Published in final edited form as:

Soft Matter. 2010 September 21; 6(18): . doi:10.1039/C0SM00183J.

A low-dimensional model for the red blood cell

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Abstract

The red blood cell (RBC) is an important determinant of the rheological properties of blood because of its predominant number density, special mechanical properties and dynamics. Here, we develop a new low-dimensional RBC model based on dissipative particle dynamics (DPD). The model is constructed as a closed-torus-like ring of 10 colloidal particles connected by wormlike chain springs combined with bending resistance. Each colloidal particle is represented by a single DPD particle with a repulsive core. The model is able to capture the essential mechanical properties of RBCs, and allows for economical exploration of the rheology of RBC suspensions. Specifically, we find that the linear and non-linear elastic deformations of healthy and malaria-infected cells match those obtained in optical tweezers experiments. Through simulations of some key features of blood flow in vessels, *i.e.*, the cell-free layer (CFL), the Fahraeus effect and the Fahraeus-Lindqvist effect, we verify that the new model captures the essential shear flow properties of real blood, except for capillaries of sizes comparable to the cell diameter. Finally, we investigate the influence of a geometrical constriction in the flow on the enhancement of the downstream CFL. Our results are in agreement with recent experiments.

1 Introduction

Blood flow is the key determinant in numerous pathologies. Since red blood cells (RBCs) occupy nearly one-half of blood ($\sim 5 \times 10^6 \text{ mm}^3$),¹ the blood flow is greatly influenced by the dynamics of RBCs. A healthy human RBC has a biconcave shape and is highly deformable.^{2,3} As a consequence of RBC size and deformability, the nature of blood flow changes greatly with the vessel diameter. In vessels larger than 200 μm , the blood flow can be accurately modelled as a homogeneous fluid.³ However, in smaller vessels, such as arterioles and venules, the two-phase nature of blood as a suspension of RBCs becomes important. Therefore, quantitative understanding of the blood flow through arterioles and venules is necessary for assessing the hemodynamic resistance and its regulation in the microcirculation as well as for analyzing oxygen transport processes. A number of numerical models have been developed recently based on a continuum description,^{4–7} a discrete approximation at the spectrin molecular level^{8–10} as well as at the mesoscopic scale.^{11–14} Fully continuum (fluid and solid) models often suffer from the non-trivial coupling between nonlinear solid deformations and fluid flow with consequential computational expense. At the microscopic scale, detailed spectrin molecular models of RBCs are also limited by the demanding computational expense. Mesoscopic modeling of RBC combines accuracy and efficiency.

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There exist several mesoscopic methods for RBC modeling.^{11–14} Dzwinel *et al.*¹³ modelled RBCs as a volume of elastic material having an inner skeleton. In other works^{11,12,14} the RBC is represented by a network of springs in combination with bending rigidity and constraints for surface-area and volume conservation. Dupin *et al.*¹² coupled the discrete RBC to a fluid described by the lattice Boltzmann method (LBM).¹⁵ Zhang *et al.*¹⁶ combined LBM for fluid flows and immersed boundary method (IBM) for the fluid membrane interaction. Noguchi and Gompper¹¹ employed multiparticle collision dynamics¹⁷ and presented encouraging results on vesicles and RBCs. Pivkin and Karniadakis¹⁴ used dissipative particle dynamics (DPD)¹⁸ for a multi-scale RBC (MS-RBC) model. Fedosov *et al.*¹⁹ further incorporated in this multi-scale model the viscoelastic property of the membrane and the external/internal fluid viscosity contrast, which are not taken into account in most previous models. All of the above methods obtained very promising results, but still suffer from the prohibitive computational cost for vessels greater than 20–50 μm in diameter. As a consequence, there have not been many mesoscopic simulations performed for the blood flow in large vessels, *i.e.*, arteries and veins, especially at high concentrations.

In the present work, we present a new low-dimensional RBC (LD-RBC) model, based on a ring of 10 colloidal particles connected by wormlike chain (WLC) springs. Each colloidal particle is simulated by a single DPD particle based on a new formulation of DPD, which augments the standard DPD with non-central dissipative shear forces between particles while preserving angular momentum.²⁰ Details of simulating colloidal particles, including the new formulations of DPD and the adopted exponential conservative interactions between particles, can be found in our previous work.²¹ To consider the bending rigidity of RBC, we incorporate into the ring model bending resistance in the form of “angle” bending forces dependent on the angle between two consecutive springs.

We validate the new RBC model in microcirculation by simulating the following effects, which are observed *in vitro* and *in vivo*: (i) Existence of a cell-free or cell-depleted layer near the wall; (ii) Fahraeus effect, *i.e.*, dependence of tube or vessel hematocrit on tube diameter; (iii) Fahraeus-Lindqvist effect, *i.e.*, dependence of apparent viscosity on tube diameter. In this work, we will study these key features of blood flow as well as RBC mechanical responses, in comparison with the experimental data. In particular, we simulate flow in a 3D tube, instead of a 2D rectangular channel used in previous studies.^{16,22}

We also test the model in more complex geometry domains. Specifically, it was shown experimentally,²³ by an *in vitro* model, that for a fixed flow rate a geometrical constriction in the flow can artificially enhance the cell-free layer. This phenomenon can be used to design microfluidic devices to separate red blood cells from the suspending plasma.²³ As a further validation of the proposed low-dimensional RBC model, we perform simulations to reproduce the above experimental observation.

