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MULTI-SCALE PARTICLE SIMULATION OF RED BLOOD CELL IN MICROCIRCULATION

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ABSTRACT

The complex rheology of red blood cell (RBC) in microcirculation has been a topic of interest for many decades. As RBC is highly deformable, shape change affects the microcirculation and such effect should be accounted accurately to understand the rheology of blood flow. A particle based model is developed to construct the red blood cell (RBC) based on the minimum energy principle. A bead-spring network is utilized to represent the cross-sectional plane of RBC membrane. The total energy of the RBC is associated with spring stretch/compression, bending and constraint of fixed area. Shape optimization of swollen RBC due to continuous deflation is performed. A bi-concave RBC shape is accurately achieved when the circular shape is deflated to 65%. Dissipative particle dynamics (DPD), a coarse-grained Mesoscopic particle simulation is used to simulate the flow. RBC in its equilibrium shape is placed inside a microchannel of height 10 μm to study the deformation of the cell under shear. Force exerted on RBC particles by plasma particles were determined and solved as the external force in the DPD equation to calculate the position and velocity of each particle. As the simulation started, the RBC experienced the shear and drag force by surrounding plasma and evolved to the characteristic parachute type shape as observed in experiments. Once the RBC reached the steady deformation, it continued with the same shape and stayed in the center of the channel. It is observed that the parachute shape and its motion along the centerline of the flow help reducing the drag and subsequently achieving the state of minimum energy. Formulation and results were validated against the experimental and computational results reported in the literature.

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Keywords: Red Blood Cells, Tank-Treading, DPD, Dissipative particle dynamics, Hemodynamics, coarse-grained model, particle simulation

INTRODUCTION

Blood is an inhomogeneous fluid containing blood cells suspended in a liquid component called plasma. About 45% of the blood is occupied by erythrocytes or red blood cells (RBCs) and they play a crucial role in oxygen transport. The rheology of RBC has been a topic of interest for many decades as blood flow dynamics depends strongly on the motion and deformation of RBCs and how they interact with the capillary wall and surrounding constituents. Changes in the property by large deformation of cell through biochemical reaction and presence of parasites and bioactive lipids influence many diseases such as sickle cell anemia and malaria (Suresh et al. 2005). Healthy RBCs demonstrate extraordinary ability to undergo reversible large deformation and it can pass through capillaries of as small as 3 μm of inner diameter (Dzwinel et al. 2003). RBCs infected by the *protozoan Plasmodium falciparum* change their intracellular structure and their elastic modulus can increase by more than a factor of 10 (Suresh et al. 2006). In this case, RBCs can no longer pass through narrow capillaries and result in higher flow resistivity and change in Hematocrit number, which is the volumetric ratio of RBCs to the whole blood. Understanding the changes in mechanical behavior of cells can help to predict diseases and their progression in early stages. Hence, it is very important to

study the mechanical behavior of RBCs and their dynamics under different shear and flow conditions in capillaries.

A number of experimental (Fischer et al., 1978; Discher et al., 1994; Dao et al., 2003; Fischer 2007; Skotheim and Secomb 2007; Abkarian et al., 2007), theoretical (Evans and Fung 1972; Skalak et al. 1973) and computational (Dzwinel et al., 2003; Dao et al., 2006; Tsubota et al., 2006; Pivkin and Karniadakis 2008) investigations have been conducted to study the structure and dynamics of RBC. There are two main approaches: continuum and discrete microscopic assumptions. The nature of blood flow changes greatly with the vessel diameter. Blood can be regarded as homogenous fluid from macroscopic point of view for the cases where vessel diameter is greater than two orders of magnitude larger than the size of RBC. In contrast to the macroscale, where blood is regarded as a continuous medium, at the microscopic level blood can be viewed as the collective motion of an ensemble of microscopically interacting discrete particles. In vessels of diameters smaller than 25 μm, the interaction among blood constituents and capillary wall can no longer be ignored. Blood must be regarded as a two-phase non homogeneous fluid consisting of liquid plasma phase and a discrete solid phase of blood cells. There are about 10^{10} blood vessels whose diameters are in the range of 5-10 μm, which are comparable with the diameter of RBC (Boryczko et al., 2003). Since RBC is highly deformable, shape change affects the microcirculation and such effect should be accounted accurately to understand the rheology of blood flow correctly.

