.

From a biological perspective, in the regions of high platelet concentration close to the top of the aneurysmal wall, platelets may tether and roll, and the presence of activated platelets is also plausible, due to a prior exposure to the...
Figure 6.11: Similar to Fig. 6.10 but now for the LLa100 cross-sections marked in Fig. 6.8II. Shown here are (a) margination behavior of the parent vessel alike to Fig. 6.10a, (b) and (c) exhibit an increased platelet concentration in the recirculation zone and a peak close to the walls where the RBCs are depleted.

higher shear rates in the orifice of the aneurysm. In the case of an unhealthy endothelium, and aneurysmal walls may possess this quality, coagulation could be induced and form a thrombus in that region.

A striking result of our simulations, is a large area of high hematocrit in the narrow necked case, which may have a series of consequences. Red blood cells release ATP which enhances the aggregation of platelets [11, 184]. This can increase the levels of agonists inside the aneurysm, promoting the activation of platelets, resulting in the formation of a thrombus. Moreover, the proximity of the red blood cells to the endothelium does not constitute a physiological condition. The endothelium plays a significant role in the regulation of thrombosis [210] and, normally, RBCs are kept away from the wall via the cell free layer. This unhealthy situation can cause the release of procoagulants into flow. Another aspect that should be noted, is that the adhesion of RBCs to the endothelium has been linked to several vascular disorders [220] and such close vicinity of RBCs to the endothelium may contribute to the wall weakening and lead to a possible rupture of the aneurysm. The ATP release from RBCs acts as a signaling molecule, triggering the release of NO from the endothelium, promoting vasodilation [70].

This study has some shortcomings. The pulsatility of the flow was neglected due to the short time of simulation ($\approx 0.2s$) and instead two cases with high and low velocities were simulated. Low parent vessel velocities resulted in a stagnation zone inside the cavity, leaving the initial distribution almost unchanged. From this we can argue that the fast flows within a cardiac cycle are the ones that determine the distribution of cells inside the aneurysms. The flow, however, traverses a spectrum of velocities and this estimation needs to be confirmed with
more detailed studies.

To our knowledge, this is the first study exploring the transport of platelets and red blood cells in aneurysmal geometries using explicit simulations of red blood cells and platelets. The aneurysmal geometries used in the present work are 10 times smaller than normal aneurysms and more detailed studies are necessary in order to assess the importance of the current results to larger vessels. Nevertheless, the current work suggests that non-trivial distributions of red blood cells and platelets are possible inside aneurysmal geometries and may contribute significantly to the formation of a thrombus inside the cavity.

“Platelets” in this study act like the latex beads used in in-vitro experiments. Real platelets have a composite reactive behavior, adhering to endothelial cells, aggregating with other platelets and rolling and tethering along the endothelial wall [204]. A fully resolved model taking into consideration the platelet dynamics could also provide some insight in the thrombus formation inside aneurysms.
Shear-induced diffusion and clustering in a blood-like suspension

Microstructure, the relative position and orientation of physical entities in a material, is a key property in understanding the rheology and transport in concentrated suspensions. We use simulations as a microscope to probe the characteristics of a shear-thinning suspension of deformable red blood cell-like particles. The shear-induced diffusion of the particles is measured for a wide range of volume fractions and shear-rates and a departure from the linear scaling with hematocrit is observed. A cluster size analysis is performed to unravel collective effects in the suspension, revealing that many-particles collisions increase with volume fraction, while the duration of each collision increases with both shear-rate and volume fraction. Finally, we present results for the diffusion of platelets in this kind of suspensions.

\[\text{\textsuperscript{0}Parts of this chapter have been submitted as: L. Mountrakis, E. Lorenz, and A. G. Hoekstra. Clustering and shear-induced diffusion in two-dimensional dense suspensions of deformable particles. Submitted to Physical Review Letters, 2015}\]
CHAPTER 7. SHEAR-INDUCED DIFFUSION OF RBCS

7.1 Introduction

In dilute suspensions of hard spheres, the collision of two isolated spheres in the Stokes regime is symmetric and reversible and diffusion arises either from the collision of three or more particles [31, 51] or due to surface roughness [43]. The collision of two or more elastic particles, such as red blood cells (RBCs), can however give rise to diffusive behavior at long times [131, 32, 119]. Even though the interaction of RBC pairs in shear flow has been studied under a variety of conditions [228, 100, 160] along with the shear-induced diffusion of RBCs in dilute suspensions [159], the mechanism behind the transport of deformable particles in dense suspensions received much less attention and is not yet fully understood. Recently, Gross et al. [81] proposed a connection between viscosity and diffusion in such systems using kinetic arguments and obtained good agreement to their simulation results. The range of validity for this connection, however, has not been identified.

In this chapter we present results from simulations of a blood-like suspension in a shear-flow environment. We look into the diffusion of RBCs and the microstructure of the suspension for various shear-rates and volume fractions. The cluster size distribution and the duration of a pair contact between RBCs are examined, to provide an image of the collective effects taking place in the suspension. Finally, we present measurements for the RBC-enhanced shear-induced diffusion of platelets in a boundless shear-flow domain.

7.2 Methods and simulation setup

We employ the combined Immersed-Boundary lattice-Boltzmann method (IB-LBM) in two dimensions as described in chapter 3, in the periodic shear-flow domain of Lees-Edwards periodic boundary conditions (LEbc). Fluid is simulated with LBM using the D2Q9 LBGK scheme and deformable biconcave membranes with a diameter of approximately $6.86 \mu m \equiv 2r$ and a thickness of $d = 1.8 \mu m$, where $r$ is the radius, represent neutrally buoyant RBCs.

For a reliable analysis of the transport of RBCs, the size of the system and the simulation time should be sufficiently large [182]. The Lees-Edwards boundary conditions provide an unbounded type of shear-flow, ideal for mean square displacement measurements and, eventually, diffusion. Yet they still constitute boundaries and introduce finite-size effects [74]. After an analysis of the spatial velocity correlations and a cluster analysis, the size of the domain was set to $400 \times 400 \mu m^2$. The correlation length-scales were found to be considerably smaller than the size of the domain (data not shown).

The shear-rates studied in this work range from $3/s$ to $1000/s$ and the volume fractions from $\phi = 0.1$ to $0.5$, with an absolute number of RBCs of $1600$ to $8000$
7.2. METHODS AND SIMULATION SETUP

![Simulation snapshots for different volume fractions and shear-rates.](image)

**Figure 7.1:** Simulation snapshots for \( \phi = 0.1, 0.3, 0.5 \) and shear-rates \( \dot{\gamma} = 10, 100, 1000/s \) zoomed into the center of the domain (160² out of 400²µm²).

respectively. A constant number of platelets (320 with \( \phi_{\text{platelet}} << 1\% \)) is also present in the system, but due to their low relative numbers, their contribution to viscosity and diffusion is insignificant. Other parameters relevant to the system can be found in Table 3.1 of chapter 3, with a notable distinction the cutoff distance \( r_{\text{cutoff}} \) of the repulsive force, which was set to 0.77LU to prevent penetration of membranes with point to point surface-distances of \( \sim 0.6\text{LU} \). Some representative snapshots with respect to the volume fraction and the shear-rates are shown in Fig. 7.1.
Apart from the volume fraction, other dimensionless numbers that characterize the system are the particle Reynolds number \( \Re_p = \frac{4 \dot{\gamma} r^2}{v_0} \) and the Capillary number \( \Ca \). The capillary number is a measure for the relative effect of viscous forces versus the elastic deformation of a particle, defined as \( \Ca = \frac{\mu v_0 \dot{\gamma}}{C_{spr}} \), where \( v_0 \) is the viscosity of the solvent and \( C_{spr} \) the elastic modulus of the cell. Thermal fluctuations are neglected in our study, since the thermal Péclet number \( \Pe_t = \frac{r^2}{D_T} \gg 1 \). For this work \( \Ca \approx \dot{\gamma} \cdot 3.3 \times 10^{-6} \text{s} \) and \( \Re_p \approx \dot{\gamma} \cdot 1.67 \times 10^{-5} \text{s} \) with \( \dot{\gamma} \) measured in SI. For our setup this yields particle Reynolds number in the range of \( 5 \times 10^{-5} \) to \( 1.7 \times 10^{-2} \) and Capillary numbers in the range of \( 10^{-5} \) to \( 3.3 \times 10^{-3} \).

