Dynamical properties of red blood cell model in shear flow

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Abstract — **Cells in a shear flow exhibit tumbling and tank-treading. This rotational movement is characterized by rotational frequency. In this work, we analyze and test a computational model of red blood cell by comparing simulated movement of a cell in a shear flow to the experimental data. We set up a computational experiment that recasts dynamical behavior of cells in a shear flow. We analyze the dependence of the rotational frequency of cells on the shear rate. Results show that the model including the stretching, bending, area and volume preservation moduli does not recover frequencies from the biological data. After adding the visco-elastic modulus, the simulations show compliance with the data.**

Keywords— computational modelling; red blood cell; shear flow; simulations

I. Introduction and Motivation

Understanding the mechanical behavior of individual red blood cells (RBC) is crucial in the dynamics of the human circulatory system. The flow of blood is mostly determined by the elastic properties of cell membranes and their interaction with each other. Gaining insights into the dynamics and morphologies of RBCs was addressed in several experimental studies [1,2].

Recently, computational models proved to be useful in computer-added discovery in biological sciences. In [3] for example, the authors provided evidence that the shear induced red blood cell tumbling-to-tank-treading transition also occurs at quite high volume fractions. Computational models also belong to powerful tools for design of microfluidic devices [4].

Proper validation of a computational model is provided by direct comparison of simulations with experimental results. For assessing static properties of red blood cells, the data from stretching experiment is widely used [2]. Here, RBC is stretched on opposed sides with known forces using optical tweezers. The prolongation is measured and the dependence of deformation index on stretching force is used to determine elastic coefficients of the model.

Further model validation concerns dynamic properties of RBC in a shear flow. Because of their elastic nature and shape, RBCs exhibit various behaviors in shear flows. First, an RBC elongates and aligns itself at a constant angle to a flow when embedded in a shear flow. Second, it may tumble, exhibit a tank-treading motion of the membrane, or both, depending on the shear rate [5]. The biological laboratory experiments concerning the tumbling and tank-treading frequency have been reported [6, 7].

A spring-network based model have been introduced in [8, 9]. Here, the cell is modeled by a triangulation of the membrane that defines the spring network. The static validation of elastic properties has been done [10] and the software implementation of the model was described in [11].

In this article, we aim at further validation of this model. We will investigate the model behavior under the shear flow. In Section II, we describe the computational model and ist main components: fluid and immersed object. Next section is devoted to description of the simulation setup. We provide the geometry of the computational domain and present how the shear flow is generated. In Section IV we present the results concerning the rotation frequency of the cell in a shear flow. We show that the model does not fit experimental data. Further in Section V we point out the visco-elasticity of biological cell's membrane and we suggest to test the model with additional visco-elastic modulus. We show the results of the adjusted model. Here, we demonstrate that inclusion of the visco-elasticity enables the model to fit the biological data. Finally, in Section VI we summarize the findings and draw conclusions.

II. Model of Red Blood Cell

Detailed description of the model has been presented elsewhere [8,9]. Briefly, to describe the mechanical processes of the cells flow, we need to take into account two basic phenomena: the fluid dynamics and cell deformation. Important part is also the coupling between those two components.

The fluid dynamics. Evolution of fluid is governed by the well-known and documented lattice–Boltzmann method. This

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method is based on fictive particles which propagate and collide over a fixed three-dimensional discrete lattice. The unknown variable is the particle density function defined for each lattice point. We use the D3Q19 version of the LB method (three dimensions with 19 discrete directions along the edges and diagonals of the lattice). The bulk properties such as fluid density and fluid velocity can be computed directly from the particle density function. More details can be found in [12].

Cell deformation. Cells are described by their membranes and these are represented by a triangular mesh containing points on the surface of the object. Mesh points are moving under the influence of fluid–cell interaction forces, as well as elasto-mechanic forces generated by the elasticity of the membrane. The elasticity is modeled using five elastic moduli: stretching, bending, local and global area conservation and volume conservation. Each module has its own stiffness coefficient, similar to the stretching coefficient of a linear spring.