Recent developments in Bio-MEMS and microfluidics have facilitated the study of microstructure of RBC experimentally (Discher et al., 1994; Dao et al., 2003) and further motivated the development of various theoretical and numerical techniques to study the rheology of RBC at microscale. Many numerical schemes based on discrete particle modeling of blood have been developed in the last decade. Migliorini et al. (2003) and Sun and Munn (2005) proposed two-dimensional lattice Boltzmann method (LBM) and produced quantitative results of axial migration of cells. RBCs were modeled as rigid rods and the deformation was not considered. Zhang et al. (2007) used LBM to simulate multiple deformable RBCs in shear flow but cells were modeled as solid elastic body and RBC shape was compared with its innate equilibrium shape. Secomb et al. (2007) represented RBC as a set of interconnected viscoelastic elements and interactions with the surrounding fluids were computed using finite element method. Hosseini et al. (2009) developed two-dimensional model using smooth particle hydrodynamics where the angle between the elements were always compared with the angle for corresponding equilibrium shape. When RBC shape is compared with its innate shape in equilibrium, curvature of the membrane at a given location is always forced to have the same shape at all times. This approach may not follow the actual physics and the shape during the tank-treading motion keep changing as the lipid bilayer treads over the cytosol and move from concave to convex portion of the cell. Also, tumbling and tank-treading behavior at low shear rate cannot be produced accurately. The above cited work utilized simplified models for RBC membrane, whose application is limited. Though these models produce good qualitative results, it is not easy to obtain quantitative results for a wide range of cases observed in the experiment.

A more comprehensive approach is based on the energy of the RBC where the optimum shape is achieved by minimizing the total energy (Li et al., 2005; Tsubota et al., 2006). Experiments have shown that RBC membrane store energy in a conservative manner which allows the membrane to undergo shape recovery after removal of external perturbation (Evans, 1980). In the last decade various models were developed based on minimum energy principle to study the rheology of RBCs. Discher et al. (1998) and Boey et al. (1998) performed Monte-Carlo simulations of large deformation of RBC. Li et al. (2005) implemented coarse-grained model for spectrin network and studied the elastic properties of the membrane. The total energy, which was calculated based on in-plane deformation, bending, area constraint and volume constraint, was minimized to recover the shape of the RBC. Cited works focused on the elastic property of the RBC and studied only the response of mechanical stretching and the dynamics of the cell in capillaries was not investigated. Recently, Pivkin and Karniadakis (2008) modeled RBC using dissipative particle dynamics (DPD) based on coarse-grained spectrin network and simulated the dynamics inside a capillary. However, cytosol and plasma fluids were not modeled explicitly and RBC membrane was treated as fully permeable. Dao et al. (2003) performed simulations with and without the presence of cytosol and showed that during the stretching process the effect of cytosol was negligible. However, during the dynamics of RBC under shear in a capillary flow, viscous interaction is significant (Abkarian et al., 2007; Fischer 2007) as the viscosity of cytosol is approximately five times larger than that of plasma. During the tank-treading motion high viscous cytosol exerts higher resistance to the motion of the lipid bilayer enclosing it. It is important to account its viscous interactions while comparing the model with experimental results. Secomb et al. (2007) discussed that by neglecting the effect of cytosol, the tank-treading frequency under shear deviated considerably from the experimental results.

The main objective of this work is to present a discrete two-dimensional RBC model based on minimum energy principle and to use dissipative particle dynamics to study the dynamics and deformation in shear and pressure driven flow in capillary of different sizes. RBC will be treated as 2-D plane deformable membrane, which simplifies flow model of microcirculation. In simple shear flow in capillary, RBC shape has a plane of symmetry, which is parallel to the flow axis. Particles representing blood cell, cytosol, plasma and capillary wall will be defined by different sets of DPD particles. A new method will be utilized to separate cytosol and plasma particles. Model parameters and scaling scheme will be selected to match the mechanical property of

RBC. The position of the cell in the lateral direction will be varied to study the migration of the cell to achieve the minimum energy. Tumbling and tank-treading motion will be studied for a wide range of shear rates. The model will be validated by comparing the results with experimental and computational results published in the literature.

