Cell resolved blood flow modeling with the Lattice Boltzmann method

Cell deformability and transport in diseases

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Appendix

A.1. HemoCell Constitutive Material Model

The HemoCell (High pErformance MicrOscopic CELlular Libary) RBC mechanical model is a superposition of four discrete forces acting on a single triangulated cellular membrane, shown in equation 1. The membrane force model is originally developed in Závodzsky et al. 2017 [91], and description quoted in the section is a needed detail of the thesis. All forces of the constitutive model have been developed to assume that during small deformations each force presents a linear regime. The separate forces display different slopes as the response types of the RBC correspond to different components of the cell and therefore the forces are independent of each other. Additionally for large enough deformations the cytoskeleton contributes to all forces. In a practical example, a small bending response is assumed to be dominated by the curvature rigidity of the bilipid membrane resulting in a linear angle force term, while large deformations of the underlying cytoskeleton yields an additional quickly diverging term. The four discrete forces are listed and elaborated below.

$$F_{total} = F_{link} + F_{bend} + F_{area} + F_{volume} \tag{1}$$

1. **Link Force**: F_{link} models the in plane stretching and compression of the underlying spectrin-network, which is implemented along the edges of the surface triangles that represent the cumulative behavior of the local spectrin links.

$$F_{link} = -\frac{\kappa_l dL}{p}\left[1 + \frac{1}{\tau_l^2 - dL^2}\right] \tag{2}$$

   Here κ_l is the link force coefficient, $dL = \frac{L_i - L_0}{L_0}$ is the normal strain defined as the relative deviation from the equilibrium length L_0. τ_l is the relative expansion ratio, chosen to be 3, when the spectrin network reaches its persistence-length. The persistence-length of a spectrin filament was chosen to be $p = 7.5$ nm. The link force coefficient κ_l is a free parameter and is used to scale the magnitude of the link force to match experimental data.

2. **Bending Force**: F_{bend} accounts for the bending response of the membrane which arises from the non-zero thickness of the spectrin-network, is implemented by pointing in the normal direction on each triangle surface element. The bending force then acts via the angle between two neighboring surface elements.

$$F_{bend} = -\frac{\kappa_b d\theta}{L_0}\left[1 + \frac{1}{\tau_b^2 - d\theta^2}\right], \tag{3}$$

Where $d\theta = \theta_i - \theta_0$. L_0 is the discretization length of the surface elements which is chosen to match the current resolution of the underlying LBM lattice $L_0 = 0.5$ µm. The limiting angle, which scales with L_0, is chosen $\tau_b = \frac{\pi}{6}$ to prevent unrealistic sharp edges while allowing curved radii as small as 0.2 µm. This is in agreement from curved radii of 0.2 µm observed from real RBCs undergoing deformations from micro pipette aspiration [323].

3. **Area Force**: F_{area} represents the combined surface response of the supporting spectrin-network and the lipid bilayer of the membrane to stretching and compression, is applied to all three vertices of each triangle face and points in the direction of the centroid.

$$F_{area} = -\frac{\kappa_a dA}{L_0}\left[1 + \frac{1}{\tau_a^2 - dA^2}\right], \tag{4}$$

with $dA = \frac{A_i - A_0}{A_0}$. τ_a is set to prohibit surface area changes of more then 30%. This is chosen under the observation of RBCs that have undergone deformations exhibiting 40% surface area change become permanently damaged [324].

4. **Volume Force**: F_{volume} is a global volume conservation force which maintains the quasi-incompressibility of the cell and is applied at each LSP pointing towards the normal of the membrane surface.

$$F_{volume} = -\frac{\kappa_v dV}{L_0}\left[1 + \frac{1}{\tau_v^2 - dV^2}\right] \tag{5}$$

where $dV = \frac{V - V_0}{V_0}$, $\tau_v = 0.01$ and $\kappa_v = 20k_B T$ is chosen to be a large but numerically stable constant.

The RBC model has been further developed to include the viscosity contrast between the internal fluid of a RBC and the surrounding blood plasma [15], and is implemented by identifying and increasing the relaxation time of the LBM nodes that lie within the RBC membrane. HemoCell is an open-source software and can be obtained at `www.hemocell.eu`.

A.2. HemoCell2D

Blood plasma is simulated using the D2Q9 LBGK scheme [78] where the RBCs are deformable membranes represented by Lagrangian surface points (LSPs) that are governed through a DEM force model. The LBM fluid and the DEM force model are coupled via the immersed boundary method. The model used in Chapter 4 is changed from the initial validation of [93] to match closer with physiological values [158, 325]. Given the update from the original model the force model description and new validation is given in this section.