Obtaining meaningful results in the low shear-rate regime, for sufficiently large strains \( \dot{\gamma} t \) makes it necessary to run the already demanding simulations for very long times. It is common in the literature to use some form of dynamic scaling, under which the timestep becomes tractable. Several IB-LBM studies use the capillary number to obtain a reasonable timestep, scaling the viscosity or the elastic modulus [114, 116, 82, 81]. This is motivated by the fact that the shear elasticity provides the most dominant contribution to the suspension stress. A similar approach, scaling viscosity and the Young’s modulus, has also been followed for simulations of Dissipative Particle Dynamics (DPD) [63, 59]. This is not the case in our simulations, for reasons explained below.

Such scaling would deprive the particle Reynolds number, the lubrication, and the interparticle forces from the appropriate scaling. The importance of this drawback lies in the fact that lubrication and interparticles forces become predominant in dense suspensions, when the gap between particles becomes comparable to the cutoff distance of these forces [209]. We therefore avoid the scaling with the elastic modulus, leading to very long simulation times; yet, in our opinion this choice contributes to a consistent and well-defined model, leading to higher quality results, as compared to the ones relying on such scaling. This is more evident for the limits of large densities and low shear-rates.

With respect to interparticle forces, apart from phenomenological models, which emulate the aggregation of RBCs (like the Morse [228, 63, 100] or the JKR models [217]), it is common to use additional repulsive forces. These forces improve numerical stability and aid in avoiding particle inter-penetration. These have either have the form of a Lennard-Jones potential [63], in the case of hard objects, of a pairwise repulsive DLVO-type colloidal force [30, 158, 182], or that of a simple power-law repulsive force [65, 114, 116, 148]. Even though in a number of studies phenomenological models are omitted, the repulsive forces seem to be omnipresent.

In the current work we are using a relatively repulsive force \( 1/h \), where \( h \) is the gap between two membrane points. The force becomes zero for distances larger than \( r_{cutoff} = 0.77 \text{LU} \equiv 0.77 \mu \text{m} \). Similar power-law forces were also used by [65, 116]. This force is introduced to counteract the unwanted effects introduced...
by IBM at this resolution, as described in chapter 3. If we account for the RBC thickness, which is 1.8µm, the extent of the cutoff distance is rather large, leading an increased effective volume of the suspension in dense cases. This has two notable consequences: on the one hand the effective volume of the cells appears to be larger [148], since when two RBCs come close, a strong force keeps them apart and prevents them from sticking, and on the other it maintains a reasonable lubrication layer between the RBCs, avoiding jamming of the suspension.

### 7.3 Results and discussion

In this section we present and discuss results obtained from simulations of an RBC-like suspension for a wide range of shear-rates and volume fractions. We analyze the mean square displacement (MSD) of RBCs, the velocity autocorrelation function (VACF) and the shear-induced diffusivity. The microstructure of the suspension for the various parameters is presented in terms of the pair distribution function. A cluster analysis follows and the sections ends with measurements of platelet diffusivity.

#### Viscosity

Blood is a shear thinning fluid: viscosity decreases with an increasing rate of shear strain. Figure 7.2a shows that the relative viscosity of the suspension \( \nu_{\text{rel}} = \nu_{\text{app}}/\nu_0 \) is decreasing with shear-rate \( \dot{\gamma} \), for large volume fraction \( \phi \). The substance we consider is also shear thinning at volume fractions \( \phi = 0.3, 0.4 \) and 0.5, weakly shear thinning for \( \phi = 0.2 \) and Newtonian for \( \phi = 0.0 \) and 0.1. Case \( \phi = 0.0 \) contains only platelet-like particles in very low volume fractions (\( \phi_{\text{platelet}} \ll 1\% \)).

In practice, the effective volume of the RBCs is larger for \( \phi = 0.4 \) and 0.5, due to the range of the repulsive force [172]. It has been found that by imposing a purely repulsive force field –akin to a polymer brush–, shear thickening can be suppressed and shear-thinning can be induced [24, 209]. Note that the arithmetical differences from the viscosity plot shown in chapter 3 is due to the difference in \( r_{\text{cutoff}} \). In dilute suspensions, where collisions are less frequent and the mean particle distance is relatively large, the effect of the force is constrained and the suspension behaves as a Newtonian fluid. The force becomes defining as the mean particle distance decreases and RBCs interact more frequently (i.e. high volume fractions).

The viscosity for \( \phi = 0.1 \) is well approximated by Einstein’s relation for dilute suspensions, \( \nu_{\text{rel}} = 1 + 2.5\phi \), as shown in Fig. 7.2b. Larger particle concentrations are better approximated with the empirical formulas of Batchelor [19, 20] or
CHAPTER 7. SHEAR-INDUCED DIFFUSION OF RBCS

Figure 7.2: Relative viscosity \( \nu_{\text{rel}} = \nu_{\text{app}}/\nu_0 \), where \( \nu_0 \) is the viscosity of the solvent and \( \nu_{\text{app}} \) the apparent viscosity measured using Batchelor’s method [19]. (a) \( \nu_{\text{rel}} \) with respect to shear-rate \( \dot{\gamma} \). The fluid exhibits shear thinning in higher volume fractions and is Newtonian in lower. Inset: Magnification in linear-log scale. Experimental results of Chien [37] for 45% are also depicted, owing the differences to changes in the \( \tau_{\text{cut-off}} \), compare to other results of section 3. (b) \( \nu_{\text{rel}} \) with respect to volume fraction \( \phi \). Depending on the \( \dot{\gamma} \) and \( \phi \), viscosity can be fitted to (i) Einstein’s relation for dilute suspensions \( \nu_{\text{rel}} = 1 + 2.5\phi \), (ii) Batchelor’s \( \nu_{\text{rel}} = 1 + 2.5\phi + 7.6\phi^2 \) [19, 20] and (iii) the semi-empirical formula of Krieger and Dougherty \( \nu_{\text{rel}} = (1 - \phi/\phi_m)^{-[\eta]\phi_m} \), where \([\eta]\) the intrinsic viscosity and \(\phi_m\) the maximum packing fraction [112]. The value \(\phi_{\text{max}} = 0.66\), is close to the random-close packing of hard ellipsoids of the same aspect ratio as RBCs [50, 81].

Krieger and Dougherty [112], yet these formulas do not consider the shear-rate dependence.

MSD and VACF

Two important measures, equivalent in a way, for studying the transport of particles in uniform flows, are the mean square displacement (MSD) and the velocity autocorrelation function (VACF). MSD is defined as

\[
\langle \Delta R_y^2(\Delta t) \rangle = \langle (R_y(t) - R_y(t_0))^2 \rangle,
\]

where \( R_y(t) \) is the position of an RBC in the \( y \) direction (the shear-gradient direction) at time \( t \), and \( \Delta t = t - t_0 \). The brackets \( \langle \cdot \rangle \) denote a statistical average over all intervals \( \Delta t \). MSD is the most common measure of the spatial extent of a motion, and can be seen as the average distance an RBC has traversed in the time interval \( \Delta t \).

VACF is defined as:

\[
C_v(\Delta t) = \frac{1}{d} \langle \mathbf{v}(t) \cdot \mathbf{v}(t_0) \rangle,
\]

where \( \mathbf{v}(t) \) is the velocity of the RBC at time \( t \).
expressing the covariance of the initial velocity $\mathbf{v}(t_0)$ of an RBC, with the velocity $\mathbf{v}(t)$ at a later time $t$. Since we are focusing on the $y$ direction, the dimensionality $d$ of the system is $d = 1$ and the velocity $\mathbf{v}(t) = v_y(t)$. MSDs and VACFs were calculated over all time offsets, similar to [182].