The simplest module is the stretching module. It generates a force between each pair of mesh points connected by the edge in the triangulation. This force models essentially a non-linear spring [13], which pulls the points together when they are further than in the relaxed state and pushes them apart, when they are closer than in the relaxed state. The explicit formula for this force between two mesh points A and B is given by

$$F_s = k_s \kappa(L)(L - L_0). \tag{1}$$

Here, k_s is the stretching coefficient, L is the current length of the edge between A and B, L_0 is the length of the edge between A and B in the relaxed state without any external forces acting on the cell, and $\kappa(L)$ represents the neo-Hookean nonlinearity of the stretching force. From this expression, it is evident that if the edge is stretched than $L > L_0$ and the force directs towards the shortening of the edge. If the edge is squeezed than $L < L_0$ and the resulting force has opposite direction and thus supports prolongation of the edge.

Expressions for other moduli like bending, surface preservation and volume preservation can be found e.g. in [9,11].

Coupling between fluid and cells. The fluid and immersed cells interact with each other. This interaction is implemented by introducing a drag force F_d between the fluid and the mesh points

$$F_d = \xi(u - v), \tag{2}$$

where $\xi$is a phenomenological coefficient, v is the velocity of the mesh point and u is the velocity of the fluid at the position of the mesh point. This approach penalizes the difference $u - v$ and thus mimics the natural no-slip condition at the boundary of the flowing cell.

III. Simulation Setup

The computational domain comprises a cubic box with dimensions $20\ x\ 20\ x\ 20\mu m$. The shear flow in our simulations

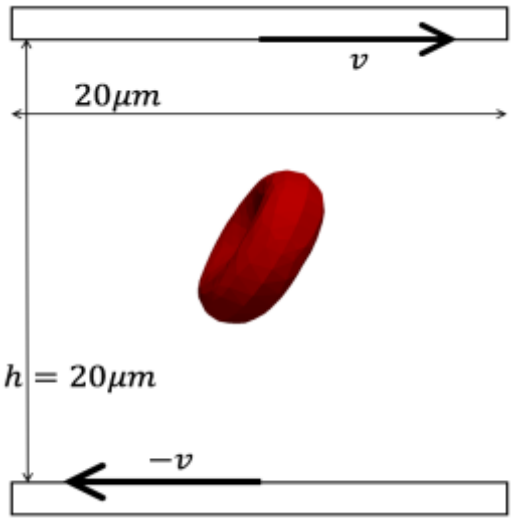

Figure 1. Simulation setting with indicated velocities of the fluid at the boundaries generating the uniform shear flow.

is generated by setting the constant velocity v and $-v$ at the top and bottom boundaries of the channel, see Figure 1. In this setting for an empty channel, the velocity field has zero y and z components and the horizontal x component linearly decreases from the value v at the top boundary to value $-v$ at the bottom boundary. This means that the shear rate is constant over the whole channel and equals to

$$\dot{\gamma} = \frac{2v}{h} \tag{3}$$

In our simulations, we work with one cell in the middle of the channel with shear flow. Simulation showed, that red blood cell in a shear flow at a certain speed exhibits tumbling motion. At higher speeds this motion becomes tank-treading, which corresponds to previously presented results [14]. During tumbling motion, the cell rotates as a whole, while during tank-treading motion, the cell leans slightly and its membrane begins to rotate around the interior of the cell.

The speed of the rotation during the tumbling and tank-treading depends on the shear rate. This dependence was measured on live cells and the data is available in [6,7,14].

To reproduce these experiments, we use the density of fluid $1050\ kg.m^{-3}$and viscosity $5\ Pa.s$. These values correspond to biological solutions of dextran that is typically used in experiments as in [6,7]. In recent study [15], the authors derived the expression for the friction coefficient and using this expression, we compute the value $\xi = 5.0$. For elastic coefficients of the model we use the following values

$$k_s = 0.008, k_b = 0.0003,\ k_{al} = 0.006,\\ k_{ag} = 0.9, k_v = 0.5. \tag{4}$$

