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Cell resolved blood flow modeling with the Lattice Boltzmann method

Cell deformability and transport in diseases

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Conclusion and Outlook

6.1. Conclusion

The conclusions drawn from this work are focused on the transport and rheology of flowing whole blood in addition to the subsequent numerical models employed to study such phenomena. The first three chapters studied cellular blood flow through a range of diseased states namely, the rigidification of red blood cells, the flow of blood through a diabetic retinal microaneurysm, and cellular blood flow through cerebral aneurysm like geometries. In the course of studying and applying the cell-resolved blood flow models insight was also built up to understand each models capabilities and limitations. Finally a heterogenous multiscale model was developed to bring cell based blood flow onto macroscale vessels. An account of the major conclusions and resulting outlook from each chapter is given below.

In Chapter 2, a stiffened RBC numerical model was developed as a proxy for a range of diseases that are known to impede the deformability of the RBC membrane. This was achieved by scaling the mechanical parameters of the original validated HemoCell model and matching the resulting computed deformations to the deformations of chemically stiffened RBCs. In particular it was identified through sensitivity analysis that scaling the link force coefficient κ_l of the HemoCell model significantly impacts membrane stiffness as compared to the other model parameters. This is sensible as the link force models the mechanical response to stretching and compression of the underlying spectrin-network of the RBC membrane, which is specifically damaged through oxidative stress in many diseases.

In vitro and *in silico* evidence on the direct impact of rigid RBCs in flowing blood was provided. The major result identified in this chapter is the decreased amount of margined platelets at the vessel wall as increased amounts of stiffened RBCs were present in flow. This is observed *in vitro* as a decreased platelet fluorescence signal at the wall in a 100 μm channel via confocal fluorescent microscopy, leveraging the Z-stack capability of the microscope. The decrease in platelet margination with increasing amounts of stiffened RBCs is confirmed with three dimensional cell-resolved simula-

tions which recreated the experimental flow chambers. It is further identified through simulation that the red blood cell free layer decreases as the amount stiffened RBCs present in flow increases. This likely results from the decreased lift of RBCs away from the channel walls as RBC stiffness increases.

Simulations of cell-cell collisions are performed to probe the influence of RBC stiffness on the individual cell level. RBC collision between alike pairs identified that as stiffness increased RBC final displacements decreased. This suggests that as membrane stiffness increases the collisions between alike RBC pairs approach the reversible behavior of two colliding rigid spheres. In heterogeneous collisions where a healthy RBC collides with a stiffened RBC, we observe that the stiffened RBC exhibits a larger final displacement after the collision compared to the deformable one. During the collision the healthy RBC deforms and is able to absorb the momentum from the collision to maintain a position that is closer to its original pre-collision position. The stiffened RBC cannot deform and as a result is displaced more in the heterogeneous collision. This effect is observed in the bulk flow simulations as higher volume fractions of healthy deformable RBCs, compared to stiffened RBCs, are present in higher shear rate regions. Here deformable RBCs clear out stiffened RBCs from high shear rate regions.

Chapter 3 builds off of the stiffened model developed in chapter 2 and applies it in a microaneurysm (MA) segmented from volumetric image data captured from a diabetic patient exhibiting retinal MAs. This study may be the first three dimensional cell-resolved studied applied in a patient specific retinal microaneurysm. The major finding in this study is the wall shear stress (WSS) patterns induced on a vessel wall. An average WSS of 2.26 ± 1.25 Pa were computed in the feeding vessel and 1.36 ± 0.92 Pa in the draining vessel, with a significant drop in the aneurysm sac 0.00052 ± 0.00085 Pa. The feeding vessel exhibited higher WSS values because it is narrower as compared to the draining vessel. Additionally WSS induced by the passing RBCs was also computed and on average contributed 0.51 ± 0.23 Pa over the entire feeding vessel and 0.47 ± 0.23 Pa in draining vessel of the original MA. However RBCs can induce much higher local WSS as they pass through the vessel, which on average was computed to be 0.93 ± 0.52 Pa in the feeding vessel and 0.74 ± 0.5 Pa in the draining vessel. Though the results are focused on a time averaged WSS, occurrences of induced WSS from passing RBCs as high as 1.66 Pa in the healthy case and marked increase to 4.1 Pa in the stiffened case was observed. These maximum WSS signals, depend on the number and orientation of cells traveling through the vessels.