METHODS

RBC MODEL DESCRIPTION

Typically, a human RBC has a biconcave shape of ~8 μm in diameter and ~2.5 μm in thickness. The cell wall is made of phospolipid bilayers and contains viscous Newtonian liquid called cytosol. From mechanical perspective, RBC can be treated as an incompletely inflated flexible capsule. The cytosol acts to preserve the interior volume of the red blood cell during deformation as well as to maintain the uniform distribution of the internal fluid pressure on the membrane. The overall shape of the RBC is determined by the elastic properties of the membrane, its surface area and the enclosed volume. The important feature of the mechanical behavior is that the order of magnitude of these elastic properties are significantly different. The resistance to area change is around five times larger than the resistance to in-plane deformation. Also, energy associated with bending rigidity of the membrane curvature is much smaller compared to in-plane deformation (Evans, 1980). These properties allow a large deformation of RBC at constant volume and facilitate its passage through narrow capillaries. The total surface area and volume of the cell is estimated to be 134 μm^2 and 95 μm^3, respectively (Li et al., 2005). If RBC is compared with sphere of equivalent area, the volume of RBC is 65% of the volume of the sphere.

The RBC cell wall contains underlying spectrin network which is tethered to the membrane. These structural networks are the basic building block of the load bearing structure of RBC, which determine the overall deformation behavior of the RBC. The modeling approach is similar to the models based on minimum energy principle (Li et al., 2005; Tsubota et al., 2006; Pivkin and Karniadakis 2008). In the present work, RBC membrane was discretized into *N* DPD particles which were connected to their neighbor particles by elastic springs (see, Figure 1a).

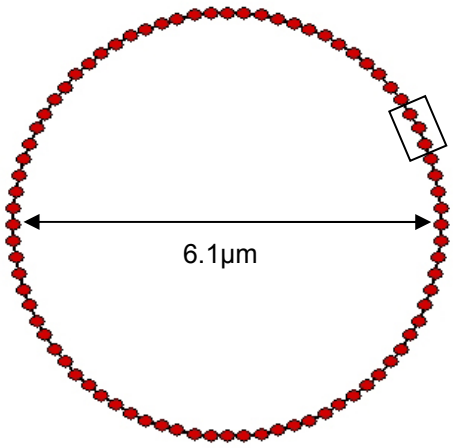
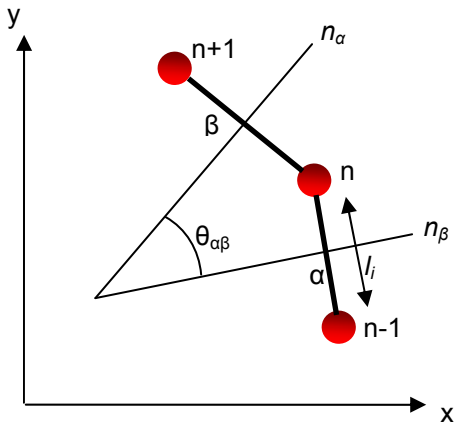


Figure 1: (a) Fully inflated RBC



(b) Three node building block

RBC vertex nodes can move freely in two-dimensional Cartesian plane according to the forces acting on them. The three points building block of the membrane is schematically shown in Figure 1(b). For any given node, *n*, its neighbor nodes one in front, *n+1*, and another in the back, *n-1*, is considered. Two elements, *α* and *β* are considered between a vertex pair (*n*, *n-1*) and (*n*, *n+1*), respectively. Length of these elements are given by $|r_n - r_{n-1}|$ and $|r_{n+1} - r_n|$, respectively, where ***r*** is the position vector of the node. The position vector of center of mass of each element is $r_\alpha = (r_n + r_{n-1})/2$ and $r_\beta = (r_{n+1} + r_n)/2$ and their normal vectors are n_α and n_β, respectively. The network of the elements form a 2-D enclosed area given by $A_t = \sum_{i=1}^{i=N} (r_i \cdot n_i) l_i / 2$, which is based on the continuum divergence theorem. The advantage of this method is that it is independent of the frame of reference and any shape of the geometry.

