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A Lattice Boltzmann Method for Simulating the Separation of Red Blood Cells at Microvascular Bifurcations *

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A computational simulation for the separation of red blood cells (RBCs) is presented. The deformability of RBCs is expressed by the spring network model, which is based on the minimum energy principle. In the computation of the fluid flow, the lattice Boltzmann method is used to solve the Navier–Stokes equations. Coupling of the fluid-membrane interaction is carried out by using the immersed boundary method. To verify our method, the motions of RBCs in shear flow are simulated. Typical motions of RBCs observed in the experiments are reproduced, including tank-treading, swinging and tumbling. The motions of 8 RBCs at the bifurcation are simulated when the two daughter vessels have different ratios. The results indicate that when the ratio of the daughter vessel diameter becomes smaller, the distribution of RBCs in the two vessels becomes more non-uniform.

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Red blood cells (RBCs) play an important role in the human body because of their ability to transport oxygen. They influence the rheological properties of blood due to their large volume fraction (45%) and particular mechanical properties. RBCs can squeeze through narrow capillaries much smaller than their own diameter and then recover their biconcave shape.[1] In linear shear flow, tumbling and tank-treading motion at low and high shear rates respectively can be found in simulations[2] and experiments.[3] A transition motion between tumbling and tank-treading, so-called swinging, was also found in the previous studies.[4−6] A number of computational modelings and simulations[7−11] of RBC rheology have been carried out since it is relevant to the transport properties of blood in the microcirculation. Recently, a new approach, the immersed boundary lattice Boltzmann method (IB-LBM) was used to simulate blood flow and the interaction of the fluid-membrane.[7,8] Compared to other methods, the IB-LBM is an ideal tool for studying blood flow in micro vessels because of its high efficiency proved by taking just hours to simulate the flow of 200 RBCs in three dimensions.[8]

In the peripheral circulatory system, the microvessels form a network to transfer energy to tissue. Blood flow at bifurcation has a great impact on the distribution of RBCs in the network, which accordingly affects the distribution of oxygen and other metabolites in microcirculation.[12] In tumor tissues, the diameter of a vessel is frequently larger than normal, which makes blood flow faster.[13] RBCs prefer to enter the downstream branch receiving the greater flow rate. It is significant to simulate the RBCs' motion at the bifurcation, which is helpful in understanding blood flow and mass transfer in microcirculation, especially in tumor tissue.

In this Letter, we combine the spring model of RBCs with the IB-LBM to simulate the motion of RBCs. The parameters of the RBC model are obtained by simulating the RBC stretching. The typical motions of RBCs in shear flow are simulated to verify our method. The separation of RBCs at microvascular bifurcation with different daughter vessel diameters is investigated.

The RBC is expressed by a 2D spring network model including 60 membrane particles, which are connected to their neighboring particles by springs.[14] This model contains three parts of energy. The elastic energies stored in the spring due to stretch/compression and bending of the membrane are, respectively, expressed as

$$E_l = \frac{1}{2}K_l \sum_{i=1}^{N} \left(\frac{l_i - l_0}{l_0}\right)^2, \tag{1}$$

$$E_b = \frac{1}{2}K_b \sum_{i=1}^{N} \tan^2\left(\frac{\theta_i - \theta_{0i}}{2}\right). \tag{2}$$

The energy representing the incompressibility is

$$E_s = \frac{1}{2}K_s \left(\frac{s - s_0}{s_0}\right)^2, \tag{3}$$

where l_0 is the reference length, l_i denotes the length of spring element i, θ_{0i} is the reference bending angle, θ_i denotes the angle of bending element i, s_0 is reference value, s is the RBC area, and N is the total number of spring elements. K_l, K_b and K_s are constant coefficients.