Vascular endothelial growth factor (VEGF), is a protein that influences vessel permeability and the growth of new blood vessels in diabetic retinopathy [183]. Additionally the expression of VEGF by the endothelial cells lining the vessel walls has been identified to be stimulated by hemodynamic shear stresses on the vessel wall [192–194]. Recent non-invasive imaging of the retina has estimated WSS 5.4 Pa in the arterioles and 2.4 Pa in the venules [223], though these calculations are based on results from non-Newtonian continuous fluid solvers. The WSS estimations in Chapter 3 provide the first quantitative range of WSS that are present during physiological cellular flow in a MA.

The study in chapter 4 bridges the spatial-temporal gap between cell based and continuum simulation, through an application of a two dimensional cell-resolved blood flow solver studying the transport of blood cells into cerebral aneurysm like geometries.

It was identified that RBCs and platelets become increasingly trapped in the aneurysmal sacs as aspect ratio increases (neck width decreases), with a step increase from aspect ratio 1 to 2. The step increase in high resident cells was attributed to a flow regime change inside the aneurysms from an inflow jet breakdown, in the large neck case, to a continuous inflow jet, in the smaller neck cases.

The small aspect ratio (large neck width) aneurysm, exhibited a recirculation zone with a layering of low and high resident cells. Pulsatility was observed to increase the washing out of high resident cells in the large neck case, but did not influence cell residence in the smaller neck cases. Ten complete heart cycles were simulated. All aneurysms were found to be red blood cell poor and platelet rich, as compared to the average parental vessel volume fraction of each respective cell type.

Chapter 5 proposes a novel heterogeneous multiscale model for blood flow with the intent to bring cell-resolved blood flow to macroscale vessels, which span many millimeters to centimeters in diameter. The model is separated into two spatial scales; a macroscale where continuum LBM solvers are employed, and a microscale where the cell-resolved model HemoCell is employed. The transport of cell volume fractions on the macroscale is achieved through the use of a regularized LBM advection diffusion solver which is coupled to the fluid field solved with the BGK LBM. Red blood cell concentration profiles, and bulk viscosity on the macroscale is informed from cell-resolved simulations carried out on the microscale. On the microscale HemoCell simulations, using Lees-Edwards boundary conditions, are carried out to measure the dynamic viscosity and RBC diffusion coefficients directly. A single microscale simulation is carried out per shear rate and hematocrit combination. Viscosity and RBC diffusion coefficients are then communicated to, and updated on, the macroscale. This is the first ever implementation of a heterogeneous multiscale model developed to solve complex flow of suspensions in three dimensions. This model was inspired by the heterogeneous multiscale model developed for shear thickening suspensions [281] that was able to model suspension flow on large scales, though only in a single dimension.

6.2. Outlook

Further validating the stiffened RBC model proposed in Chapter 2 is a promising avenue for future research concerning the rheological effects of stiffened RBCs in flow as a result of disease. Optical tweezer experiments, for example, could be carried out on RBCs of varying stiffnesses which would lead to a more direct estimation of the responses of the RBC membrane to oxidative perturbations. The ektacytometry measurements made in Chapter 2 are from collections of stiffened RBCs. Optical tweezer measurements in comparison, are a more direct estimation of the individual mechanics of a RBC membrane. Additionally if such a measurement protocol could be setup, the membrane properties of diseased cells could be probed directly. In sickle cell anemia this could be used to understand the ranges of stiffness present in the disease, and especially in RBCs that are not yet exhibiting the hallmark sickle shape. In diabetes this could be applied to search for a correlation between cell stiffness and diabetic sugar levels (A1C level). This could estimate the rigidity of RBCs during poor A1C levels in comparison to normal A1C levels. Of course the matching of a numerical model to such experimental data would increase

impact that cell-resolved simulations could offer to the study of such diseases. Simulation could then resolve the interactions with diseased cells and vessel walls further understanding the adhesion dynamics of such cells.

The experimental and simulation study carried out in Chapter two is an example of the cooperation between two separate disciplines. Due to the high hematocrits considered, the platelet fluorescence signal is considerably attenuated in confocal microscope experiments, limiting the depth that the full-flowing distribution of platelets could be resolved. Using the Z-stack capability of the confocal microscope for a future study, one could fix the focal depth of the microscope to a deeper region and measure the speed of flowing platelets. This could be confirmed with simulation to further match experiment and simulation of flowing blood. This method could be applied to other cell types which would allow deeper probes into the channel and thus further experimentally resolving cell volume fraction profiles of flowing whole blood.