RBC membrane has elastic resistances to stretching, bending and area expansion. The total free energy of the cell is given by (Tsubota et al., 2006),

$$E_{Total} = E_{Spring} + E_{Area} + E_{Bending} \quad (1)$$

where E_{Spring}, E_{Area} and $E_{Bending}$ is the energy associated with stretch/compression, changes in area and bending of the membrane.

The elastic energy stored in the stretch/compression spring due to the change in length l_i from its reference l_0 is expressed as,

$$E_{Spring} = \frac{k_{Spring}\, k_B T}{2} \sum_{i=1}^{N} \left(\frac{l_i - l_0}{l_0} \right)^2 , \qquad (2)$$

where l_i is the lenght of the i^{th} spring at given instant and l_0 is the unstretched reference lenght. The area conservation constraint is given by,

$$E_{Area} = \frac{k_{Area}\, k_B T}{2} \sum_{i=1}^{N} \left(\frac{A_t - A_0}{A_0} \right)^2 , \qquad (3)$$

where A_t is the total area of the cell at any instant and A_0 is the desired total area.

Lipid bilayers exhibit bending and compressional stiffnesses. The elastic energy can be expressed as a function of the angle between two neighboring elements (α, β) and given by,

$$E_{Bending} = k_{Spring}\, k_B T \sum_{adjacent\ pair\ \alpha,\beta} \left[1 - \cos\left(\theta_{\alpha\beta} - \theta_0 \right) \right] , \qquad (4)$$

where $\theta_{\alpha\beta}$ is the angle between the normal to the adjacent face elements. The reference angle θ_0 is the angle of unstressed bilayers. For numerical calculation, the following formula is applied,

$$\cos\left(\theta_{\alpha\beta} - \theta_0 \right) = \cos\theta_{\alpha\beta} \cos\theta_0 + \sin\theta_{\alpha\beta} \sin\theta_0 ,$$

where $\cos\theta_{\alpha\beta} = n_\alpha \cdot n_\beta$ and $\sin\theta_{\alpha\beta} = \pm \left| n_\alpha \times n_\beta \right|$. The positive sign is taken when $\left(n_\alpha - n_\beta \right) \cdot \left(r_\alpha - r_\beta \right) \geq 0$.

In the present work, θ_0 was taken to be zero degree, i.e. the bending stress is zero for when the cell membrane was flat. The total force on each nodal point can be calculated by minimizing the total energy (E_{Total}) with respect to the position vector of each nodal point ($\boldsymbol{r}_i$).

$$F_i = -\frac{\partial E_{Total}}{\partial r_i} \qquad (5)$$

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The analytical expression for the total energy was calculated using Eqs. (1-4). As given by Eq. (5), total energy is differentiated with respect to the position vector of each node to determine the force. Once the total force on each node is calculated, the evolution of velocity and position of all the points are determined based on Newton's second law of motion,

$$m_i \frac{dv_i}{\partial t} = F_i + F_i^{ext} ; \qquad \frac{dr_i}{\partial t} = v_i , \qquad (6)$$

where v_i is the velocity and F_i^{ext} is the external force acting on the node.

SOLUTION METHODOLOGY

Dissipative particle dynamics (DPD) is used to simulate the dynamics of the RBC in microchannel. DPD is a particle-based mesoscopic simulation method introduced by Hoogerbrugge and Koelman (1992), which captures both hydrodynamics and colloidal behavior of the system. Each DPD particle represents a cluster of actual molecules of the flow field and move in a Lagrangian fashion (Español and Warren 1995; Groot and Warren 1997).