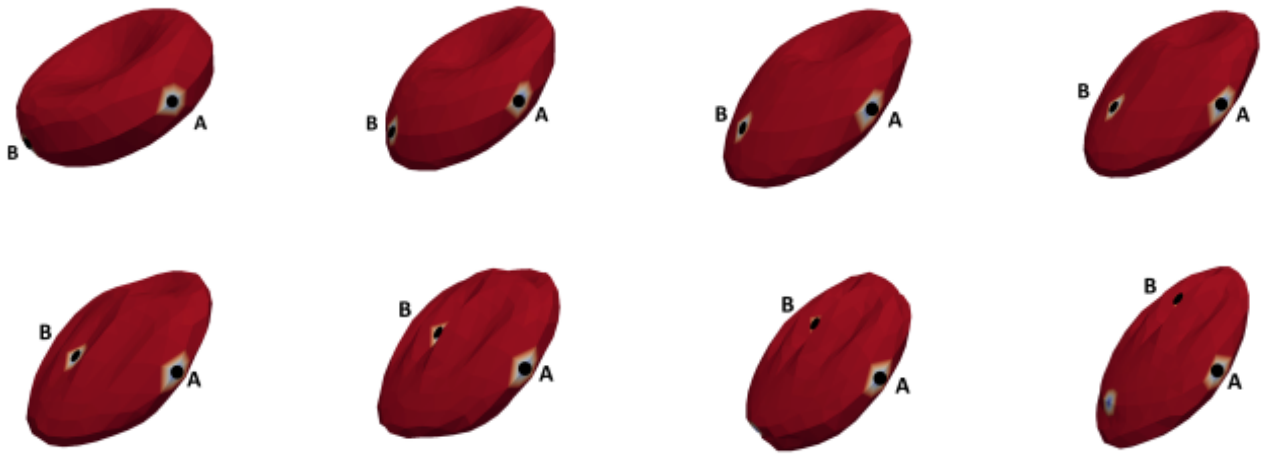

Figure 2. Tank-treading motion of a cell under shear rate 200 s^{-1}. Two specific mesh points are highlighted. Point A is located on the y-axes of rotation. Point B rotates around the inside of the cell.

These values have been determined from stretching experiments mentioned in [2]. For discretization of time we use the time step equaling to $0.1\mu s$. Snapshots of tank-treading cell is depicted in Figure 2. From these snapshots we can clearly see that the membrane rotates around the inner part of the cell and the shape changes from the relaxed bi-concave shape into ellipsoid-like shape that does not change much.

IV. Results

During the simulation, we record coordinates of the mesh points. In Figure 3, x-coordinate of one specific point is depicted. The curve shows characteristic periodic evolution from which we extract period of one rotation T. Then we calculate the rotation frequency of the cell f as

$$f = \frac{1}{T} \tag{5}$$

In [14] they work with shear rate up to 200s^{-1}. To have the same values in our experiment, we use (3) to compute the corresponding value of velocity resulting in $0.002ms^{-1}$. In the simulations we thus used 10 values from $0.0002ms^{-1}$ to $0.002ms^{-1}$.

The results are presented in Figure 4. We can clearly see that our model exhibits different behavior than expected. Frequency of rotation is higher. We performed several tests to see whether

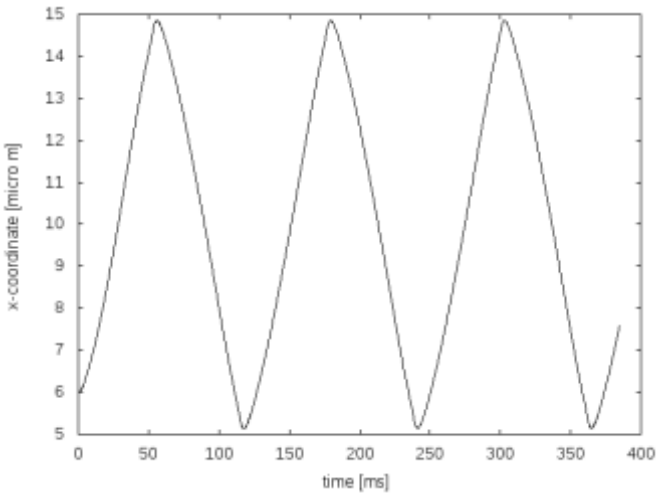

Figure 3. Evolution of x-coordinate of one specific point during the tank-treading motion