The plasma dynamic viscosity of $\mu = 1.29$ mPa was chosen, which results from a kinematic plasma viscosity of $1.26 \cdot 10^{-7}$ m/s and plasma density of 1025 kg/m^3. However since this is a lower viscosity than the previously validated model, we rescale the coefficients of the force model by the same factor of the reduction of the plasma viscosity and re-validate the model. The force coefficients and relevant parameters of the 2D model are shown in table 1. The DEM membrane model for the RBCs consists of four separate forces.

1. A Hookean spring force acting between connecting LSP points to represent stretching and compression of the RBC.

$$\mathbf{F}_{spr} = -C_{spr}(|\mathbf{r}_{i+1} - \mathbf{r}_i| - r_0)\mathbf{e}_{i,i+1} \tag{6}$$

   Here r_0 is the equilibrium spring length, $\mathbf{e}_{i,i+1}$ is the unit vector connecting the two LSP points, and C_{spr} is the spring constant.

2. A bending resistance force acting on two neighboring LSP points.

$$\begin{aligned} \mathbf{F}_{trs} &= -f_{trs}\mathbf{n}_i \\ f_{trs} &= -C_{trs}((\mathbf{r}_i - \mathbf{r}_{i-1}) \cdot (\mathbf{r}_{i+1} - \mathbf{r}_i)) \end{aligned} \tag{7}$$

   Here $\mathbf{n}_i$ is the normal vector of the LSP point resulting from the angle between $\mathbf{r}_i$ and $\mathbf{r}_{i+1}$. f_{trs} is the magnitude of the force which depends on the bending force constant C_{trs} and the angles between neighbouring LSP points r_i and r_{i+1}.

3. An area conservation force. Due to the discretization of the cell the total force may not be zero. In order to maintain an equilibrium cell volume (area in 2D) a relaxation mechanism is applied to correct for this non-zero total force.

$$\mathbf{F}_{area} = -C_{area}(A - A_0)\mathbf{n}_i \tag{8}$$

   Here A_0 is the equilibrium cell area with C_{area} being the area force constant.

4. A repulsive force to prevent cells from sticking due to overlap of the IBM kernels and helps tune the emerging rheology of the suspension.

$$\mathbf{F}_{rep} = -C_{rep}(h^{-2})\mathbf{e}_{i,j},\ h \geq h_{cutoff} \tag{9}$$

   Here C_{rep} is the repulsion force constant, $\mathbf{e}_{ij}$ is the unit vector of two LSP points of two difference cells. h_{cutoff} is the threshold distance to ensure the repulsive force acts only if the two LSP points $\mathbf{r}_i$ and $\mathbf{r}_j$ are close enough to interact, otherwise $h_{cutoff} = 0$ which results in a force that is zero.

RBCs following this model are initialized as discs but are deflated to an equilibrium shape following an area ratio $A_{rbc}/A_{sphere} = 0.45$. This area ratio and the DEM model ensures that the equilibrium shape of the RBC is biconcave. The description of the IBM kernel used to couple the DEM method to the LBM fluid is omitted because we use exactly the same kernel employed for the initial validation of this model [93]. HemoCell2D is an open-source software and can be obtained at `www.hemocell.eu`.

Parameter	Value
plasma density, ρ	1025 kg/m^3
kinematic viscosity, η	$1.26 \cdot 10^{-7}$ m^2/s
# of LSPs per RBC	26
# of LSPs per platelet	8
spring constant, C_{spr}	$0.37 \cdot 10^{-3}$ N/m
bending constant, C_{trs}	$0.74 \cdot 10^{-9}$ N/rad
area constant, C_{area}	$7.25 \cdot 10^{4}$ N/m^2
cell-cell constant, C_{rep}	$1.35 \cdot 10^{-22}$ Nm^2
cut off distance, h_{cutoff}	0.6 lattice units
LBM relaxation constant, τ	1.1
spatial resolution, Δx	1 µm
timestep, Δt	$1.5 \cdot 10^{-7}$ s

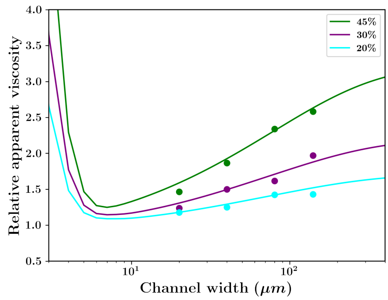
Table 1: Model parameters and constants.

Validation

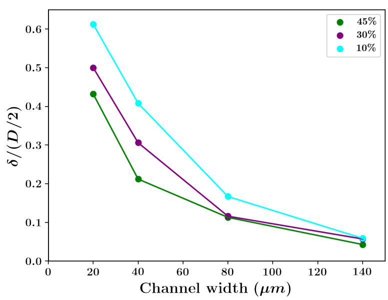
HemoCell2D, with the parameters from Table 1, is able to reproduce the the Fåhraeus-Lindqvist effect, Figure 1a, and the existence of a cell free layer and its decrease in thickness with an increase of vessel diameter, Figure 1b.