Each DPD particle interacts with surrounding particles through a set of distance and velocity dependent forces within a certain cutoff radius. The total momentum of the interacting particles are conserved hence the system exhibits correct hydrodynamics of the flow. There are three types of forces in DPD, which are conservative, $\vec{f}_{ij}^{\,C}$, dissipative, $\vec{f}_{ij}^{\,D}$, and random, $\vec{f}_{ij}^{\,R}$, and are expressed as:

$$\vec{f}_{ij}^{\,C} = \alpha\, \omega^C(r_{ij})\, \vec{e}_{ij} , \qquad (7)$$

$$\vec{f}_{ij}^{\,D} = -\gamma \omega^D(r_{ij}) \left(\vec{e}_{ij} \cdot \vec{v}_{ij} \right) \vec{e}_{ij} , \qquad (8)$$

$$\vec{f}_{ij}^{\,R} = \sigma\, \omega^R(r_{ij})\, \zeta_{ij}\, \Delta t^{-1/2}\, \vec{e}_{ij} . \qquad (9)$$

$\vec{f}_{ij}$ represents the total force on particle i due the surrounding j particles. The vector $\boldsymbol{r_{ij}}$ points from i to j such that $\boldsymbol{r_{ij}} = \boldsymbol{r_j} - \boldsymbol{r_i}$ and $v_{ij} = v_j - v_i$; $\boldsymbol{e_{ij}}$ is the unit vector pointing in direction from j to i. Conservative force takes the usual form of a gradient of two particle interaction with soft quadratic potential, where the parameter α is the maximum repulsion between the particles. The weight function ω^C decreases monotonically with particle-particle separation distance and becomes zero beyond the cutoff length and is given by,

$$\omega^C(r_{ij}) = \begin{cases} \left(1 - \dfrac{r_{ij}}{r_c} \right), & (r_{ij} < r_c) \\ 0, & (r_{ij} \geq r_c). \end{cases} \qquad (10)$$

Parameters γ and σ are the strength of dissipative and random forces, respectively. ζ_{ij} is a random number with zero mean and unit variance. It is the same for a pair of interacting particles at each time step and $\zeta_{ij} = \zeta_{ji}$ ensures that the momentum of the interacting pair of particles is conserved. Weight functions $\omega^D(r_{ij})$ and $\omega^R(r_{ij})$ for dissipative and random forces are given by,

$$\omega^{\mathrm{D}}(r_{\mathrm{ij}}) = \left(\omega^{\mathrm{R}}(r_{\mathrm{ij}})\right)^2 = \begin{cases} \left(1 - \dfrac{r_{\mathrm{ij}}}{r_{\mathrm{c}}}\right)^2, & (r_{\mathrm{ij}} < r_{\mathrm{c}}), \\ 0, & (r_{\mathrm{ij}} \geq r_{\mathrm{c}}). \end{cases} \quad (11)$$

Español and Warren (1995), using fluctuation-dissipation theorem, established the relation between forcing parameters and weight functions of Equations (8) and (9), which is given by,

$$\sigma^2 = 2\gamma k_{\mathrm{B}}T\ , \quad \omega^{D}(r_{\mathrm{ij}}) = \left(\omega^{R}(r_{\mathrm{ij}})\right)^2 . \quad (12)$$

Equation (11) ensures that DPD is simulating a Hamiltonian system in canonical ensemble. Dissipative force acts to relax the system whereas the random force keeps the system in thermal motion. So, Equations (8) and (9) together works as a thermostat.

Different set of DPD particles were defined to represent plasma, RBC membrane points and boundary of the capillary. Their relative interactions were controlled by the force parameters. External body force on each particle was applied to drive the flow in the channel. Time evolution of DPD particles was governed by Newton's second law, which is given by Equation (6).