The paper is organized as follows. In section 2 we describe the RBC model and explain the scaling to real units in section 3. Section 4 presents RBC mechanical response under stretching. Section 5 contains results on the cell-free layer, the Fahraeus effect, and the Fahraeus-Lindqvist effect. In section 6, we investigate the influence of a geometrical constriction on the distribution of RBCs in the flow. We conclude in section 7 with a brief discussion.

2 Dissipative particle dynamics (DPD) modeling

The RBC is modeled as a ring of 10 colloidal particles connected by wormlike chain (WLC) springs. Each colloidal particle is simulated by a single DPD particle with a new formulation of DPD, in which the dissipative forces acting on a particle are explicitly divided into two

separate components: *central* and *shear* (non-central) components. This allows us to redistribute and hence balance the dissipative forces acting on a single particle to obtain the correct hydrodynamics. The resulting method was shown to yield the quantitatively correct hydrodynamic forces and torques on a single DPD particle,²⁰ and thereby produce the correct hydrodynamics for colloidal particles.²¹ This formulation is reviewed below.

We consider a collection of particles with positions $\mathbf{r}_i$ and angular velocities $\boldsymbol{\Omega}_i$. We define $\mathbf{r}_{ij} = \mathbf{r}_i - \mathbf{r}_j$, $r_{ij} = |\mathbf{r}_{ij}|$, $\mathbf{e}_{ij} = \mathbf{r}_{ij}/r_{ij}$, $\mathbf{v}_{ij} = \mathbf{v}_i - \mathbf{v}_j$. The force and torque on particle i are given by

$$\begin{aligned}\mathbf{F}_i &= \sum_j \mathbf{F}_{ij}, \\ \mathbf{T}_i &= -\sum_j \lambda_{ij} \mathbf{r}_{ij} \times \mathbf{F}_{ij}.\end{aligned}\quad (1)$$

Here the factor λ_{ij} (introduced in²⁴) is included as a weight to account for the different contributions from the particles in different species (solvent or colloid) differentiated in sizes while still conserving the angular momentum. It is defined as

$$\lambda_{ij} = \frac{R_i}{R_i + R_j}, \quad \text{and } \lambda_{ij} = 1/2 \quad \text{when } R_i = R_j \quad (2)$$

where R_i and R_j denote the radii of the particles i and j , respectively. The force exerted by particle j on particle i is given by

$$\mathbf{F}_{ij} = \mathbf{F}_{ij}^U + \mathbf{F}_{ij}^T + \mathbf{F}_{ij}^R + \tilde{\mathbf{F}}_{ij} \quad (3)$$

The radial conservative force can be that of standard DPD, *i.e.*,

$$\mathbf{F}_{ij}^U = a_{ij} \left(1 - \frac{r_{ij}}{r_c}\right) \mathbf{e}_{ij} \quad (4)$$

with r_c being the cut-off distance. The *translational force* is given by

$$\begin{aligned}\mathbf{F}_{ij}^T &= -\left[\gamma_{ij}^\perp f^2(r) \mathbf{1} + \left(\gamma_{ij}^\parallel - \gamma_{ij}^\perp\right) f^2(r) \mathbf{e}_{ij} \mathbf{e}_{ij}\right] \cdot \mathbf{v}_{ij} \\ &= -\gamma_{ij}^\parallel f^2(r_{ij}) (\mathbf{v}_{ij} \cdot \mathbf{e}_{ij}) \mathbf{e}_{ij} - \gamma_{ij}^\perp f^2(r_{ij}) [\mathbf{v}_{ij} - (\mathbf{v}_{ij} \cdot \mathbf{e}_{ij}) \mathbf{e}_{ij}]\end{aligned}\quad (5)$$

It accounts for the drag due to the relative translational velocity $\mathbf{v}_{ij}$ of particles i and j . This force is decomposed into two components: one along and the other perpendicular to the lines connecting the centers of the particles. Correspondingly, the drag coefficients are denoted by $\gamma_{ij}^\parallel$ and $\gamma_{ij}^\perp$ for a “*central*” and a “*shear*” component, respectively. We note that the central component of the force is identical to the dissipative force of standard DPD.

The *rotational force* is defined by

$$\mathbf{F}_{ij}^R = -\gamma_{ij}^\perp f^2(r_{ij}) [\mathbf{r}_{ij} \times (\lambda_{ij} \boldsymbol{\Omega}_i + \lambda_{ji} \boldsymbol{\Omega}_j)] \quad (6)$$

while the *random force* is given by

$$\tilde{\mathbf{F}}_{ij} dt = f(r_{ij}) \left[\frac{1}{\sqrt{3}} \sigma_{ij}^{\parallel} \text{tr}[d\mathbf{W}_{ij}] \mathbf{1} + \sqrt{2} \sigma_{ij}^{\perp} d\mathbf{W}_{ij}^A \right] \cdot \mathbf{e}_{ij} \quad (7)$$

where $\sigma_{ij}^{\parallel} = \sqrt{2k_B T \gamma_{ij}^{\parallel}}$ and $\sigma_{ij}^{\perp} = \sqrt{2k_B T \gamma_{ij}^{\perp}}$ to satisfy the fluctuation-dissipation theorem, $d\mathbf{W}_{ij}$ is a matrix of independent Wiener increments, and $d\mathbf{W}_{ij}^A$ is defined as $d\mathbf{W}_{ij}^{A\mu\nu} = 1/2(d\mathbf{W}_{ij}^{\mu\nu} - d\mathbf{W}_{ij}^{v\mu})$. We used the generalized weight function $f(r) = (1 - \frac{r}{r_c})^s$ with $s = 0.25$ ²⁵ in eqn (5)–(7). Our numerical results in previous studies^{20,26} showed higher accuracy with $s = 0.25$ compared to the usual choice $s = 1$. The standard DPD is recovered when $\gamma_{ij}^{\perp} \equiv 0$, *i.e.*, when the “*shear*” components of the forces are ignored.