It is well known that in non-Brownian suspensions, MSD typically exhibits two distinct regimes: over short shear strains $\dot{\gamma}\Delta t$ the velocity of a particle is self-correlated leading to a super-diffusive quadratic behavior $\langle \Delta R_y^2(\Delta t) \rangle \propto (\Delta t)^2$ (ballistic regime) and at large shear strains the diffusive regime $\langle \Delta R_y^2(\Delta t) \rangle \propto (\Delta t)$, where the interactions of particles have lead to decorrelation. This behavior is also observed in our model as shown in Fig. 7.3. In the higher volume fraction
though, a slight departure for the ballistic regime is observed, with an exponent more close to $\alpha \approx 1.7$. This exponent has also been observed in two-dimensional foams \[142\], attributed to the large and localized non-affine displacements, and in athermal suspensions of deformable particles \[81\], associated with dynamical heterogeneities. Although the measurement of viscosity can be accurate even with quite small systems and relatively short simulation times, the calculation

**Figure 7.4:** Velocity autocorrelation function $C_v(t)/C_v(0)$ with respect to shear-rate $\dot{\gamma}$ and volume fraction $\phi$. 
7.3. RESULTS AND DISCUSSION

Figure 7.5: (a) Diffusion along the shear gradient direction $D_y$ in units of $\dot{\gamma}r^2$ (equivalent to the inverse Péclet number $1/Pe = D_y/(\dot{\gamma}r^2)$), with respect to volume fraction and hematocrit. $D_y$ was calculated from the mean square displacement. and (b) Schmidt number $Sc_{D_y} = \frac{\nu}{D_y}$

of the self-diffusion requires significantly larger systems running for longer shear strains [182]. Small shear-rates require proportionally longer run times and as it is shown in Fig. 7.3, many cases of $\dot{\gamma} = 3/s$ have just established the diffusive regime.

As observed in Fig. 7.4, the form of the normalized VACF seems independent of the shear-rate for a given volume fraction, and only for $\phi = 0.4$ and $0.5$ it differentiates considerably. The negative part of the VACF that can be distinguished for $\dot{\gamma}\Delta t < 5$ is due to two-particle collisions. Following a collision, the individual particles reverse, on average, their velocity [51]. This negative part is reduced (or even absent) in the higher concentrations of $\phi = 0.4$ and $0.5$, suggesting that collisions with more than two particles are taking place.

Shear-induced diffusion

Self-diffusion, the stochastic drift of particles in uniform flows in absence of concentration gradients, is anisotropic, necessitating the use of a self-diffusion tensor [71, 31]. Here however, we focus on diffusion along the shear-gradient direction $y$, for the simple reason that these measurements are straightforward. Methods for estimating the full-diffusion tensor, including the off-diagonal elements, can be found in [31, 182]. Preliminary analysis on the component parallel to the flow reveals a behavior different than that of the shear gradient direction.

Both MSD and VACF provide a way to measure the diffusion of RBCs. The velocity correlation function can be related to diffusion via the “Green-Kubo”
relation:

\[ D = \int_0^\infty C_v(\tau) d\tau, \]  

(7.3)

implicitly assuming that the integral converges. Regardless of the form of VACF, Eq. 7.3 always allows us to compute the diffusion coefficient, with the negative contribution of VACF also having to be included in the calculation, otherwise the obtained value is overestimated [135, 182]. Diffusion from the MSDs is obtained as \( D_y = \lim_{t \to \infty} \frac{1}{2t} \langle \Delta R_y(t)^2 \rangle \). Because both methods yield numerically similar results, we limited the study to diffusion obtained from MSD measurements (data not shown).

Breedveld et al. [31], using dimensional arguments, suggested that the diffusion tensor of a hard sphere suspension should scale as \( D = \tilde{r}^2 \hat{D}(\phi) \), where \( \hat{D}(\phi) \) is a dimensionless symmetric tensor. The arguments stem from the fact that the only relevant length-scale is the particle radius \( r \), and considering the shear-induced character of the process, the relevant timescale must be that of \( \dot{\gamma}^{-1} \). Suspensions of deformable particles however, include additional timescales, like the one imposed by the elastic modulus and is expressed in the Capillary number \( \text{Ca} \) and another one from the interparticle force, which is expected to manifest in the case of higher volume-fractions.

As shown in Fig. 7.5a, \( D_y/(\dot{\gamma}r^2) \) is increasing with \( \phi \), with diffusion following the linear scaling in low volume fractions. However, for higher volume fractions, \( D_y/(\dot{\gamma}r^2) \) scales \( \propto \dot{\gamma}^{-0.5} \). Gross et al. [81] also observed a deviation of the diffusion from the linear scaling, for a three-dimensional suspension of deformable particles in Couette flow. The scaling they observed had the form of \( D/(r^2\dot{\gamma}) \propto \text{Ca}^{0.25} \). Via kinetic and scaling arguments, they connected diffusivity \( D/\dot{\gamma} \) to viscosity, in a form that predicts \( D/\dot{\gamma} \propto \text{Ca}^{-q/2} \) in the shear-thinning regime and \( \propto \text{const} \) in the Newtonian regime. \( q \) indicated the scaling of the viscosity with respect to shear-rate \( (\nu \propto \text{Ca}^{-q}) \). These findings are not confirmed by our simulations, in which the ratio \( \nu/D_y \) seems to be \( \propto \dot{\gamma}^{-1} \) and not \( \propto \dot{\gamma}^{q/2-1/2} \) (Fig. 7.5b). This is less likely to be a 2D effect, since the kinetic and scaling arguments hold in our simulations as well. One of the principal assumptions of the study was that the shear-elasticity provides the most dominant contribution to the suspension stress, disregarding the contribution of interparticle forces, which is considerable at high volume fractions. Differences in the resolution and the reach of the repulsive force, can explain the shift between our results and [81] with respect to the volume fraction, highlighting the role of repulsion. Further investigation is necessary.

The mechanisms behind the deviation from linear scaling of diffusion are not fully understood. Since RBCs are deformable particles, stretching and tank-treading under shear (see section 3.3.1), one could associate the stretch and the angle of orientation to the decrease in diffusion. A decrease in the collisional
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Figure 7.6: (a) Average orientation angle \langle \theta \rangle and standard deviation of the angle (inset) as a function of volume fraction for several values of the shear-rate, (b) average diameter of an RBC \( D_{\text{max}} \) as a function of shear-rate. \( D_{\text{max}} \) is defined as the average maximum distance between the surface points of an RBC. (c) Collisional cross-section as obtained from the discretized form of \( R = \int 2\pi P(\theta)(d + D_{\text{max}} \sin(\theta))d\theta \). The fittings to \( R = c_1 \log \dot{\gamma} + c_2 \) are also shown for \( \phi = 0.4 \) and 0.5. For \( \phi = 0.4 \) we obtain \( \{c_0, c_1\} = \{0.02\mu m, 3.24\mu m\} \) and for \( \phi = 0.5 \), \( \{0.026\mu m, 3.49\mu m\} \) respectively.

cross-section would result in smaller post-collisional migrations and eventually to smaller values of diffusion. Even though there is an increase of the average orientation angle \( \langle \theta \rangle \) with respect to \( \phi \) (along with an increase in the standard deviation), there no notable deviation with respect to the shear-rate (Fig. 7.6a). The average diameter of an RBC \( D_{\text{max}} \) (shown in Fig. 7.6b) reveals two interesting facts: (a) cells are stretched in all cases of high shear-rates and (b) the cells are always stretched in high volume fractions. The increase in high shear-rates is an effect of the shear forces and the deformability of the RBCs. However, given that the extent of this stretch is uneven in high shear-rates and that for \( \phi = 0.5 \) a stretch is observed even for \( \dot{\gamma} = 3/s \), a part on the increase can be attributed to particle-interactions and the interparticle force, increasing with the volume fraction. If we combine the average diameter and the angle distribution to obtain a collisional cross-section, by integrating over all angles \( R = \int_0^{2\pi} P(\theta)(d + D_{\text{max}} \sin(\theta))d\theta \), where \( P(\theta) \) the distribution of angles and \( d \) is the RBC thickness, we find that the change in \( R \) is not sufficient to explain a departure from the linear scaling in high volume fractions (Fig. 7.6c).