NUMERICAL IMPLEMENTATION AND SCALING ANALYSIS

An in-house code in FORTRAN was developed to implement a two-dimensional model for blood flow in a microchannel of height H and length L. The computational domain was descretized into $N_x \times M_y$ number of square unit cells of side length equal to r_c. DPD particles were generated with a unique identification number and distributed randomly into each indexed cell. The total number of simulated particles in the domain was $\sigma_{DPD} \times N_x \times M_y$, where σ_{DPD} is the number of particles in each cell. As the forces were effective within the cutoff radius, particles far from r_c were excluded in the computation. A cell division and link-list approach was implemented to enhance the computational efficiency (Allen and Tildesley 1989). A modified version of velocity-Verlet integration scheme was used to solve the governing equation (Groot and Warren 1997). Top and bottom walls of the computational domain were treated by freezing DPD particles in two extra layers of the domain and bounce back boundary condition was applied at the interface of fluid and wall. RBC in its equilibrium shape was imported and placed at the given location inside the domain. Plasma particles interact with RBC particles through DPD forces given by Eqs. (7-12) and used as F_{ext}. The deformation and motion of the RBC were determined based on Eq. (6).

The DPD equations were solved in terms of DPD reference scales of r_c, k_BT and m_{DPD}. Each computational cell was divided into 4 bins for statistical averaging of the result. The model parameters are chosen to exhibit the properties of actual RBC as close as possible. The bending rigidity of RBC was measured experimentally and its corresponding value is given to be 50 k_BT (Noguchi and Gompper, 2005). Energy associated with in-plane shear stress and area change was much stronger and the parameters k_A and k_S were taken to be 6000 and 1000, respectively. This would assure that the total contour length and area of the cell would be constant and correspond to its large scale deformation at constant internal volume and surface area.

For length scale the cutoff radius was set to r_c=1 μm and taken as the reference length. The average blood velocity in 10 μm capillary is typically about 1 mm/s (Pivkin and Karniadakis, 2008). Taking this velocity as the reference velocity and equating it with the unit velocity in DPD (1 r_c/t_{DPD}), the reference time in DPD is calculated to be t_{DPD}=0.001 sec. The conventional parameters in DPD correspond to DPD fluid of very low viscosity. To increase the viscosity dissipative force parameter and the number density was set to γ=45 and σ_{DPD}=6, respectively. For dynamics of the flow in a channel of height 10 μm, a computational domain of 10×40 is considered and a body force F_p is applied. Body force for various average velocities were selected accordingly as the F_p is proportional to the average velocity of the flow in a channel.

RESULTS AND DISCUSSION

At first, shape optimization is performed to construct the structure of RBC in equilibrium when there is no external force on it. It is insightful that by constraining the total length of the geometry, different shapes can be attributed for a given reference area. As an initial shape, RBC was assumed as a fully inflated circle of diameter 6.1 μm as shown in Figure 1(a). The membrane was descretized into N=80 particles that were connected by the network of springs. Shape change simulations were performed based on the minimum energy principle. The reference area (A_0) of the cell was gradually decreased from its initial circular area. A transient simulation was carried out to solve the equations (1) to (6). As the parameters for area was much stronger compared to bending, the resulting area of the shape was the same as the reference area. Figure 2 shows the optimum shape based on the minimum energy for different reference area (A_0). Figure 2(a) and 2(b) is the optimum shape for the minimum energy when A_0 is 85% and 75% of the area of the equivalent circle, respectively. When A_0 was reduced to 65% of the area of the equivalent circle, a biconcave shape of RBC was achieved as given by Figure 2(c).