Colloidal particles are simulated as single DPD particles, similarly to the solvent particles but of larger size. The particle size can be adjusted with the coefficient a_{ij} of the conservative force (see eqn (4)). However, the standard linear force in DPD defined as in eqn (4) is too soft to model any hard-sphere type particles. To resolve this problem, we adopt an exponential conservative force for the colloid–colloid and colloid–solvent interactions, but keep the conventional DPD linear force for the solvent–solvent interactions. We have found that these hybrid conservative interactions produced colloidal particles dispersed in solvent without overlap, which was quantified by calculating the radial distribution function of colloidal particles.²¹ Moreover, the timestep is not significantly decreased, in contrast to the small timesteps required for the Lennard-Jones potential.²⁴ The radial exponential conservative force is defined as

$$F_{ij}^U = \frac{a_{ij}}{1 - e^{b_{ij}}} \left(e^{b_{ij} r_{ij}/r_c^e} - e^{b_{ij}} \right) \quad (8)$$

where a_{ij} and b_{ij} are adjustable parameters, and r_c^e is its cutoff radius. This exponential force along with the standard DPD linear force is sketched in Fig. 1. The size of a colloidal particle can thus be controlled by adjusting the value of a_{ij} in eqn (8).

The intrinsic size of colloidal particle is determined by the radius of the sphere effectively occupied by a single DPD particle.²¹ In Fig. 2, the domain occupied by a colloidal particle is depicted by the distribution of its surrounding solvent particles. A thin solvation layer of solvent is established next to the boundary of the spherical domain.

To construct the cell model, however, we allow particles in the same RBC to overlap, *i.e.*, the colloidal particles in the same cell still interact with each other through the soft standard DPD linear force (see eqn (4)). The radius of each colloidal particle is chosen to be equal to the radius of the ring, and hence the configuration of RBC is approximately a closed-torus as shown in Fig. 3.

The WLC spring force interconnecting all cell particles in each RBC is given by

$$F_{WLC}^U = \frac{k_B T}{\lambda_p} \left[\frac{1}{4 \left(1 - \frac{r_{ij}}{L_{max}} \right)^2} - \frac{1}{4} + \frac{r_{ij}}{L_{max}} \right] \quad (9)$$

where r_{ij} is the distance between two neighbor beads, λ_p is the persistence length, and L_{max} is the maximum allowed length for each spring. Since the cell also has bending resistance, we incorporate into the ring model bending resistance in the form of “angle” bending forces

dependent on the angle between two consecutive springs. The bending forces are derived from the COS (cosine) bending potential given by

$$U_{ijk}^{COS} = k_b [1 - \cos \theta_{ijk}] \quad (10)$$

where k_b is the bending stiffness, and θ_{ijk} is the angle between two consecutive springs, which is determined by the inner product of $\mathbf{r}_{ij}$ and $\mathbf{r}_{jk}$. Then the bending force on particle j

$$\text{is derived as } F_j^{COS} = - \frac{\partial U_{ijk}^{COS}}{\partial \mathbf{r}_j}.$$

The DPD interactions among different particle types (solvent (S), wall (W), and cell (C) particles) are listed in Table 1. Random force coefficients for different interactions were

obtained according to $\sigma_{ij} = \sqrt{2k_B T \gamma_{ij}}$ with $k_B T = 0.1$. The number densities of both solvent and wall particles were set to $n_S = n_W = 3.0$.

3 Scaling to physical units

The human RBC has an average diameter $D_0^P = 7.82 \mu m$ (superscript P denotes “physical”), and therefore the following length scaling is adopted

$$r_c = \frac{D_0^P}{D_0^D} [m] \quad (11)$$

where the superscript D denotes “DPD”.

Due to the fact that we will perform RBC stretching simulations, it is natural to involve the Young's modulus into the scaling as the main parameter. Matching the real and model

Young's modulus $Y^D \frac{(k_B T)^D}{r_c^2} = Y^P \frac{(k_B T)^P}{m^2}$ provides us with the energy unit scaling as follows

$$(k_B T)^D = \frac{Y^P}{Y^D} \frac{r_c^2}{m^2} (k_B T)^P = \frac{Y^P}{Y^D} \left(\frac{D_0^P}{D_0^D} \right)^2 (k_B T)^P \quad (12)$$

In addition, we define the force scaling by

$$N^D = \frac{(k_B T)^D}{r_c} = \frac{Y^P}{Y^D} \frac{D_0^P}{D_0^D} \frac{(k_B T)^P}{m} = N^P \quad (13)$$

The time scale is given by

$$\tau = \frac{t_i^P}{t_i^D} s = \left(\frac{D_0^P}{D_0^D} \frac{\mu_p^P}{\mu_p^D} \frac{Y_0^D}{Y_0^P} \right) s \quad (14)$$

where t_i is the model time and μ_p is the pure plasma viscosity.