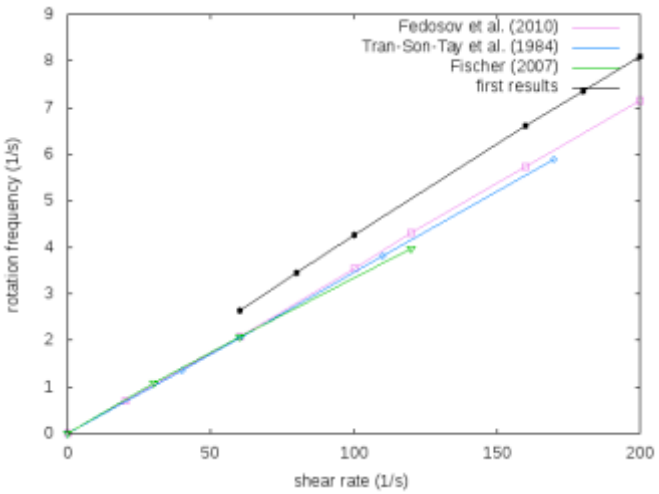

Figure 4. Rotation frequency for the original model (black line) and experimental data (other colors) taken from [6,7,14].

the model can be adapted to fit the experimental data. We tried to slightly change the elastic coefficients, this however did not have any effect on the rotating frequency.

V. Model Revisited

The biological membrane of a RBC exhibits visco-elastic properties [16]. Our model does not include such properties. In general, visco-elasticity is a property of the material that penalizes fast changes of the shape. Since the tank-treading motion of the cell introduces permanent changing of the membrane's shape, there is a hope that including visco-elasticity could have a effect on rotational frequency of the cell. In [17], an attempt has been made to include visco-elastic module into the model with promising results. In the following, we will test this implementation. The basic principle is to include visco-elastic contribution F_{vis} to the elastic forces. This contribution takes into account how fast the length of an edge of the mesh changes. The force acts against these changes according to the following expression

$$F_{vis} = k_{vis} \frac{dL}{dt} \tag{6}$$

We have performed identical experiments with this extended model. In (6) however, the proper value of k_{visc} needs to be chosen. We identified that $k_{visc} = 1.5$ is optimal value. Using this value, we obtained results presented in Figure 5. We can clearly see that the rotational movement of the cell slowed down and the frequency perfectly fit the experimental data.

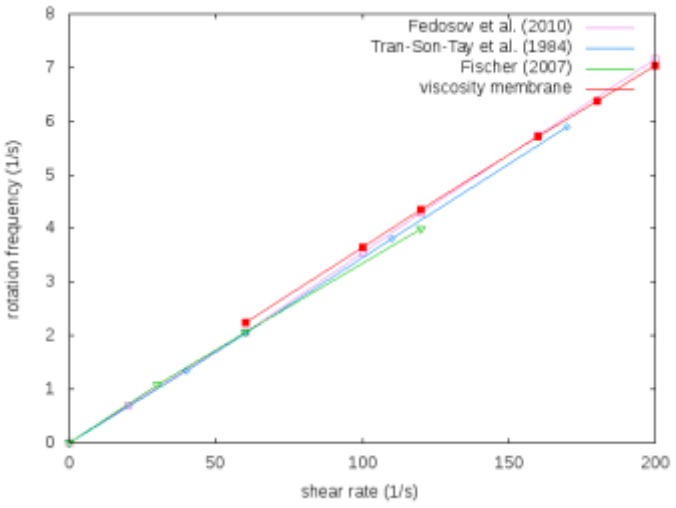

Figure 5. Rotation frequency for adjusted model including visco-elastic modulus (red line) and experimental data (other colors) taken from [6,7,14].

VI. Conclusions

In this paper, we tested the model of RBC that has been previously calibrated on static stretching experiments. Our aim was to verify, whether the dynamical properties of the model correspond to the biological behavior of the cell. We considered the rotation frequency of a cell that is immersed in a shear flow. The computational results were compared to the available biological data.

At first, we did not get the good correspondence. The frequency of rotating cell in simulations was roughly 20% higher.

This discrepancy was assigned to visco-elastic properties of biological membranes. The original model did not account for viscous forces. We tested a previously introduced model extension. Eventually, the viscous modulus added to the model caused that the rotation has been slowed down to fit the data.