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The forces are obtained from

$$E = E_l + E_b + E_s, \tag{4}$$

$$\boldsymbol{f}_i = -\frac{\partial E}{\partial \boldsymbol{r}_i}. \tag{5}$$

The values of the parameters change with the number of particles in this model. In order to validate the parameters, a simulation of RBC stretching similar to the experiment[15] is performed. We keep $K_l : K_b : K_s = 1 : 1 : 1000$ in the simulation.[14] Stretching force is imposed in the 5% of particles with the largest absolute value of x coordinates to let the axial diameter of RBC be 9.4 μm, 12 μm, 13.4 μm, 14.6 μm and 15 μm when the stretching force is set to be 40 pN, 80 pN, 120 pN, 160 pN and 200 pN, respectively. Figure 1 shows the relationship between the reference length l_0 and K_l. In order to make the stretching property of the RBC model agree with the experiment,[15] the values of l_0 and K_l should be chosen to satisfy the corresponding values in the five curves shown in Fig. 1. Hence the value of l_0 is set to be in the range of 0.292–0.317 μm and the value of K_l can be chosen in the range of 1.9×10^{-17}–4.0×10^{-17} Nm, since the range from 0.292 μm to 0.317 μm for l_0 corresponds to the range of the axial diameters of RBCs in the natural state (7.4–8.3 μm). This setting is close to the axial diameters of RBCs with 7.8 μm observed in the experiment.[16] Table 1 displays the parameters used in this study.

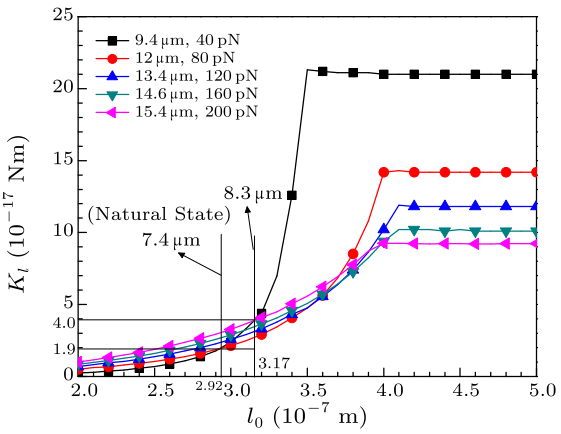


Fig. 1. The relationship between the reference length l_0 and K_l when a single RBC is subjected to different stretching forces.

Guo's scheme[17] of lattice Boltzmann equation (LBE) is employed by adding a force term to account for the influence of body forces on the fluid,

$$f_i(\boldsymbol{x} + \boldsymbol{e}_i\Delta t, t + \Delta t) - f_i(\boldsymbol{x}, t) = -\frac{1}{\tau}[f_i(\boldsymbol{x}, t) - f_i^{\rm eq}(\boldsymbol{x}, t)] + \Delta t F_i. \tag{6}$$

A D2Q9 model is performed in our work. The equilibrium distribution function and forcing term can be, respectively, written as

$$f_i^{\rm eq} = \omega_i\rho\Big[1 + \frac{\boldsymbol{e_i u}}{c_s^2} - \frac{u^2}{2c_s^2} + \frac{(\boldsymbol{e_i u})^2}{2c_s^4}\Big], \tag{7}$$

$$F_i = \Big(1 - \frac{1}{2\tau}\Big)\omega_i\Big(\frac{\boldsymbol{e_i} - \boldsymbol{u}}{c_s^2} + \frac{\boldsymbol{e_i u}}{c_s^4}\boldsymbol{e_i}\Big)\boldsymbol{F}. \tag{8}$$

This scheme will be used to solve the Navier–Stokes equations with the force term produced by the immersed boundary method (IBM).

Table 1. Parameters in the RBC model.