The above rationale however assumes that the same mechanisms that drive diffusion in dilute systems would also apply to dense systems. Our results in Fig. 7.6 challenge this assumption and suggest that higher order collisions should be taken into account. It is likely that collisions with more than two particles are driving the deviation from the linear scaling.

Figure 7.5b also shows the Schmidt number \( \text{Sc} = \nu/D_D \), a dimensionless number defined as the ratio of momentum to mass diffusivity. \( \text{Sc} \) is used to characterize fluid flows in which there are simultaneous momentum and mass diffusion convection processes, usually referring to systems with Brownian particles. In the
present case, the value of Sc indicates a dominance of the momentum diffusion (viscosity), which decreases with a rate \( \propto \dot{\gamma}^{-1} \).

**Correlation time, diffusion length**

The timescale on which particle velocities decorrelate can be quantified from the VACF. Assuming an exponential decay of VACF, Eq. 7.2 can be fitted to an exponential form

\[ C_v(t) = \langle v_y(t)^2 \rangle e^{-t/\tau_c} \]

thus obtaining a correlation time \( \tau_c \) [81]. This is valid only for small strains, due to the negative part of the \( C_v(t) \). We estimated \( \tau_c \) as the time in which VACF loses 1/e of its initial correlation: \( C_v(\tau_c) = e^{-1} \). Even though \( \dot{\gamma} \tau_c \) presents small variations with respect to shear-rate, the correlation time is decreasing with volume-fraction (Fig. 7.7a), demonstrating that in dense suspensions velocities decorrelate faster. The characteristic distance that the particle has traveled before its velocity changed significantly, can be seen from the mean square displacement at time \( \tau_c \),

\[ l_D = \sqrt{\langle \Delta R_y^2(\tau_c) \rangle} \]

(figure 7.7b). RBCs exposed to low shear-rates need to travel longer distances for their velocities to decorrelate, and the same applies for increasing volume fractions, except for \( \phi = 0.5 \). While the decrease of \( l_D \) from \( \phi = 0.4 \) to 0.5 can be associated with a form of mean free path which decreases with volume fraction (similar to [81]), the increase from \( \phi = 0.1 \) to 0.4 is counterintuitive and suggests the appearance of collective motion effects. The increase of the characteristic distance with \( \phi \) was also observed in [81], yet it could not be explained.
Figure 7.8: Two dimensional pair distribution function $g(x, y)$, as calculated from the distances between the centers of the particles. Lighter gray corresponds to higher probability, units of distance are in $\mu$m and color-scale is per subplot. An asymmetry and a preferred orientation with increasing shear-rate and volume fraction can be distinguished.

Pair distribution function

The suspension microstructure is entirely dictated by the spatial arrangements of particles [186]. This microstructure can be described by the pair-distribution function $g(r)$, which describes the probability of finding particles at distance $r$ from a reference particle normalized by the number concentration of the suspension [146]. Contrary to hard spheres where the spherical shape is clearly visible in $g(x, y)$, RBCs are deformable with a biconcave shape and may have neighboring particles at distances shorter than their larger diameter. These properties blur their shape in the $g(x, y)$, as shown in 7.8. Yet very useful information can be extracted from such an analysis.

Figure 7.8 corroborates our findings so far. In the dilute case, where particle interactions are less frequent, $g(x, y)$ has a uniform distribution lacking local maxima, and a shape close to that of an RBC is distinguishable. With an increasing volume fraction, local maxima develop close to the small RBC radius. The ripples present in low $\dot{\gamma}$ for $\phi = 0.3 - 0.5$ indicate rouleux-like structures. These structures may have similar shapes to rouleux, but due to the repulsive force they
do not hold the aggregating function of blood-rouleux, and are rather a product of the increasing volume fraction. A second peak can also be observed in some cases, close the large RBC diameter of \( r = 7.5\mu m \), indicating that neighboring RBCs are often aligned in the flow. As also shown in Fig. 7.6b, RBCs are pretty much stretched at higher shear-rates of \( \dot{\gamma} = 0.5 \).

If we plot the same data as \( g(d_r) \) with respect to \( d_r = \sqrt{x^2 + y^2} \), we obtain the radial distribution functions, see Fig. 7.9. In the dilute case (\( \phi = 0.1 \)) particles tend to present a flat distribution with increasing distance. Without the presence of hydrodynamic interactions, \( g(d_r) \) would have the shape of a step function, but due to their presence there is a gradual increase. In \( \phi = 0.2 - 0.5 \), a peak is found close to the small RBC diameter, as also indicated by the pair distribution function. The first subplot of Fig. 7.8 shows the location of the first

---

**Figure 7.9:** Radial distribution function (RDF) \( g(d) \), as obtained from the data of 7.8. The first plot corresponds to the distance of first RDF peak, located in the vicinity of the small RBC diameter 2\( \mu m \).
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\textbf{Figure 7.10}: Detail from the simulation of $\phi = 0.3$ and $\dot{\gamma} = 30/s$. The RBCs that belong to the same cluster have the same color. Platelets are not shown.

$g(d_r)$ maximum $d_{\text{max}}$, which is a decreasing function of shear-rate and volume fraction. This distance is comparable to the cutoff distance of the repulsive force ($d_{\text{max}}$ is measured as distance between the centers). The ripples and alignment of RBCs are also present as peaks in $d_r \approx 5\mu m$ and $d_r \approx 7.8\mu m$ respectively.

Fedosov et al. [63] do not observe peaks in the radial distribution function without the use of an aggregating force, a Morse potential in their case. They argue that it is important for the rouleaux formation and the shear thinning behavior of blood. The peaks in our case are most probably due to the presence of the repulsive force, and not due to aggregation. The force constitutes a wall under which particles are obstructed from surpassing and it is possible that parts of particle concentration that would lie below the cutoff distance, to accumulate close to the point of cutoff. The lack of an aggregation force in our case indicates a shear thinning mechanism different to the breaking of rouleaux.

**RBC clustering**

As a step towards studying the collective motion of RBCs, we perform a cluster analysis of the suspension. Two RBCs are considered to be “in contact” and belong to the same cluster, when the distance between two of their surface points is less than a cutoff distance. While it is common the hard-sphere literature to choose the peak of RDF as the cutoff distance, in this case it is not so effective. RBCs are biconcave and can be in contact at distances larger than the one defined from RDF. The cluster cutoff distance was chosen to be $0.77 \mu m$, the same as the
cutoff for the repulsive force. Below it, two cells are considered to interact, and given the repulsive nature of the force, they are considered in collision. A snapshot of the system with colored clusters is presented in Fig. 7.10.

The mechanisms and function of such clusters is different from the hydro-clusters of hard-sphere suspensions [30] or the force chain networks in granular matter [35]. Hydro-clusters are related to the shear thickening of hard-sphere suspensions, formed by strong lubrication forces among the particles. In our case, the repulsive force keeps the particles in a large enough distance, preserving a lubrication layer and preventing their sticking. What keep RBCs close are the force interactions driven by shear, rendering the approach closer to a force chain network. However, due to the RBCs deformability and energy storing potential, there are no jamming effects in the volume fractions we consider.

The collection of RBCs that are in contact, form a cluster and the number of particles in one cluster, defines the size $s$ of the cluster. The total number of clusters with size $s$ at time $t$ is denoted as $n(s, t)$. The average number of clusters $n(s)$ is obtained over a time period $T$, and is defined as [48]:

$$ n(s) = \frac{1}{T} \sum_{t=t_0}^{t_0+T} n(s, t). \quad (7.4) $$

In the present analysis $T = 7\dot{\gamma}^{-1}$, several times larger as compared to $\tau_c$ and long enough to capture the duration of RBC contacts. The quantity we are interested in, is the cluster size distribution $p_n(s) = n(s)/\sum_{s_0=1}^{\infty} n(s_0)$. For the $\phi$ and $\dot{\gamma}$ we consider, $p_n(s)$ is shown in Fig. 7.11.