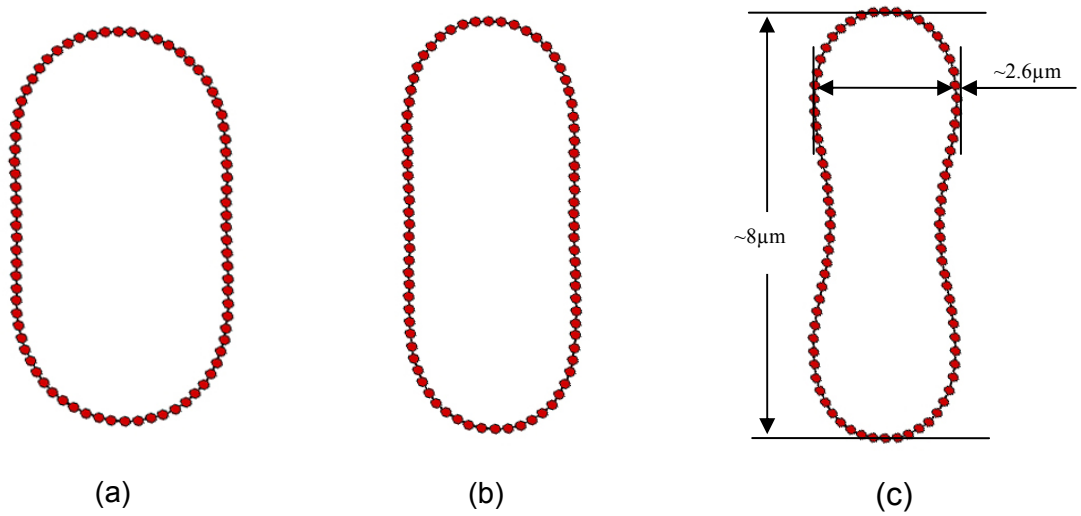

Figure 2: Shape evolution of cell based on minimum energy for a given area. Starting from a circle of radius 6.1 µm. Total boundary length is constrained (19.2 µm) (a): 85% deflation (b): 75% deflation (c): 65% deflation (Shape of RBC)

Dynamics and deformation of RBC was studied in the channel flow. First, a simple fluid flow of pure plasma in the channel of height 10 µm was simulated. No-slip boundary condition was imposed on the top and bottom wall and periodic boundary condition was imposed on the left and right face of the domain. When a particle exited from the right face, it was reentered from the left face. The fully developed velocity profile was parabolic and the maximum velocity was in the middle of the channel.

After the flow was fully developed, RBC in its equilibrium shape was placed in the middle of the channel. Force exerted on the cell by the plasma particles were determined and used as an external force in the Equation (6) to calculate the position and velocity of each node. As the simulation started, the RBC experienced the shear and drag force by surrounding plasma. It moved with the flow and its shape started changing and eventually evolved to the characteristic parachute shape. As the shear was high near the wall, the thickness of the cell was small near the wall compared to the mid section of the cell. The gradual evolution of parachute shape is shown in Figure 3. This behavior was in agreement with experiments and computational simulations (Secomb et al. 2007, Pivkin and Karniadakis 2008, Husseini et al. 2009).

For the average velocity of 1 mm/s RBC acquired the final parachute shape after moving 30 µm in the flow direction (see, Figure 3), which agreed well with experiments and computational results (Secomb et al., 2007; Pivkin and Karniadakis 2008, Hosseini and Feng, 2009).

Parachute shape helped to reduce the drag force and consequently reduced the total energy of the RBC. Once the final shape was achieved, the RBC continued moving with the same shape along the flow. It also tried to remain in the middle of the channel and the shape was symmetric about the center line of the channel as velocity gradient is small in the middle compared to the region close to the wall.

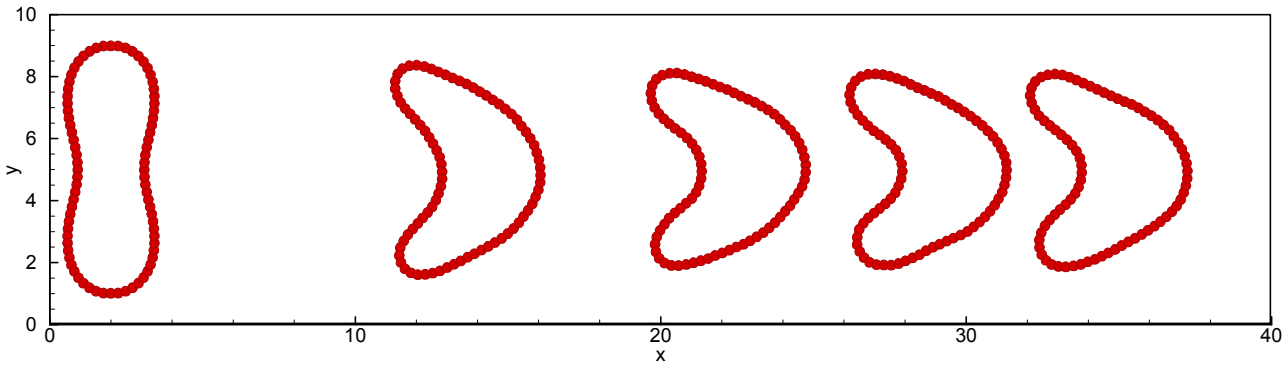

Figure 3: Evolution of shape of RBC in a flow. Channel height=10 µm, average velocity=1 mm/s. Starting with equilibrium shape it becomes fully developed after moving 30 µm