4 RBC mechanics

Here we investigate the elastic properties of the modelled RBC in health but also at various stages of malaria. To probe the RBC mechanical response and the change of its mechanical properties at different malaria stages, we subject the cell to stretching deformation analogously to that in optical tweezers experiments.²⁷ The stretching force is applied in opposite direction to two particles separated by the distance of one diameter of the ring. Note that the viscous properties of the cell and suspending medium do not affect the final stretching, since the RBC deformations are measured after the equilibrium stretched state is achieved for a given force. Firstly, we examine the effect of coarse-graining on stretching response by varying the number of particles (N_c) to model the RBC. Fig. 4 shows the RBC shape evolution from equilibrium (0 pN force) to 100 pN stretching force at different N_c . Note that an increase in the number of particles making up the RBC results in a smoother RBC surface. However, this feature seems to be less pronounced for higher N_c . When we stretch the RBCs with different N_c , we find somewhat different mechanical responses as depicted in Fig. 5. The parameter values used to model the RBC in each case are listed in Table 2. At different N_c we keep the same values of ρ and k_b , while L_{max} and the conservative force parameter a (eqn (4)) are inversely proportional to N_c . Here, ρ determines the Young's modulus, and along with L_{max} and a give the right size of RBC. To match both axial and transverse RBC deformations with the experimental data,²⁷ k_b is adjusted to reach a good agreement, which also gives some contributions to the Young's modulus. The fitted Young's modulus of a RBC is found to be $20.0 \mu\text{N m}^{-1}$. This is in agreement with the value obtained in the finite element simulations.²⁷ The low-dimensional RBC model does not have a shear modulus.

In comparison with the experimental data,²⁷ again we find that an increase of N_c results in better agreement but after $N_c = 10$, the change becomes very small. To gain sufficiently good agreement and keep the computation cost low, we choose $N_c = 10$ for all rest simulations shown herein; this is the accurate minimalistic model that we will employ in our studies.

Fig. 6 (*upper*) presents as points experimental²⁷ axial and transverse RBC deformations at healthy and different stages of the malaria parasite development, and fitted curves are derived from simulations. Here, the fitted Young's modulus of a RBC is found to be 20.0, 54.0, 76.0 and $199.5 \mu\text{N m}^{-1}$ for healthy, ring, trophozoite and schizont parasite stages, respectively. These values are comparable with the experiments.^{27,28} Note that this low-dimensional RBC model with $N_c = 10$ is able to capture the linear as well as the non-linear RBC elastic response. The parameters specified for modeling healthy RBCs and malaria-infected cells at different stages are listed in Table 3.

To estimate the variations of the RBC volume and surface area, we calculate the relative change of the area of the ellipse (A_c) formed by the ring under stretching deformations as $(A_c - A_{c0})/A_{c0}$. Here A_{c0} is the area of the ring before any deformation. The axial diameter of RBC is taken as the major-axis of the ellipse and the transverse diameter is taken as the minor-axis. For healthy RBCs we find that it varies within only 8% in the range of all stretching forces (see Fig. 6 (*lower*)). Therefore, the surface area and hence the volume of RBCs remain approximately constant in this model.

5 RBC dynamics

This section details some key features that an accurate model simulating blood flow has to reproduce. These effects are macroscopic observables arising from mesoscopic (cell-cell and cell-hydrodynamics) interactions, namely the cell-free layer (CFL), the Fahraeus effect and the Fahraeus-Lindqvist effect. There are several experiments *in vivo* and *in vitro* studies

quantifying these phenomena. Below, we show that our low-dimensional RBC model reproduces them quantitatively.

We simulate the flow of a mixture of RBCs in a tube with diameter D , subjected to a body force to mimic a pressure gradient; we also employ periodic boundary conditions in the flow direction (see Fig. 7). The solid wall is represented by fixed frozen particles with thickness of $1 r_c$. Before freezing, the wall particles with a predefined number density ($n_W = 3.0$) have reached equilibrium in a separate simulation. To prevent the penetration of other particles (solvent and cell) into the wall, a reflective (bounce-back) boundary can be used in addition to the interactions between wall and other particles. An adaptive procedure is used to employ additional shear-force on the solvent and cell particles within $1 r_c$ from the wall. This ensures that a no-slip boundary condition is achieved at the wall, and also allows a nearly uniform fluid density next to the wall.²⁹ The tube hematocrit (H_t) varies from 20 to 45% and the tube diameter varies from 10 to 120 μm . The pseudo shear rate of flow defined as $\dot{\gamma} = U/D$ is kept larger than 50 s^{-1} in order to capture the hydrodynamic properties of blood at high shear rates. Here U is the average flow velocity. The parameters listed in Table 1 are determined by matching the calculated CFL and apparent viscosity with the experiments for $H_t = 45\%$ and $D = 40 \mu\text{m}$. Then, we predict the results for other cases with those parameters.