The Fåhraeus-Lindqvist is the decrease of the apparent viscosity of whole blood as blood vessel size decreases [20]. An empirical relationship of this effect has been derived from a comprehensive database of in vitro measurements [29]. Our model shows good agreement with the apparent viscosity curves of Pries, as shown in Figure 1a. We reproduce this effect over discharge hematocrits of H_d = 20, 30, and 45% in straight vessels of a diameter range of 20-140 µm. We follow the Pries validation methods used by Bagchi [57]. The results are averaged over 0.1 s, which we found to be sufficient to converge to a stable apparent viscosity value. In our simulations, like Bagchi, we found that μ_{rel} is sensitive to U_{mean}, the mean flow velocity in our tubes, and the actual number of simulations performed is much greater than the points shown.

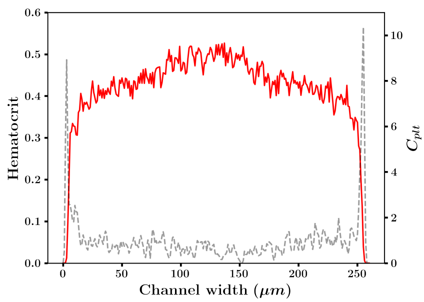
The thickness of the cell free layer is dependent on hematocrit and vessel size. Shown in Figure 1b is the decrease of dimensionless thickness of the CFL as vessel size increases. We calculate the cell free layer as a number density distribution across the diameter of the vessel. Our method of calculating the CFL is based on Bagchi [57], Durlofky and Brady [326] and Zhou and Pozrikidis [327]. Here we take horizontal segments of 1 µm in width across the entire diameter and count the number of Lagrangian surface points (LSP) of each cell type within that segment. We assume that each LSP carries an equal fraction of the total surface area of each RBC.



(a)



(b)



(c)

Figure 1: (a) Relative apparent viscosity as a function of vessel diameter at varying discharge hematocrits of 20, 30 and 45 %. Empirical viscosity are plotted as lines from [29]. (b) The dimensionless cell free layer thickness as a function of vessel diameter and discharge hematocrit. (c) Hematocrit and platelet concentration (C_{plt}) profile in parental vessel of the aspect ratio 2 geometry.

List of Publications

First Author

1. Benjamin Czaja, Gábor Závodszky, Victor Azizi Tarksalooyeh, and Alfons G Hoekstra. Cell-resolved blood flow simulations of saccular aneurysms: effects of pulsatility and aspect ratio. *Journal of The Royal Society Interface*, 15(146):20180485, 2018

   Contribution: B. Czaja conceived and designed this study, performed the analysis and wrote the paper. G. Závodzsky conceived this study and provided scientific advice, specifically concerning the aneurysms and related haemodynamics. V. Azizi implemented the boundary conditions in HemoCell2D and provided technical support. A.G. Hoekstra conceived and supervised this research. All authors edited the manuscript and gave the final approval for the publication.

2. Benjamin Czaja, Mario Gutierrez, Gábor Závodszky, David de Kanter, Alfons Hoekstra, and Omolola Eniola-Adefeso. The influence of red blood cell deformability on hematocrit profiles and platelet margination. *PLOS Computational Biology*, 16(3):e1007716, 2020

   Contribution: B. Czaja conceived and designed this study, performed the experiments and simulations, and wrote the paper. M. Gutierrez designed the study, performed the experiments and formal analysis, and wrote the paper. G. Závodzsky conceptualized the research, provided supervision on the numerical analysis, and edited the paper. D. de Kanter created the supplementary videos for the paper. A.G. Hoekstra conceptualized the research, provided supervision, funding acquisition, and administered the project. O. Eniola-Adefeso conceptualized the research, provided supervision to the experiments, and administered the project. All authors contributed to editing the final draft of the manuscript.

3. Benjamin Czaja, Jonathan de Bouter, Morgan Heisler, Gábor Závodszky, Sonja Karst, Marinko Sarunic, David Maberley, and Alfons Hoekstra. Cell induced wall shear stress in a diabetic retinal microaneurysm. *Journal of Biomechanics*, Under Review, 2020

   Contribution: B. Czaja conceived and guided this research, performed simulations and analysis, and wrote 50% of the manuscript. J. de Bouter performed model segmentation, implemented pulsatility, performed simulations and analysis, and wrote 50% of the manuscript. M. Heisler captured and provided the volumetric image data. G. Závodzsky guided and provided scientific advice, specifically concerning the aneurysm hemodynamics. S. Karst provided clinical guidance concerning diabetic eye disease. M. Sarunic provided guidance for the image acquisition. D. Maberley provided clinical guidance and coordinated collaboration between the Canadian and Dutch research groups. A. Hoekstra conceived, coordinated, and supervised this research. All authors edited the manuscript and gave final approval for the publication.