In chapter 3, it was observed that cells do not significantly penetrate the aneurysm sac for any of the variations of the aspect ratio, and is not significantly influenced by pulsatile flow. This may be a major limitation caused by the initialized cell populations in the aneurysm domains along with the performance of HemoCell. To first address the problem of cell initialization additional simulations could be carried out with domains uniformly populated with cells. This would provide insight to how cells are transported into the aneurysmal sacs and how that may change when cells are present in the aneurysm sac. Additionally the time resolution of this study reached a simulated second, which is practically not sufficient to reach equilibrium sac hematocrits. Many physical seconds are likely needed to be simulated in order to receive a more complete picture of the cell transport and flow inside MAs. The current performance could be improved by applying load balancing techniques as the domain considered in this chapter is highly anti-symmetric, and as a result half of the allocated atomic blocks (compute cores) were left idling. While the other cores that lay within the domain were left with the full computational burden. Even balancing of the computational load across all compute cores would significantly speed up such simulations of tortuous vessels and allow longer time resolution.

Adaptive optics optical coherence tomography is a developing technology and specifically as an application to map the vasculature in the retina provides a new exciting frontier for cell-resolved blood flow simulation. The volumetric data allows cell-resolved models like HemoCell to be applied in real microvasculature to study diseases of the retina. As the quality of the images progress, such segmentations will therefore easier to achieve streamlining the image capture-segmentation-simulation processes, leading to ability to conduct larger parametric cell-resolved studies of diabetic retinopathy. This will allow such pilot studies, as conducted in Chapter 3, to be developed into complete imaging/simulation studies of the diabetic retina.

Additionally the structure of the vessel walls were assumed to be smooth and completely sealed. Due to the deterioration of the endothelial cells lining the vessel walls in diabetic retinopathy, vessel are famously permeable, and have been observed to leak. The development of special boundary conditions may be needed to accurately model diabetic retinopathy. Vessel permeability can be quantified through high quality fluorescein angiography images of the early, mid, and late development stages of microa-

neurysms. The marriage of new imaging techniques with cell-resolved modeling could provide a new paradigm to understand the flow and transport of blood cells *in vivo*.

Chapter 4 presents the capability of performing cell suspension simulations on scales predominately restricted to continuum solvers. This is useful as it can bring unprecedented resolution to the calculation of important physiological parameters. In the context of cerebral aneurysms, cell residence time is a valuable parameter as it quantifies the likelihood for thrombus formation or inflammation to occur. Using continuum methods to compute residence times, may lead to inaccuracies as such methods do not account for the fluid-structure interaction between blood cells and the suspending blood plasma. Platelet margination for example could not be resolved with a continuum model using tracer particles. Physical conclusions from course grained cell methods, like two dimensional blood flow solvers, should be drawn carefully as volumetric flow effects are left out. The advantages of 2D cell-resolved solvers lie within the ability to probe large parameter spaces to determine scaling relationships. Specific cases can then be identified to be further resolved with three dimension models.

The multiscale model for blood flow proposed in Chapter 5 is developed to capture the complex fluid behavior and cell transport of whole blood on macroscale vessels. This model could be specifically developed to capture the three dimensional cellular blood flow inside a cerebral aneurysm. Boundary conditions on the macroscale in combination with microscale simulations need to be developed to accurately handle the interaction between blood cells and vessel walls. This would allow the heterogeneous multiscale method to be applied in tortuous vessels and may alleviate imposed cell concentrations in existing multiscale models for blood flow in the brain.

Though this model is focused primarily on rheology, it is not limited to it. By following the heterogeneous multiscale modeling paradigm, additional models focusing on chemistry or biology, for instance, could eventually be appended to the model. This leverages the need for accurate rheology on all scales in the vasculature in order to provide a foundation for additional models aimed at capturing the variety of physical, chemical and biological processes of blood. For instance platelet-plug formation, in-stent restenosis, and acute ischemic stroke models could be built off this multiscale model for blood flow stitching together a diverse set of numerical models that achieve accurate bio-physical modeling of cellular blood flow.