5.1 Cell-free layer

The cell-free layer (CFL) is a near-wall layer of plasma absent of RBCs since they are subject to migration to the tube center in Poiseuille flow. The fluid viscosity of the CFL region is much smaller than that of the core populated with RBCs, thereby providing an effective lubrication effect for the core in the flow. In small tubes, the CFL thickness is significant with respect to the tube diameter resulting in a smaller relative apparent viscosity in comparison with those in larger tubes, where the CFL thickness becomes negligible with respect to the tube diameter.

To determine the CFL thickness we computed the outer edge of the RBC core, which is similar to CFL measurements in experiments.^{30,31,32} Fig. 8 shows a snapshot of the outer edge of the RBC core as well as the computation of the thickness of CFL as the distance from the average location of core edge to the tube wall. The edge of the RBC core is determined as the position of the outermost cell particles plus the radius of a single particle, and averaged over all the snapshots taken after the flow reaches steady state. Discrete samples of δ from the obtained curves were taken every $0.5 \mu\text{m}$ in x . Varying the resolution yields slightly different values of δ ; the standard deviation ranges from 0.1 to $0.3 \mu\text{m}$ in all the runs. Fig. 9 presents CFLs for different tube diameters and tube hematocrits obtained using the low-dimensional model in comparison with *in vitro*^{33,30} and *in vivo* experiments.^{31,32} To verify the model we also compare with the predictions from a multi-scale RBC (MS-RBC) model developed recently by Fedosov *et al.*,¹⁹ in which the RBC is constructed by 500 DPD particles connected by a network of springs combined with bending energy. This MS-RBC model had been proved to be able to reproduce the hydrodynamics of blood correctly.¹⁹

CFLs are found to be wider for lower H_t values and larger tube diameters indicating migration of RBCs to the tube center. It appears that the values of the CFL thickness calculated from the two different models (LD-RBC and MS-RBC) agree well in general. However, in small tubes ($D = 10 \mu\text{m}$), the CFLs predicted by the LD-RBC model are slightly larger, especially for high H_t ($H_t = 0.45$), the discrepancy is more significant. A possible reason for this discrepancy will be discussed later.

A comparison of the simulated CFLs with those obtained in experiments^{30,31,32,33} (see Fig. 9) also shows some discrepancies. Note that our simulations mimic blood flow in rigid and long tubes. Thus, the CFL measurements are carried out after the steady state is reached and further cell migration can be neglected. Bugliarello *et al.*³³ and Reinke *et al.*³⁰ conducted *in vitro* experiments of blood flow at different discharge hematocrits (H_d) in glass tubes where the CFL was measured. Taking into account the Fahraeus effect (see details in the next section), which predicts that H_t should be significantly lower than H_d , our simulation results show a good agreement with their results. CFL values from *in vivo* experiments plotted in Fig. 9 show satisfactory agreement with simulations for high concentration of blood ($H_t = 0.3-0.45$), whereas for low H_t the agreement is rather poor. In fact, available *in vivo* measurements^{31,32} of CFLs show a significant scatter in the results. Yamaguchi *et al.*³⁴ found the CFL in cat cerebral microvessels to be approximately 4 μm (not shown in Fig. 9) and independent of vessel diameters. Maeda *et al.*³¹ reported CFLs in the range 1–2 μm for vessel diameters 25–35 μm at $H_t = 0.45$, where the rabbit mesentery was perfused. Kim *et al.* obtained CFLs in the range of 0.8–3 μm increasing from the diameter 10 μm to 50 μm at $H_t = 0.42$ where the rat cremaster muscle was used. The variability of *in vivo* measurements of the CFL and their discrepancies with simulations shown in Fig. 9 may be due to several reasons^{30–34} such as the existence of the glycocalyx layer, variations in vessel width, use of a short vessel in length, close proximity of the site of CFL measurements to vessel bifurcation, vessel elasticity, insufficient spatial resolution of the measurements, and the difference in size and rheological properties between the RBCs of different species, *e.g.*, rat RBCs and human RBCs.

5.2 Fahraeus effect

The Fahraeus effect is the reduction in tube hematocrit in microvessels relative to the supply hematocrit (also called the feed or discharge hematocrit, H_d , hereafter). This hematocrit reduction depends mainly on the tube diameter and hematocrit. This phenomenon was first reported by Fahraeus (1929)³⁵ and now bears his name. It predicts that the tube hematocrit, H_t , is smaller than the discharge hematocrit, H_d , because of the nonuniform distribution of RBCs across the vessel and the higher velocity of the cells compared to the mean fluid velocity.

Most mathematical descriptions of a steady blood flow in a cylindrical tube using a two-phase fluid model yield three relations for apparent viscosity, tube hematocrit, and core hematocrit based on the overall mass balance of the RBCs and blood in the tube. Consider a two layer model³⁶ for the blood flow with a cylindrical tube of radius R consisting of a central core of radius R_c which contains a RBC suspension of uniform hematocrit H_c , and a cell-free layer outside the core containing plasma. The overall mass balance of the cells in the tube is defined by:

$$QH_d = 2\pi \int_0^R r u(r) h(r) dr \quad (15)$$

in which $Q = 2\pi \int_0^R r u(r) dr$ is the volumetric flow rate of blood and

$$h(r) = \begin{cases} H_c, & 0 \leq r \leq R_c, \\ 0, & R_c < r \leq R, \end{cases} \quad (16)$$

where H_c has a relationship with H_t specified as

$$H_t R^2 = H_c R_c^2. \quad (17)$$

Combining eqn (15) with (16) and (17), we obtain:

$$H_d = \frac{2\pi H_t R^2}{R_c^2} \int_0^{R_c} r u(r) dr. \quad (18)$$

Keeping the same tube hematocrit, the discharge hematocrit increases, when the CFL increases, that is when tube hematocrit is low (relatively more space in the center of the channel) and/or when the tube diameter is large. Fig. 10 shows that our simulations reproduce the Fahraeus effect to a good accuracy in most cases, compared to the empirical formula by Pries *et al.* (1992)³⁷ (based on various experiments), for the hematocrit ratio (H_t/H_d) as a function of tube diameter (D) and tube hematocrit (H_t). However, we note that for small tube ($D = 10 \mu\text{m}$) and high H_t ($H_t = 0.45$), the discrepancy is significant, which results from the inaccurate predictions of the CFL and flow velocity for small tubes by the present model. We will discuss this further in the end of the next section.

5.3 Fahraeus-Lindqvist effect

The Fahraeus-Lindqvist effect (after the discovery by Fahraeus and Lindqvist (1931)³⁸) predicts that the apparent viscosity increases as the tube hematocrit increases (more cell crowding in the tube means higher resistance, hence higher macroscopic viscosity) and/or the tube diameter increases. The relative importance of the CFL to the tube diameter becomes small for large tubes and the lubrication provided by the CFL becomes negligible. The work of Pries *et al.*³⁷ provides a comprehensive database for the description of relative apparent blood viscosity as a function of tube diameter and hematocrit. The combined data base comprises measurements at high shear rates ($> 50 \text{ s}^{-1}$) in tubes with diameters ranging from 3.3 to 1,978 μm at hematocrits of up to 0.6.³⁷ They also presented empirical fitting equations predicting the relative apparent blood viscosity from tube diameter and hematocrit.

The relative apparent viscosity μ_{rel} is defined as

$$\mu_{rel} = \frac{Q_p}{Q}, \quad (19)$$

where Q_p is the volumetric flow rate of a pure plasma flow in the same tube under the same pressure drop P . We compare the velocity profiles of blood flow ($u(r)$) and pure plasma flow ($u_p(r)$) under the same pressure drop P in Fig. 11.

Fig. 12 shows that our simulations reproduce the Fahraeus-Lindqvist effect to a good accuracy in most cases, compared to the empirical formula by Pries *et al.*³⁷ for the apparent viscosity as a function of both tube diameter and tube hematocrit. However, when the tube diameter is close to 10 μm for $H_t = 45\%$, our values are higher than the empirical correlations.

This error can be explained as follows. When the tube size is decreasing, the 3D shape and structure of RBC become increasingly important for the dynamics of blood flow. Therefore, it is expected that this low-dimensional RBC model fails to accurately simulate the blood flow in small tubes, especially at high concentrations. If we examine a single RBC subjected to flow in a small tube, its biconcave shape is expected to transit to a stable parachute

shape.^{39,40} However, in our simulations the low-dimensional RBC, while it acquires a parachute-like shape, does not stay in a parachute-like shape stably, but instead, it flips and becomes flat parallel to the flow direction, and then transits back to a parachute-like shape again. Therefore, on one hand, the CFL becomes wider than expected and provides more lubrication for the blood. On the other hand, these continuous transitions increase the flow resistance, and thus increase the blood viscosity. Also, they make easier for the RBCs to approach each other and form clusters to block the tube, which further increases the blood viscosity. By contrast, at high H_t the latter effect is more significant than the former lubrication effect. To quantify the shape transitions of RBC, we employ the gyration tensor to characterize the different RBC shapes. It is defined as follows

$$G_{mn} = \frac{1}{N_c} \sum_i \left(r_m^i - r_m^C \right) \left(r_n^i - r_n^C \right), \quad (20)$$

where r^i are the cell particle coordinates, r^C is the RBC center-of mass, N_c is the number of particles in a cell (which equals 10 here), and m and n represent different components of coordinates. For this low-dimensional RBC model, the gyration tensor for the initial flat ring shape has two large eigen-values corresponding to the ring diameter and the third zero eigen-value. Transition to the parachute-like shape can be characterized by the third eigen-value as it increases above zero. After that, when the cell becomes flat parallel to the flow direction, the minimum eigen-value decreases to zero again. Fig. 13 (*left*) shows the variation of the minimum eigen-value, characterizing the shape transitions of RBC in a thin tube for early times; after that, the RBC continues its shape transitions, as depicted in Fig. 13 (*right*) for longer times. This is observed only in small tubes of sizes comparable to the cell diameter. In larger tubes, since more cells are involved in the flow, the shape transitions of each RBC are constrained by its neighbor RBCs (see Fig. 7).

6 Blood flow through a constriction

As mentioned in section 5.1 there are regions of the flow that have essentially no cells, *i.e.* cell free layers. When there is a geometrical constriction in the flow, the constriction will enhance the downstream cell free layer artificially. Therefore, the width of the distribution of cells after the constriction shrinks (see Fig. 14), but at different levels, depending on the geometry of the constriction and the deformability of RBCs. Next, we investigate the effects of those different factors. Here we aim to simulate the set-up in the experiment of,²³ where the discharge hematocrit H_D is 2.6%.