4. Benjamin Czaja, Gábor Závodszky, and Alfons Hoekstra. A heterogeneous multiscale model for blood flow. *In preperation for Journal of Computational Science*, 2020

   Contribution: B. Czaja conceived the research, developed and implemented the model, and wrote the paper. G. Závodzsky conceptualized the research, provided supervision on the numerical analysis, and edited the paper. A. Hoekstra conceived, coordinated, and supervised this research. All authors edited the manuscript and gave final approval for the publication.

Co-Author

1. Gábor Závodszky, Britt van Rooij, Ben Czaja, Victor Azizi, David de Kanter, and Alfons G Hoekstra. Red blood cell and platelet diffusivity and margination in the presence of cross-stream gradients in blood flows. *Physics of Fluids*, 31(3):031903, 2019

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2. Saad A Alowayyed, Maxime Vassaux, Ben Czaja, Peter V Coveney, and Alfons G Hoekstra. Towards heterogeneous multi-scale computing on large scale parallel supercomputers. *Supercomputing Frontiers and Innovations*, 6(4):20–43, 2020

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3. Kevin de Vries, Anna Nikishova, Benjamin Czaja, Gábor Závodszky, and Alfons G. Hoekstra. Inverse uncertainty quantification of a cell model using a gaussian pro-

cess metamodel. *International Journal for Uncertainty Quantification*, 10(4):333–349, 2020

Contribution: K. de Vries designed and implemented the model and wrote the paper. A. Nikishova conceived and supervised the research and edited the paper. B. Czaja supervised the research, wrote the HemoCell Red Blood cell section and provided support for the experimental data. G. Závodzsky and A.G. Hoekstra supervised the research, and revised the manuscript. All authors read and approved the final version of the manuscript.

4. Daan van Ingen, Benjamin Czaja, Gábor Závodszky, and Alfons Hoekstra. Lees-edwards boundary conditions within the cell resolved lattice boltzmann framework hemocell. *Under Preparation*, 2020

Contribution: D. van Ingen implemented the Lees-Edwards boundary conditions in HemoCell, carried out the simulations, and contributed to writing the manuscript. B. Czaja supervised the daily research, carried out the simulations, provided analysis, and contributed to writing the manuscript. G. Závodzsky supervised the research and wrote the manuscript. A.G. Hoekstra supervised the research, and revised the manuscript.

Conference Presentations - Oral

- B. Czaja, G. Závodzsky, V. Azizi, and A. Hoekstra, Pulsatile flow in 2D cell resolved blood flow simulations of curved vessels with aneurysms, *8th World Congress of Biomechanics*, Dublin, Ireland, 2018

- B. Czaja, G. Závodzsky, and A. Hoekstra, Cell resolved simulations of saccular aneurysms: effects of pulsatility and aspect ratio, *Virtual Physiological Human Conference*, Zaragoza, Spain, 2018

- B. Czaja, G. Závodzsky, M. Gutierrez, A. Hoekstra and O. Eniola-Adefeso, The effect of mixing deformable and stiffened red blood cells in flow on hematocrit profiles and platelet margination, *6th International Conference on Computational & Mathematical Biomedical Engineering*, Sendai City, Japan, 2019

- B. Czaja, M. Gutierrez, G. Závodzsky, D. de Kanter, A. Hoekstra and O. Eniola-Adefeso, Simulation and Experimental Evidence for the Decrease of Platelet Margination with an Increase in Volume Fraction of Stiffened Red Bloody Cells in Flow, *CompBioMed Conference*, London, United Kingdom, 2019

- B. Czaja, G. Závodzsky, and A. Hoekstra, A Heterogeneous Multiscale model for Blood Flow, *International Conference on Computational Science*, Amsterdam, the Netherlands, 2020

Conference Presentations - Poster

- B. Czaja, G. Závodzsky, V. Azizi, and A. Hoekstra, The effects of pulsatility in 2D cell resolved blood flow simulations of curved vessels with aneurysms, *Blood Flow: Current State and Future Prospects*, Paris, France, 2017
- B. Czaja, J. de Bouter, M. Heisler, G. Závodszky, S. Karst, M. Sarunic, D. Maberley, A. Hoekstra, The influence of flowing Red Blood Cells on Wall Shear Stress in a Diabetic Retinal Microaneurysm, *Virtual Physiological Human Conference*, Paris, France, 2020

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