Raiskinmäki et al. [173] using kinetic arguments developed the kinetic clustering model (KCM), in which the cluster size distribution follows a Poissonian, $n(s) \propto s^{-3/2} \exp(-s/s_0)$, with $s_0$ denoting a typical cluster size. KCM was used to study the basic mechanisms of shear thickening in particulate suspensions, in the regime dominated by hydrodynamics forces. A similar type of distribution, with a difference in the exponent ($5/2$ instead of $3/2$) was used by Ding & Aidun [48] to uncover a universal scaling relation for the cluster size distribution, independent of particle shape and concentration. A noteworthy difference in this approach is that the above studies were used in purely hydrodynamical interactions, while in the present case, an additional force, that dominates higher volume fractions, exists.

In the dilute case of $\phi = 0.1$, cluster sizes with $s > 1$ are not frequent and the maximum cluster size $s$ remains well under 10 in all examined shear-rates. The collisions of more than 2 particles, as expressed by $p_n(s > 2)$, seems to be 10 times less frequent than 2-particle collisions. In higher volume fractions these collisions are more frequent and some collective motion can be assumed. The extreme case of $\phi = 0.5$ indicates that one big cluster dominates the flow.
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Figure 7.11: Cluster size $s$ distribution with respect to volume fraction $\phi$ and shear-rate $\dot{\gamma}$. The mean gap size between RBCs for volume fraction $\phi = 0.5$ is comparable to $2 \cdot r_{\text{cutoff}}$, resulting in a hyper-cluster. The tails of the distribution for $\phi = 0.4$ and 0.5 are ascribed to the loss or recruitment of RBCs from the larger clusters during the examined time-period.

However, the mean gap size between RBCs is comparable to $2 \cdot r_{\text{cutoff}}$ and it is less likely that the picture will change by increasing the domain size. Spatial velocity correlations indicated that no finite size effects were present (smaller simulations of $100 \times 100\mu m^2$ indicated the contrary).

The percentage of “free” RBCs $p_n(s = 1)$ is shown in Fig. 7.12a. It is a decreasing function of hematocrit, with only a slight dependence on the shear-rate observed at $\phi = 0.3$ and 0.4. At $\phi = 0.5$, this percentage is increased, stemming from the fact that $p_n(s = 1)$ corresponds to a ratio of $n(s = 1)$ to the
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Figure 7.12: (a) Percentage of single RBCs \( p_n(s = 1) \) (RBCs not belonging to a cluster), (b) average cluster size \( \langle s \rangle \) and (c) Typical cluster size \( s_0 \) obtained from fitting data to \( p_n(s) = C s^{3/2} e^{-s/s_0} \). Error-bars correspond to the standard deviation errors on the fitted parameters, performed in the log-log space.

total number of clusters \( \sum_{s_0=1}^{\infty} n(s_0) \), and not to the absolute number of clusters found in the domain. Since the total number of clusters is decreased, due to the dominance of a hyper-cluster, \( p_n(s = 1) \) appears increased.

The average cluster size \( \langle s \rangle \), defined as \( \langle s \rangle = \sum_{s=0}^{\infty} s \cdot p_n(s) \) remains under 3 RBCs for up to \( \phi = 0.3 \), after which it increases exponentially to \( \approx 10 \) for \( \phi = 0.4 \) and \( \approx 10^3 \) for \( \phi = 0.5 \). The scaling seems proportional to \( \phi^4 \) (Fig. 7.12b). An attempt to fit the data to the KCM using non-linear least squares and obtain a typical cluster size is shown in Fig. 7.12c. The fittings to KCM have a small standard deviation for \( \phi \) up to 0.3, with the typical cluster size increasing with the volume fraction. For higher values of \( \phi \), the fitting algorithm fails, due to the presence of the aforementioned tails. For \( \phi = 0.1 \), the typical cluster size is below 1 RBC, which seems unlikely and has to do with the extend of the cluster cutoff distance. While the value for the typical cluster size \( s_0 \) depends on the cutoff distance for the cluster definition, the behavior with respect to hematocrit remains unchanged [48, 173]. Since interactions of RBCs are sporadic in \( \phi = 0.1 \) (as also shown in Figs. 7.8 and 7.9), the fit which considers also two or more RBC collisions underestimates the typical cluster size. It is worth noting that the fit was not constrained to represent a distribution (i.e. the sum to be one).

RBC contact duration

Strong lubrication interactions are suppressed in our simulations and particles do not stick. Yet in high volume fractions their motion and dynamics is not fully understood, as found with the departure of RBC diffusivity from the linear scaling with the shear-rate. The duration of RBC contacts is an interesting measure, for
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The duration of a contact $t_c$ is defined as the maximum time interval in which the distance of any of the surface points between a pair of RBCs, remains under $r_{\text{cutoff}}$. If, for any reason, the two RBCs escape this distance, $t_s$ is stored and a new measurement starts. The contact of two RBCs can break either due to the repulsive force, or due to their relative motion. The duration distribution, shown in Fig. 7.13, appears to follow an exponential distribution. The exponential distribution describes the time between events in a Poisson process, i.e. a process in which events occur continuously and independently at a constant average rate, which seems to be in agreement with the KCM approach.

Since the suspension is governed mostly by two-particle collisions for $\phi = 0.1$, the extent of $p_c(t_c)$ indicates the duration of a collision in the dilute limit. After approximately $\dot{\gamma} t_c = 2$, none of the pair contacts have survived. For larger
hematocrits however, the distribution is more wide-spread, indicating that more than two-particle collisions are present, and sustain a “bond” for larger times.

An interesting result from this analysis is that even though the correlation time $\tau_c$ (Fig. 7.7a) decreases with the volume fraction, the time two RBCs are in contact increases with the volume fraction. This can be seen from both the mean contact duration $\dot{\gamma}(t_c)$ (Fig. 7.14a) and the typical contact duration $T_c$ obtained from the exponential fit. This translates to two RBCs being in contact for longer times, up to 2 times when compared to the dilute case. A similar increase is observed for the shear-rates, when comparing $\dot{\gamma} = 3/s$ with $\dot{\gamma} = 1000/s$. This increase with the shear-rate can be attributed to the scaling of the repulsive force: higher shear-rates yield higher velocities in absolute numbers, and since the force lacks appropriate scaling, higher velocities are taking longer to counteract. As in the clustering distribution, the fit was not constrained to represent a distribution (i.e. the sum to be one).

RBC enhanced diffusion of platelets.

This last section addresses the RBC-enhanced, shear-induced diffusion of platelets, as measured in our simulations in a LEbc type of domain. The RBC-enhanced motion of platelets has been recognized earlier [7, 201]. Several diffusion or drift-diffusion models have been proposed [56, 225, 183, 99, 90, 195] and computational simulations are employed to study the relevant parameters and behavior of platelets [42, 230, 174, 147, 203].

The LEbc domain constitutes a privileged method for measuring the diffusion
of platelets, due to the lack of platelet margination, observed in both bounded types of shear and channel flow for whole blood [8, 203]. Hence, measurements of platelet diffusivity in these cases are either short-lived, until they marginate, or are restricted in measurements in the cell-free layer [42, 230, 174, 203].

As shown in Fig. 7.15, the diffusion of platelets is mainly determined by the motion of the RBCs. In their absence, diffusivity is several orders of magnitude smaller, while the diffusivity of platelets is following the diffusivity of RBCs, also in absolute numbers. In view of this result, the driving force behind platelet margination is not a potential disparity between the diffusivities of RBCs and platelets, but rather an effect of bounded flows. Vahidkhah et al. [202] argue that natural anisotropies in the RBC distribution create local clusters and cavities, which a platelet can use as an express lane and marginate towards the wall. A similar functioning was visually observed in our simulations as well, yet the lack of wall prevents segregation. This assumption needs further investigation, since this subject is still under active research [195, 174, 118, 203].