The channel height (z) is set to be 75 μm everywhere, including the constriction, whereas the channel width (y) is 100 μm . We consider four different lengths and widths of the constriction as listed in Table 4. The length of the channel before and after the constriction is taken to be 200 μm (see Fig. 14).

We extract the widths of distribution of RBCs up- and downstream, respectively denoted W_1 and W_2 (see Fig. 15), in the same way as we compute the cell free layer in section 5.1. A plot of the ratio W_2/W_1 versus the Reynolds number Re is shown in Fig. 16. The Reynolds

number is calculated as $Re = \frac{\rho Q}{\eta H}$ where ρ is the number density of all particles in the blood, η is the apparent viscosity of blood with $H_D = 2.6\%$ calculated by the empirical formula of Pries *et al.*,³⁷ Q is the flow rate and H is the channel height. The range of Reynolds number was chosen according to the typical value of the Reynolds number used in the experiment, which is about 0.01.²³ The average cell free layer before the constriction is found to be about 4 μm in all the simulations, which is exactly the same as reported in the experiment.²³

Firstly, we studied the effect of the constriction geometry. A plot of the ratio W_2/W_1 versus the Reynolds number Re is shown in Fig. 16 for four different lengths/widths of the constriction (); see also the representative images of the different geometries. The CFL is found to be enhanced significantly for the longer and/or narrower constriction, which is consistent with the experimental observation.²³ From Fig. 16, we also note that in the chosen range of Reynolds number, the ratio W_2/W_1 depends only slightly on the flow rate. This observation is also consistent with the experiment,²³ where insignificant dependence on flow rates was reported.

We also examine the effect of boundary conditions in the z (spanwise) direction. In Fig. 16, we compare the results with those obtained by using a periodic boundary condition in the z direction. With unbounded boundaries, the W_2/W_1 ratio depends strongly on the flow rate.

It was reported in the experiment²³ that the deformability of the red blood cell is another key factor to understand the enhancement of the cell-free layer. Thus, we compare healthy cells with malaria cells. At the schizont parasite stage, malaria cells are about 10 times as rigid as healthy cells (see section 4). In Fig. 17, we plot the ratio W_2/W_1 versus the length of constrictions (constriction 2–4 in Table 4) for both healthy and malaria cells. We observe that the hardened RBCs also show an enhanced downstream cell-free layer. However, the enhancement is less pronounced if compared against the normal RBCs, which is also consistent with the experimental observation.²³

7 Summary

We have developed a low-dimensional RBC model which is able to accurately reproduce RBC mechanics, rheology of blood, and dynamics of blood flow in vessels greater than 10 μm in diameter. The RBC is modelled as a closed-torus like ring consisting of 10 colloidal particles connected by WLC springs. Bending forces derived from the COS bending potential is incorporated to mimic the bending rigidity of RBC. Each colloidal particle is simulated by a single DPD particle as described in our previous work.²¹ The simulations achieve good accuracy in comparison with available experimental results and empirical correlations.

Specifically, we performed stretching simulations of RBC for healthy and different malaria stages. The simulated curves give excellent fits to the experimental data.²⁷ The fitted Young's modulus of a RBC is found to be $20.0 \mu\text{N m}^{-1}$ for the healthy RBC, $54.0 \mu\text{N m}^{-1}$ for the ring stage, $76.0 \mu\text{N m}^{-1}$ for the trophozoite stage, and $199.5 \mu\text{N m}^{-1}$ for the schizont stage, which is consistent with the experiments.^{27,28} This demonstrates that this low-dimensional RBC model is able to capture linear as well as non-linear RBC elastic response.

Furthermore, we modelled blood as a suspension of RBCs and performed simulations to study some key features that an accurate model simulating blood flow has to reproduce, *i.e.*, the cell-free layer (CFL), the Fahraeus effect, the blunt velocity profile, and the Fahraeus-Lindqvist effect. The tube hematocrit H_t ranged from 0.2 to 0.45 and tube diameters varied from 10 to 120 μm . Our simulations yield good agreement with experimental data and empirical correlations in most cases, except when the tube diameter becomes comparable to the diameter of RBC in high concentrate blood, *e.g.*, $H_t = 0.45$. It is due to the insufficiently accurate representation of the 3D structure and shape of RBC in this low-dimensional model.

Finally, we studied the effect of a geometrical constriction on the enhancement of the downstream cell-free layer in the flow. In particular, we investigated the dependence of this effect on the flow rate, the length and width of the constriction and the deformability of the

cells. We find that longer and/or narrower constriction, and highly deformable cells will further increase the enhancement of the downstream cell-free layer.

Compared with the multi-scale RBC (MS-RBC) model, the proposed model takes much less computational cost. Particularly, each RBC consists of only 10 DPD particles, which is $\frac{1}{50}$ of the 500 DPD particles in the MS-RBC model. Furthermore, the diameter of each LD-RBC is 4 in DPD units, only one half of the MS-RBC, which is 8 in DPD units. Therefore, for the same simulation the domain can be $\frac{1}{25}$ of that in the MS-RBC simulations, and as a result in our model we need only $\frac{1}{8}$ of the solvent particles used in the MS-RBC simulations, while keeping the same number density. Thanks to this low computational cost, the model significantly improves the efficiency of simulating blood flow in large and long vessels, *e.g.*, in arterioles and arteries. We are currently using this model to compute the bulk viscosities of blood, accounting also for the effect of aggregation, in a wide range of shear rates and we will report our results in a future publication.