Parameter	Value	Value (LBM)
K_l	4.0×10^{-17} Nm	0.0019
K_b	4.0×10^{-18}–4.0×10^{-17} Nm	0.00019–0.0019
K_s	4.0×10^{-14} Nm	1.9
l_0	3.1×10^{-7} m	0.517
θ_{0i}	−0.07–0.33	−0.07–0.33
s_0	1.36×10^{-11} m^2	37.78
D_e	4.9×10^{-19} Nm	0.000023
B	3.84 μm^{-1}	2.3

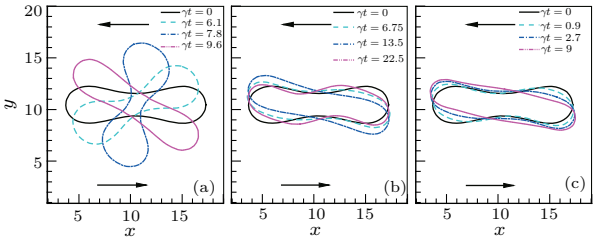


Fig. 2. Motions of RBC in shear flow: (a) tumbling motion at a shear rate γ of 50 s^{-1}, (b) swing motion at a shear rate of 150 s^{-1}, (c) tank-treading motion at a shear rate of 500 s^{-1}.

We employ the IBM to deal with the coupling of fluid–RBC interaction by distributing membrane forces $f(\boldsymbol{x}_m)$ to the adjacent fluid grid points $\boldsymbol{x}_f$ and updating the membrane configuration $\boldsymbol{x}_m$ according to the local flow velocity $\boldsymbol{u}(\boldsymbol{x}_f)$,[7]

$$\boldsymbol{F}(\boldsymbol{x}_f) = \sum_m D(\boldsymbol{x}_m - \boldsymbol{x}_f)\boldsymbol{f}(\boldsymbol{x}_m), \tag{9}$$

$$\boldsymbol{u}(\boldsymbol{x}_m) = \sum_f D(\boldsymbol{x}_f - \boldsymbol{x}_m)\boldsymbol{u}(\boldsymbol{x}_f), \tag{10}$$

$$D(\boldsymbol{r}) = \frac{1}{16}(1 + \cos\frac{\pi x}{2})\Big(1 + \cos\frac{\pi y}{2}\Big), \quad |x| \le 2, \ |y| \le 2. \tag{11}$$

To verify our method, the motions of RBCs in shear flow are simulated. The linear shear flow field is obtained by adding the velocity boundary condition at the bottom and top. The computation domain is 20×20. K_b is chosen as 4.0×10^{-18} Nm. It is seen from Fig. 2 that the typical RBC motions observed in experiments and simulations[2–6] can be reproduced. At the low shear rate (50 s^{-1}), the RBC makes tumbling motion, tank-treading can be found at the higher shear rate (500 s^{-1}), and swinging is obtained at the shear rate of a transition value (150 s^{-1}).

Figure 3 provides the separation of 8 RBCs at the bifurcation when two daughter vessels have different diameters. The value of K_b is set to be 4.0×10^{-17} Nm. The pressure at the inlet and outlet is set to be 25.04 mmHg and 25 mmHg, respectively. The internal angle of the two daughter vessels is 90°. Figure 3(a) shows a symmetric bifurcation with the same daughter vessels whose diameters are 9.9 μm. It is seen that there is an almost uniform separation of RBCs at the bifurcation due to the same flow rate at the branches. Five RBCs enter the upperside branch and three RBCs flow into the downside. It is also seen that the velocities of the RBCs are almost the same in the two daughter vessels. Figure 3(b) gives the motions of RBCs when the diameter of the upperside branch is changed into 8.5 μm and the diameter of the downside branch is enlarged to 11.3 μm. It is seen that, since the flow rate in the downside branch is larger, more RBCs prefer to enter it. Under this condition, six RBCs flow into the downside branch and these RBCs move faster than those in the upperside branch. When the diameter of the upper side branch is further constricted to be 7.1 μm and the downside one is further enlarged to be 12.7 μm, the motion of RBCs at the bifurcation show a different pattern compared to the above two patterns. In this situation, the flow rate in the downside branch is large enough to let all RBCs move in it.