To test this behavior further, the RBC was placed 1 μm above the central axis of the channel. Figure 4 shows the progressive development of the shape as the RBC moved along the flow. At the start, RBC took asymmetric shape where the top portion close to the wall was thin whereas the central and lower portion, which was close to the middle of the channel was bulkier as the shear was low in the middle of the channel. Also, the cell was elongated in the upper half of the channel as the velocity gradient was high near the wall. As the simulation progressed, the cell shifted to the center of the channel. After moving towards the cente0line of the flow, RBC started evolving into parachute type shape. Eventually the shape was fully developed and was symmetric to the center-line of the flow. Then the RBC continued moving in the middle of the channel. The lateral migration and shape evolution showed the same behavior observed in the experiment (Secomb et al., 2007).

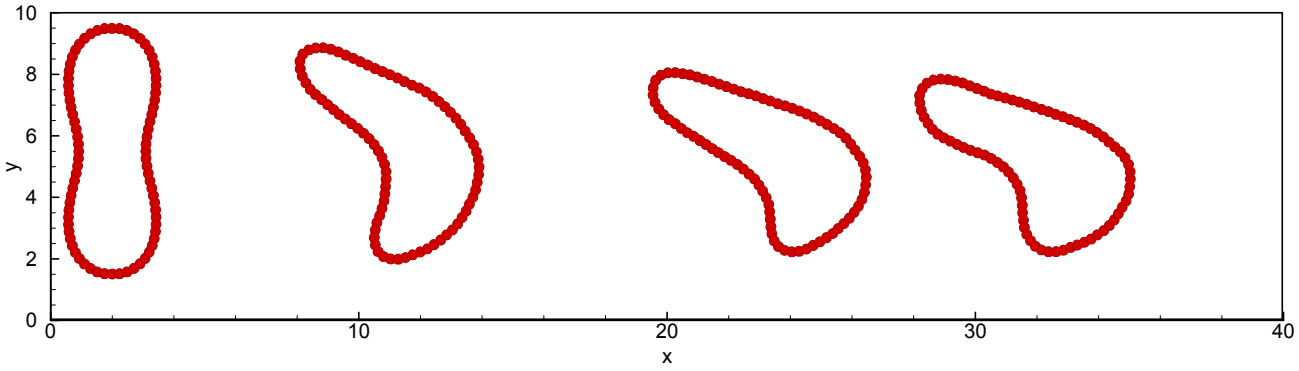

Figure 4: Evolution of shape of RBC in a flow. Channel height=10 μm, average velocity=1 mm/s. RBC in equilibrium shape is placed 1 μm above the center line of the channel. RBC shifts back to the central line and eventually takes the parachute shape

CONCLUSIONS

Complex rheology and discrete nature of blood at microscale has been a topic of interest since a long time. Continuum assumptions have not been successful as blood flow at microscale involves the interaction of highly deformable blood cells with surrounding constituents. A particle based simulation technique was utilized to address this problem. A two-dimensional model of red blood cell based on dissipative particle dynamics was developed to study the deformation and dynamics under a wide range of shear and flow rates. The cell membrane was represented by particles connected by elastic springs. The total energy, which was calculated based on in-plane deformation, bending and area constraint was minimized to recover the shape of RBC. RBC was simulated inside a 10 μm channel at different locations from the central axis to study the lateral migration of the cell and it was observed that the RBC moves towards the central-line to minimize the total energy as shear stress is less in the middle of the channel and develops the characteristic parachute type shape as observed in experiments.

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