7.4 Conclusions

In this chapter we have looked into the micro-structure and the dynamics of the model presented in chapter 3. The repulsive force has a larger cutoff radius than the one used earlier, preventing RBCs from sticking and guaranteeing a lubrication layer between them. The fluid is Newtonian in low volume fractions.
and presents a shear thinning behavior for larger $\phi$. The shear-induced diffusion of this suspension exhibits a departure from the linear scaling with the shear-rate. For $\phi = 0.5$ we obtained $D_y/\dot{\gamma} \propto \dot{\gamma}^{0.5}$. This behavior is not fully understood, and the analysis provided by Gross et al. [81] who have similar findings for a similar system, is not confirmed by our results. An increase in diffusivity due to a potential increase in the collisional cross-section, is itself not enough to explain this departure, indicating that the nature of collisions is different at high volume fraction, in which collective effects are taking place.

A cluster analysis shows evidence for such collective motion, with many particle collisions taking place as volume fraction increases, as is expected. While for up to $\phi = 0.3$ the average cluster size reaches to slightly above 2 (signifying 2 particle collisions), for $\phi = 0.4$ and $\phi = 0.5$ the average cluster size is exponentially increased. Examining the duration of the collision has shown that the mean duration is increasing with respect to both shear-rate and volume fraction, attributed to the collective motion for $\phi$, and for $\dot{\gamma}$ to the velocity in absolute numbers which the repulsion force has to counteract.

The diffusion of platelets in such a suspension is mainly determined by the motion of the RBCs, since it follows the diffusion of RBCs and in their absence is several orders of magnitude smaller.
Part IV

Outlook
A microscopic model for primary hemostasis

The normal response of the body in case of an injury is the formation of a thrombus at that site, to prevent further bleeding. This process is called hemostasis and can be divided in two steps: primary and secondary. In primary hemostasis platelets adhere to the wall of the (injured) blood vessel forming a plug, while in secondary hemostasis the formation of a fibrin mesh for the stabilization of the structure is in focus. Secondary hemostasis activates the coagulation cascade, which involves numerous chemical reactions between molecules and cells, leading to the production of fibrin.

It a highly regulated response, which has to balance the constant repair of the blood vessels with the creation and the lysis of thrombi, while keeping blood in a fluidic state. Computational models of thrombosis help in understanding this complex phenomenon, by testing hypotheses and identifying the key functions and parameters behind the formation of a thrombus. In the current chapter, we extend the fully-resolved model introduced in chapter 3, with a ruleset describing primary hemostasis through the adhesion and aggregation of platelets.
CHAPTER 8. PRIMARY HEMOSTASIS MICRO-MODEL

8.1 Definition of a primary hemostasis model

The main components of a thrombus are the platelet plug (a platelet aggregate) and a cross-linked fibrin mesh. In this section we present a model for platelet-plug formation, as a step towards building a thrombosis model. The basic elements in our model are: the platelets, the endothelial cells (EC) and the extra-cellular matrix (ECM). Platelets are represented as closed circular membranes, described in Chapter 6, while EC and the ECM as a lining of the flow boundaries with point elements, having a similar density to platelets.

In principle, coagulation is understood as a process taking place on the surface of the cells [144]. The glycoproteins (GPs) that are present in the surface of platelets, function as receptors and engage in the adhesion of platelets to the ECs and the ECM, and in their aggregation. These receptors also allow the platelets to tether and roll in EC, before establishing a firmer connection. Practically, every discretization point of the platelet membrane, or the EC/ECM lining represents a collection of receptors. Platelet activation is also an important function, triggered by chemical or physical agonists [215]. Their shape changes by extruding pseudopod and release granular contents, augmenting platelet aggregation and activation.

There are various types of receptors assisting in platelet adhesion and aggregation, like selectins, integrins (GP*), and immunoglobulins [104]. As a first approximation in our model, this variety has been collapsed into two general types of receptors: one type responsible for weak collagen and von Willebrand Factor (vWF) bonds termed R1, and one for the fibrinogen and the firmer collagen bonds, termed R2. An illustration of the functional entities of the model is shown in Fig. 8.1.

Apart from the receptors, important factors and cell-adhesion molecules are considered to have a constant concentration in the plasma. These would include the vWF, thrombin, fibrinogen, and collagen. However, due to the importance of thrombin in establishing vWF bonds of type R1, a local build up of thrombin concentration is considered at the receptor points. This build up is performed at a constant rate.

Receptors R1 and R2 are locked by default and can be unlocked and allowed to establish bonds, under a specific ruleset. They have a spring constant, an equilibrium length, and a maximum length beyond which the bond will break. Together with the spring constant, the maximum length defines the maximum force this bond can withstand.
8.1. DEFINITION OF A PRIMARY HEMOSTASIS MODEL

Figure 8.1: Schematic of the micro-model, describing (a) the aggregation of platelets with receptors R1 and R2, (b) the adhesion of platelets to the endothelial cells (EC) using the same receptors and (c) the adhesion of platelets to the extracellular matrix (ECM) with receptors R1. The release of CEPAC from the EC and the platelets, as discussed in section 8.3, is also depicted.

A R1 bond is weak compared to the firmer R2 type. More information on receptors R1 and R2 follow.

Receptor Type R1 Receptors R1 represent the vWF adhesion receptor complex (GPIb-IX-V) and the collagen receptors GPIa/IIa and GPVI. The first is involved in the initial tethering and rolling of platelets over the ECM and intact endothelium [204]. The latter binds platelets to a damaged endothelium which exposes the underlying collagen to circulation [101]. These two types lead to two “pathways” for unlocking R1: the vWF and the collagen R1 pathways.

Local shear rates above a threshold of 1000s$^{-1}$ can unlock R1 via the vWF pathway [137], which once unlocked, remains unlocked for a few milliseconds. As soon as a R1 bond has been made, thrombin starts to build up at the receptor site with a constant rate. If the concentration of thrombin reaches a threshold value, the R2 receptor at that site will be unlocked.

The collagen R1-pathway constitutes a shortcut of the above, circumventing the necessary thrombin build-up for the unlocking of receptor type R2. This way, a bond can be made to collagen on the EC/ECM surface directly, by only full-filling the condition of minimal distance
between the receptor cites. This binding immediately unlocks receptor R2 at that site.

**Receptor Type R2** R2 receptors represent the integrins, GPIa, GPIIb, and GPIIIa altogether. They can be unlocked by the exposure of a platelet to high shear rates for sufficient time, or when the thrombin concentration at the receptor point reaches a threshold value. R2 can also be unlocked immediately, by a R1-type of collagen bond at the same receptor site. Once unlocked, fibrinogen bonds can be made, provided that two unlocked R2 receptors are within a minimum distance (1µm).

For firm adhesion to occur, platelet bonds have to withstand the shear stress due to the blood flow. The initial tethering and rolling over the intact ECs and over the ECM at the site of injury, slows the platelets down, increasing their ability to form stronger bonds at the site of injury. Rolling is mediated through R1 bonds, which can break at any time if they are stretched too far. Between the breaks, other R1 bonds have been established linking the platelet to the endothelium, or another platelet. This process of formation and breaking of R1 bonds leads to rolling along the endothelium or to a platelet aggregate. A platelet can also detach again and be dragged with the flow, or it can stay at a location where the drag forces are not strong enough to break these bonds. Then, thrombin can build up and R2 receptors can be eventually unlocked, leading to the firm R2 type of binding.

### 8.2 Preliminary results

Nesbitt et al. [154] have shown that inactive discoid platelets can tether on non-coated surfaces if they have been exposed to high shear stress for a short-time. In an in-vivo experiment they let blood flow over a very steep stenosis, behind which platelets tether and form semi-stable aggregates parts of which get dragged away in the flow frequently. A snapshot of the experiment is shown in Fig. 8.2a. This setup was simulated with a preliminary implementation of the receptor R1. The shear rates at the stenosis are sufficient to unlock R1 receptors (up to 10000s⁻¹), after which vWF bonds can be made. For a more stable adhesion and aggregation, stronger fibrinogen bonds would have to be made. This result, hints on the existence of a peak in the adhesion probability at medium shear rates in which below that
8.3 DISCUSSION AND OUTLOOK

In this chapter we formulated a model for primary hemostasis, extending the fully-resolved model of chapter 3. A ruleset under which platelets can aggregate and adhere to ECs/ECM, was presented. The various platelet and EC/ECM receptors were grouped into two types: R1 responsible for weak vWF or collagen bonds, and R2 responsible for firmer fibrinogen or collagen bonds.