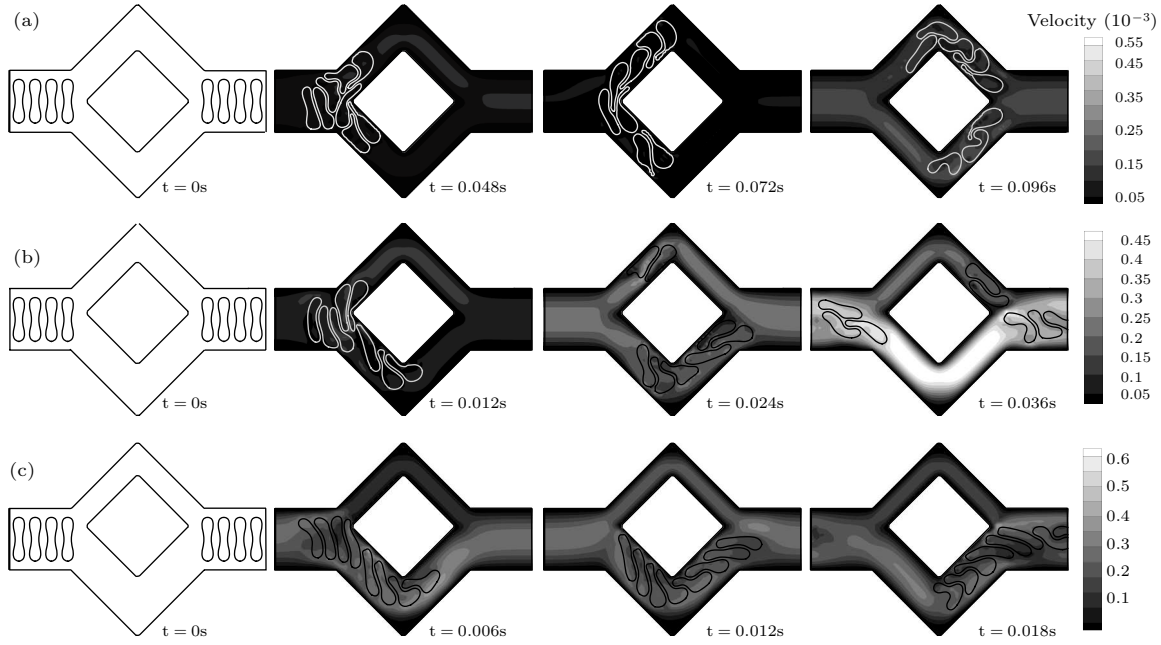


Fig. 3. Separation of RBCs at the bifurcation with different diameters of daughter vessels. The diameters of the daughter vessels are (a) 9.9 μm; (b) 8.5 μm and 11.3 μm, respectively; (c) 7.1 μm and 12.7 μm, respectively.

In summary, we have developed a method to simulate the motion of RBCs by combining the RBC spring model with the IB-LBM. By simulating the stretching of a single RBC, the parameters of the RBC model are validated. To verify our method, the tumbling, swinging and tank-treading motion in linear shear flow are well reproduced. Finally, we simulate the separation characteristics of RBCs at the bifurcation. It is confirmed that the RBCs prefer to enter the branch with the greater flow rate. Our results show that all RBCs will enter into one branch with a larger size instead of two when the ratio of the downside vessel diameter to the upperside vessel diameter is greater than 9:5. The results provide possible evidence for why the diameters of the neoplastic vasculature in solid tumors are larger than those in normal tissues. It is clearly shown that more RBCs prefer to move in larger vessels and thus can provide more nutrients and oxygen to the surrounding tissues. On the other hand, we may use the separation characteristics of RBCs to design a drug delivery method in cancer treatment.

The IB-LBM used for simulating RBCs was first proposed by Zhang *et al.*[7] The notable advantages of this method are easy for coding, parallel computing, and extension to 3D simulation. Additionally, it shows high efficiency in taking just several hours to simulate 8 RBCs on a personal computer with one CPU in our work.

Since we use the simplest scheme of Delta function in the immersed boundary method, the numerical precision in the simulation may not be quite high. However, it is enough for reproducing the motion of RBCs observed in experiments. Moreover, we employ a relatively simple computational domain in the simulation. It is necessary to improve the mesh generation part of the LBM program to deal with the flow in com-

plex structures. The 2D model partially conserves the RBC structure while ignoring some information. It is necessary to consider a 3D simulation in further work.

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