The model also has limitations. As mentioned above, the model is unable to represent the exact 3D shape and structure of RBCs, which gives rise to the difficulty in simulations of blood flow in capillaries of sizes comparable to the cell diameter. A finer model with a few more internal layers of particles may help to resolve this problem. Moreover, this model does not include all information about the RBC membrane, which consists of a lipid bilayer with an attached cytoskeleton formed by a network of the protein spectrin linked by short filaments of actin. The membrane's elasticity is attributed to the attached spectrin network, as is the integrity of the entire RBC when subjected to severe deformations in capillaries as small as 3 μm . The metabolic activity can affect this spectrin network and thereby the entire RBC properties, through the consumption of adenosine triphosphate (ATP), according to ref. 41, 42 and 43. Therefore, it will be an interesting future topic to incorporate into this low-dimensional RBC model a membrane with an active spectrin network.

Acknowledgments

This work was supported by the NSF/CBET (0852948) and NIH (R01HL094270) grants. Computations were performed at NSF's NICS facilities.

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Fig. 1.

The exponential force distribution adopted in this work. Here, $r=r_{ij}/r_c^e$ and $F=F_{ij}^U/a_{ij}$.

Fig. 2.
The number density of solvent particles around a single colloidal particle with solvation indicated by a thin surface layer of higher density.

Fig. 3.
A sketch of the low-dimensional closed-torus like RBC model.

Fig. 4. RBC shape evolution at different N_c (number of particles to model a RBC) and stretching forces.

Fig. 5. RBC axial and transverse diameters under deformation for healthy RBCs at different N_c in comparison with the experiments.²⁷

Fig. 6. (*Upper*) RBC axial and transverse diameters under deformation for healthy and malaria RBCs, in comparison with the experiments.²⁷ (*Lower*) Estimation of the relative change of the area (A_c) formed by the ring under stretching deformations to quantify the variations of the RBC surface area in this model.

Fig. 7. Blood flow simulated in a tube with $D = 40 \mu\text{m}$ at $H_t = 0.45$. Solvent particles are not displayed here for better visualization of the RBCs.

Fig. 8.

An example of a RBC core edge and computation of cell-free layer thickness for $H_t = 0.3$ and $D = 20 \mu\text{m}$. (The horizontal axis is the centerline of the tube).

Fig. 9.
Cell-free layer thickness *versus* tube diameter (D).

Fig. 10.

The Fahraeus effect: the increase of apparent hematocrit (H_t/H_d) with tube hematocrit (H_t) and tube diameter (D). The simulation data () are compared with empirical correlations () by Pries *et al.*³⁷

Fig. 11.

The velocity profile of blood (—) relative to the velocity of plasma (---) under the same pressure drop P , computed for tube diameter $D = 40 \mu\text{m}$ at different tube hematocrits. The positions where the cell-free layer starts for each case are marked by the vertical -.- lines for reference.

Fig. 12.

The apparent viscosity as a function of tube diameter at different tube hematocrit. Simulation data (●) are compared with empirical correlations (---) by Pries *et al.*³⁷

Fig. 13.

The minimum eigen-value of the gyration tensor characterizing the shape transitions of RBC in the tube flow, for (*left*) short times and (*right*) longer times. Here the tube diameter $D = 9 \mu\text{m}$.

Fig. 14.
A snapshot of the red blood cells in the channel with a geometrical constriction.

Fig. 15.
The number density distribution of RBCs along the entire channel.

Fig. 16.

The ratio of the widths of distribution of RBCs W_2/W_1 versus Reynolds number Re for different geometries of the constriction (see Table 4).

Fig. 17.

The ratio of the widths of distribution of the red blood cells W_2/W_1 with respect to cell stiffness for various L (constriction 2–4, see Table 4). Here, $Re \approx 0.01$.

Table 1

Parameters of the DPD interactions in simulations

Interaction	Radial conservative force linear (eqn (4))	$\parallel =$	r_c
S-S and S-W	$a = 2.5$	4.5	1.5
C-C (same cell)	$a = 500$	4.5	1.2
	radial conservative force exponential (eqn (8))		
C-C (different cell)	$a = 2500, b = 20, r_c^e = 2.0$	4.5	2.0
S-C	$a = 2500, b = 20, r_c^e = 1.0$	900	1.5
W-C	$a = 500, b = 20, r_c^e = 2.3$	900	2.5

Table 2

Parameters of the conservative force (eqn (4)), the WLC spring and bending stiffness specified to model healthy RBCs at different N_c

N_c	a (eqn (4))	L_{max}	p	k_b
6	2000	2.17	0.0005	50
10	500	1.3	0.0005	50
20	100	0.65	0.0005	50

Table 3

Parameters of the conservative force (eqn (4)), the WLC spring and bending stiffness specified to model healthy RBCs and malaria-infected cells at different stages of parasite development

RBC	a (eqn (4))	L_{max}	p	k_b
healthy	500	1.3	0.0005	50
ring	2000	1.3	0.0001	50
trophozoite	3250	1.3	0.00005	200
schizont	2750	1.3	0.00005	500

Table 4

Widths and lengths of the four types of geometries of the constriction adopted in this work

Constriction	$w(\mu\text{m})$	$L(\mu\text{m})$
1	50	50
2	25	50
3	25	100
4	25	200