Important factors, like vWF, fibrinogen and collagen were not explicitly considered, and were assumed to have a constant concentration in the plasma. Factors relevant to the coagulation cascade were also not considered. These factor are important for the formation of fibrin strands, that stabilize the structure and form a thrombus.

One potential way of doing this would be by grouping these factors

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1 Unpublished in-vitro experiments from the “Université libre de Bruxelles” find such a peak at around 100s⁻¹ hinting a lower critical shear rate for the unlocking of R1α receptors (1000s⁻¹ in the simulation).

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Figure 8.2: Towards reproducing the in-vivo experiments of Nesbitt et al. [154]. (a) In-vivo blood flow through a steep stenosis behind which platelets tether and form semi-stable aggregates (from [154]). (b) Snapshot from a 2D simulation reproducing the onset of the formation of aggregates behind a micro-stenosis. Simulations performed by Eric Lorenz.

...
into one scalar measure, accounting for the balance of pro- and anti-
coagulants\(^2\). This can be modeled as an advection-diffusion field,
with negative values representing an anti-coagulant level and posi-
tive a pro-coagulant. EC/ECM and platelet receptor sites can act as
sources and sinks for the CEPAC concentration.

Such an addition would gradually extend the approach towards mod-
eling the formation of a thrombus. However, this is an active field of
research and the goal of a model explicitly considering platelets and
parts of their function, is not the implementation the model per-se. It
is rather targeted, complementary to the experiment, towards the un-
derstanding of the process of thrombosis, by formulating hypotheses
and testing them. Fully resolved models that reproduce the essential
rheology and transport of blood, are one extra tool in comprehending
the complex response of hemostasis.

\(^2\)This field is coined CEPAC in Fig. 8.1, standing for the “Combined Effect of Pro- and
Anti-Coagulants”.
In the present thesis we have looked into the transport of RBCs and platelets using with fully resolved models. The modeling aspects of such an endeavour are not trivial, and attention has also been given to the methods used. Throughout this work, the combined immersed boundary-lattice Boltzmann method (IB-LBM) was employed. Lattice Boltzmann method (LBM) resolves the fluid flow, and the cells are coupled to it with the immersed boundary method (IBM). Cells are represented as a collection of Langrangian surface particles interacting with a force model.

In Chapter 3 a simple two-dimension model for blood-like suspensions was presented. This simple model, based on Hookean springs, bending resistance and surface-conservation, was able to reproduce some of the essential blood phenomena, such as the shear-thinning, the formation of a cell free layer, and, on the single cell level, the transition from tumbling (T) to tank-treading (TT). However, by using a coarse lattice resolution, a few drawbacks of IBM were noticed: an increased sticking of IBM membranes was observed, while the type of the IBM interpolation kernel significantly affected the T-TT transition. A repulsive force between RBCs was introduced to counter-act some of these effects.
A sensitivity analysis on the parameters of IBM was performed in chapter 5. Two main results came out from this analysis: (a) the hydrodynamic radius of an IBM sphere is different from the radius it interacts with other IBM spheres, and (b) inadequately resolved spheres failed to migrate in bounded shear flow. The latter is a result that escapes numerical accuracy, and the method cannot capture the relevant physics. The commonly used interpolation kernel $\phi_2$ failed to capture the migration of the sphere, raising some issues for its validity, however denser sphere meshes may prove otherwise. Because these methods combine different approaches, predicting beforehand their behavior and shortcomings is not straightforward. The parameter space we explored was sufficient to catch the role and the tendencies for each parameter, but was not exhaustive. This work was performed in three-dimensions and the importance of these results on two-dimensions should be addressed anew.

The two dimensional model was also applied in small aneurysmal geometries. These geometries were one order of magnitude smaller, however they indicated an interesting behavior worth further exploration. A large high-hematocrit region with trapped platelets, was identified in the cavity of the aneurysm and close to the vessel walls. Should this arrangement be happening in real aneurysms, a number of consequences arise. The high-hematocrit region constitutes an unhealthy situation, since RBCs are normally kept away from the vessel wall via the cell free layer. An ATP release from RBCs under pressure would promote vasodilation, pointing to wall weakening and, potentially, the rupture of an aneurysm. The formation of a thrombus in such situation is also plausible from an increase of the levels of agonists inside the aneurysm, promoting platelet activation. This study had several limitations, two evident being the small size of the aneurysms and the boundary conditions, which were set to periodic. Periodic boundary conditions disregard the constant supply of platelets from the inlet and could lead to a decrease migration of platelets inside the aneurysmal cavity. The above constitute hypotheses and need to be tested experimentally. This process had started in collaboration with colleagues from the “Université libre de Bruxelles”, but due to some technical difficulties in obtaining a transparent 3D printed aneurysm geometries, it hasn’t progressed yet.

The repulsive force introduced in 3, appeared to play a major role in the behavior of the suspension in high volume fractions, as observed in Chapter 7. Practically, this force introduces an increased effective volume for the RBCs, reducing their mean interaction distance. This
effect is more prevalent in dense suspension, which have lower mean gap sizes. In dense suspensions the force is strong enough to keep cells apart, resulting in an omnipresent, for our simulations, lubrication layer. Similar behavior has also been observed in suspension of hard spheres by imposing a purely repulsive force field, akin to a polymer brush [24, 209]. The collective motion effects we observed resulted in a deviation from linear scaling of the shear-induced diffusion of RBCs with the shear-rate, with a mechanism that has yet to be understood.

Software engineering in the demanding case of dense suspensions of deformable particles, is an important aspect. One cubic millimeter of blood, contains $\approx 10^6$ RBCs, and the performance of a blood solver can define the limits of our explorations. In Chapter 4 the implementation of a parallel 3D solver for suspensions of deformable cells, coined ficsion, was presented. ficsion is based on Palabos, an open-source LBM solver. The scaling of the code, both in weak and strong scaling scenarios, was close to linear for up to 8k processors. The perfectly load balanced cases and the favorable computation to communication ratio returned these results, which act as a ceiling for real case scenarios. It is for example known, that RBC distributions are inhomogeneous in channel flow, with a CFL near the wall and an elevated hematocrit in the center.
CHAPTER 9. CONCLUSIONS
Part V

Appendices
A.1 Meshing and stress-free model

In the current section we describe the meshing strategy and the stress-free model used in chapter 4.

The average shape of an RBC can be described as a surface satisfying the equation

\[ y = R \sqrt{1 - \frac{x^2 + z^2}{R^2}} [c_0 + c_1 \frac{x^2 + z^2}{R^2} + c_2 \left(\frac{x^2 + z^2}{R^4}\right)], \]

(A.1)

with \((R,c_0,c_1,c_2) = (3.91 \mu m, 0.0135805, 1.001279, -0.561381)\) [57, 169].

The coarse-grained study by Pivkin [169] shows one can use an arbitrarily number of vertices for the surface of an RBC (with a certain cost in accuracy), yet the meshing of this surface remains a non-trivial task. A high degree of homogeneity, in terms of triangle areas, vertex distances and edge angles, is necessary to eliminate any residual stresses from the triangulation.

Fedosov et al. [59] investigated three types of triangulation strategies – point charges, advancing front using commercial grid generation software, and energy relaxation – and identified the drawback of local
Figure A.1: Top: Initial triangulation of an RBC, also corresponding to the equilibrium shape for the stress-free model. Bottom: Equilibrium shape as obtained from the relaxation of the corresponding triangulation, using the mean model. Numbers denote the number of vertices, and the codenames Random, ICO and OCT the method of construction: Random for the open source computational geometry library CGAL [3], and ICO and OCT by mapping the points of a subdivided regular icosahedron and octahedron, to the surface of an RBC, as described in Eq. A.1. The equilibrium shapes are dependent on the triangulation, due to the residual stresses arising from inhomogeneities. A stress-free model is employed to overcome this effect.

stresses on the membrane equilibrium shape. This led to a formulation of a stress-free RBC, in which the equilibrium vertex-distances are obtained from the RBC-triangulation.