The additional term from (6) however requires to set proper coefficient k_{visc}. At the current stage of knowledge, we do not know the connection between the biological values of visco-elasticity of the membrane reported in [16] and k_{visc}. The thorough investigation will be necessary in this matter. Here, we only demonstrate that such model extension does positively influence the dynamical behavior of cell in a shear flow.

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References

[1] M. Abkarian, M. Faivre, and A. Viallat „Swinging of red blood cells under shear flow", Phys. Rev. Lett. 98:188302., 2007

[2] J. P. Mills, L. Qie, M. Dao, C. T. Lim, and S. Suresh, "Nonlinear elastic and viscoelastic deformation of the human red blood cell with optical tweezers," *Molecular & Cellular Biomechanics*, vol. 1, no. 3, pp. 169–180, 2004.

[3] T. Krüger, M. Gross, D. Raabe, and F. Varnik, "Crossover from tumbling to tank-treading-like motion in dense simulated suspensions of red blood cells", Soft Matter 9, 9008, 2013.

[4] Gleghorn et al., "Capture of circulating tumor cells from whole blood of prostate cancer patients using geometrically enhanced differential immunocapture (GEDI) and a prostate-specific antibody. Lab Chip. 10:27–29, 2010.

[5] M. Nakamura, S. Bessho and S. Wada, "Spring-network-based model of a red blood cell for simulating mesoscopic blood flow", Int. J. Numer. Meth. Biomed. Engng., 29: 114–128, 2013

[6] R. Tran-Son-Tay, S. P. Sutera & P.R Rao, "Determination of RBC membrane viscosity from rheoscopic observations of tank-treading motion", Biophys. J. 46, 65–72, 1984

[7] T. M. Fischer "Tank-tread frequency of the red cell membrane: Dependence on the viscosity of the suspending medium", Biophys. J. 93, 2553–2561, 2007

[8] I. Cimrák, M. Gusenbauer, T. Schrefl, "Modelling and simulation of processes in microfluidic devices for biomedical applications", Computers and Mathematics with Applications, Vol 64(3), pp. 278-288, 2012.

[9] K. Bachratá, H. Bachratý, “On modeling blood flow in microfluidic devices”, ELEKTRO 2014: 10th International Conference, IEEE, Slovakia, ISBN 978-4799-3720-2, pp. 518-521,2014.

[10] R. Tóthová, I. Jančigová, M. Bušík, “Calibration of elastic coefficients for spring-network model of red blood cell”, Information and Digial Technologies (IDT) 2015, International Conference, IEEE, Slovakia, ISBN 978-1-4673-7185-8, pp. 376-380, 2015.

[11] I. Cimrák, M. Gusenbauer, I. Jančigová, “An ESPResSo implementation of elastic objects immersed in a fluid”, Computer Physics Communications, Volume 185, Issue 3, Pages 900-907, 2014.

[12] B. Dunweg, A. J. C. Ladd, "Lattice-Boltzmann simulations of soft matter systems", Advances in Polymer Science 221, 89–166, 2009.

[13] I. Jančigová, R. Tóthová, “Scalability of forces in mesh-based models of elastic objects”, ELEKTRO 2014: 10th International Conference, IEEE, Slovakia, ISBN 978-4799-3720-2, pp. 562-566, 2014.

[14] D. A. Fedosov, B. Caswell, G. E. Karniadakis, “Cell deformation in shear flow” Computational Hydrodynamics of Capsules and biological Cells, CHAPMAN & HALL/CRC Mathematical and Computational Biology Series, pp. 204-209 ISBN 78-1-4398-2006-3, 2010.

[15] M. Bušík, I. Cimrák, “The calibration of fluid-object interaction in immersed boundary method”, Experimental fluid mechanics 2016, 15.-18.11.2016, Mariánské Lázně, Czech Republic, preprint available at cell-in-fluid.fri.uniza.sk/en/content/publications.

[16] R.M. Hochmuth, P.R. Worthy, E.A. Evans, "Red cell extensional recovery and the determination of membrane viscosity". Research paper, Biophys. J. 26 (1), pp. 101–114, 1979.

[17] M. Bušík, "Viscoelasticity in spring network models for proper dynamics of cell membrane", Journal of Information, Control and Management Systems, [S.I.], v. 13, n. 1, apr. 2015.