We generate the mesh by recursively sub-dividing an octahedron or icosahedron similar to [127, 115], and projecting the vertices onto the surface of Eq. A.1. To eliminate residual stresses along with the dependence of the mechanical properties of a cell on triangulation, we employ a stress-free model, in which all equilibrium quantities, length, triangle area and instantaneous angles, are local, and obtained by the initial RBC-shape, in a similar fashion to Fedosov et al. [59]. As mean model, we refer to the model which the equilibrium values are global (as opposed to the local for the stress free), following Pivkin’s coarse graining argumentation [169]. As it is shown in Fig. A.1, the irregularity of the triangulation generates local stress artifacts for the mean model, altering the equilibrium shape of the RBC.
A.2 Validation of a single 3D RBC

A.2.1 Optical tweezers experiment

A typical case to validate the deformation of an RBC is to stretch it [141, 45, 169]. In the optical tweezer experiment of Mills et al., two silica microbeads were attached to the RBC at diametrically opposite points and the axial and transverse diameter of the deformed RBC are measured with respect to the applied force. In our simulations we distribute the applied total stretch force to the \( N = \epsilon N_v \) vertices and we measure the corresponding diameters. \( N_v \) is the total number of vertices and \( \epsilon \) is the percentage, which can be seen as the contact area of the silica-bead to the RBC and has been set to 4% in our study. Figure A.2 shows the RBC stretching response for two different models, the mean-value and stress-free.

A.2.2 Wheel experiment

One additional setup with experimental data is the so-called “wheel experiment” [221]. In this experiment, the RBC is aligned with the shear flow, “rolling” like a wheel. This induces a deformation upon the RBC, which is quantified with the deformation index \( DI \):

\[
DI = \frac{D_{\text{max}}/D_0 - 1}{D_{\text{max}}/D_0 + 1} \times 100\%.
\]  

(A.2)
Figure A.3: Simulation results and comparison with experimental data from [221] for the Wheel experiment.

\[ D_0 \] is the initial undeformed maximum diameter of the RBC and \( D_{\text{max}} \) the maximum diameter measured under the shear flow. The capillary number \( Ca \) is defined as \( Ca = \frac{\eta \dot{\gamma} D_0}{2\mu_0} \), where \( \eta \) is the fluid viscosity, \( \mu_0 \) the shear modulus of the RBC as calculated from Eq. 4.13, and \( \dot{\gamma} R^2 \) the shear rate. As is shown in Fig. A.2.2, satisfactory agreement with experimental data is obtained.

A.2.3 Single cell in shear flow

When an RBC is found in shear flow, two main types of motion can be distinguished: the tumbling motion (T), where the cell flips like a solid body; tank-treading motion (TT), where the cell maintains a fixed orientation angle while the membrane and the interior fluid undergo a steady rotary motion. In these experiments a single RBC was positioned in the center of a bounded shear-flow and the T and TT frequencies were measured. As TT frequency we define the rate of change of the orientation angle between the RBC and the shear-flow gradient, while as T frequency the rate of change of the angle between the shear-flow gradient and the straight line connecting two tagged surface particles. The simulation results demonstrate the ability of the model to recover the transition of T to TT (Fig. A.4a), while the TT frequency seems to be in close agreement with experimental results (Fig. A.4b).
A.2. VALIDATION OF A SINGLE 3D RBC

Figure A.4: (a) Tank-treading frequency normalized by the shear rate $\dot{\gamma}$ (Experimental data from Tran-Son-Tay et al. [197] and Basu et al. [18]). (b) Tumbling frequency as a function of the shear rate.
Revisiting IB-LBM

In this section we provide supporting material for the results presented in chapter 5.

**B.1 Finite size effects**

A finite size analysis was performed for the results presented in section 5.3. We compared results for all three cases, between the domain used ($20r \times 20r \times 20r$) and by doubling the size of the domain in each direction, namely $(40r \times 40r \times 40r)$. Results are presented in Fig.B.1. In this analysis, we chose the coarse sphere representation, $r = 2.7LU$ with $N_v = 258$ vertices, $\tau = 1.0$ and the IBM interpolation kernel $\phi_3$. The results obtained, as shown in Fig.B.1, are qualitatively and quantitatively very similar. Since the “larger” domain of $40r \times 40r \times 40r$ is 8 times computationally more demanding in terms of time and storage than the “smaller”, the latter was chosen for the simulations.

To conclude, the finite size analysis produced adequately similar results to justify the use of the smaller domain.
Figure B.1: Finite size analysis of the cases presented in section 5.3. (a) Case of measuring the hydrodynamic radius from the suspensions viscosity. Evolution of the hydrodynamic radius $r_{\text{hyd}}$, as calculated from Eq.5.18 with respect to the dimensionless time $\dot{\gamma}t$. The different equilibration times are noticed for the two domain sizes. The values obtained differ $\approx 2.7\%$, deemed as acceptable by the authors considering the computational cost. (b) Case of two spheres colliding in shear flow. Parametric plot of relative distances in the $x$ and $y$-directions for the two different domain sizes. The values for the calculated $r_{\text{int}}$ between the two domains differ at $\approx 0.5\%$ of the particle radius. (c) Case of head collision of two forced spheres. Evolution of the gap size normalized by the radius for the two different domain sizes. The difference between results from the two domains is within $\approx 6\%$.

### B.2 Departure from the spherical shape

In this appendix we track the deformation of the sphere as they collide in shear flow, as presented in section 5.3.2. The metric used for the deformation is defined $D = (\max \{r_i\} - \min \{r_i\})/r$, with $r_i = |\mathbf{R}_i| - \frac{1}{N_v} \sum_{i=1}^{N_v} |\mathbf{R}_i|$ being the distance of vertex $i$ from the center of a sphere with $N_v$ vertices. It is a very sensitive measure and can sense local divergences.

Figs. B.2a and B.2b track this deformation with respect to the relative distance in the $x$-direction, $\Delta X/r$. These two cases represent one case where the post-collision migration is negligible (Fig.B.2a) and one in which it is significant (Fig.B.2a). In both of the samples the deformation $D$ is less than $0.8\%$, yielding a maximum difference in
B.3. METRIC FOR LUBRICATION FAILURE

Defining the gap $h_{\text{fail}}$, in which the lubrications fail, is not a straightforward task. The radii of the spheres are not exact in order to measure deviations from Eq. 5.19, and different means have to be employed. We have noticed in the log-log plot of the gap versus time (like Fig. B.3a) that after failure, it becomes linear in log-log space with an exponent $n$, which is $-1 < n < 0$. The exponent before can be seen as less than $-1$, hence if multiplied by time $t$, the 2 regimes can be distinguished, as shown in Fig. B.3b.

By visual inspection we verified that the gaps $h_{\text{fail}}$ have been identified correctly in the cases presented.
Figure B.3: (a) Gap $h$ in units of radius, versus dimensionless time, for varying lattice spacings $\Delta x$. Symbol $\times$ identifies $h_{\text{fail}}$, the gap in which the lubrication forces fail. (b) Quantity $ht/r$, used to identify $h_{\text{fail}}$. Symbol $\times$ identifies $h_{\text{fail}}$ as the local minimum of this quantity, while $+$ identifies the first local maximum.
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List of publications

Journal articles


Contributions of co-authors


Author contributions: L.M., E.L. and A.G.H. designed research, L.M. performed research and analyzed data, L.M., E.L. and A.G.H. wrote the paper.


Author contributions: L.M., E.L. and A.G.H. designed research, E.L. implemented the model, L.M. E.L performed research and analyzed data, L.M., E.L. and A.G.H. wrote the paper.


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Conference presentations


Selected talks
