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Predicting dynamics and rheology of blood flow: A comparative study of multiscale and low-dimensional models of red blood cells

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Abstract

We compare the predictive capability of two mathematical models for red blood cells (RBCs) focusing on blood flow in capillaries and arterioles. Both RBC models as well as their corresponding blood flows are based on the dissipative particle dynamics (DPD) method, a coarse-grained molecular dynamics approach. The first model employs a multiscale description of the RBC (MS-RBC), with its membrane represented by hundreds or even thousands of DPD-particles connected by springs into a triangular network in combination with out-of-plane elastic bending resistance. Extra dissipation within the network accounts for membrane viscosity, while the characteristic biconcave RBC shape is achieved by imposition of constraints for constant membrane area and constant cell volume. The second model is based on a low-dimensional description (LD-RBC) constructed as a closed torus-like ring of only 10 large DPD colloidal particles. They are connected into a ring by worm-like chain (WLC) springs combined with bending resistance. The LD-RBC model can be fitted to represent the entire range of nonlinear elastic deformations as measured by optical-tweezers for healthy and for infected RBCs in malaria. MS-RBCs suspensions model the dynamics and rheology of blood flow accurately for any vessel size but this approach is computationally expensive for vessel diameters above 100 microns. Surprisingly, the much more economical suspensions of LD-RBCs also capture the blood flow dynamics and rheology accurately except for small-size vessels comparable to RBC diameter. In particular, the LD-RBC suspensions are shown to properly capture the experimental data for the apparent viscosity of blood and its cell-free layer (CFL) in tube flow. Taken together, these findings suggest a hierarchical approach in modeling blood flow in the arterial tree, whereby the MS-RBC model should be employed for capillaries and arterioles below 100 microns, the LD-RBC model for arterioles, and the continuum description for arteries.

Keywords

microcirculation; apparent viscosity; cell-free layer; dissipative particle dynamics

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1 Introduction

Red blood cells (RBCs) constitute nearly one-half of the blood volume ($\sim 5 \times 10^6/\text{mm}^3$), and therefore blood flow is greatly influenced by their biophysical characteristics. Typically, a human RBC has a biconcave shape of approximately $8 \mu\text{m}$ in diameter and $2 \mu\text{m}$ in thickness, and is highly deformable [1,2]. The behavior of RBCs in flow is affected by their viscoelastic rheological properties [3] and by their concentration or hematocrit. As a consequence of RBC size and deformability, the features of blood flow may change greatly with the vessel diameter. In vessels with diameter larger than approximately $200 \mu\text{m}$, blood flow can be accurately modeled as a homogeneous fluid using a continuum description in terms of the Navier-Stokes equations [2]. However, in vessels with a smaller diameter, i.e., in arterioles, venules, and capillaries, the two-phase nature of blood as a suspension of RBCs is essential. Therefore, detailed *quantitative understanding* of blood flow in microcirculation requires explicit modeling of RBCs and is necessary for many physiological processes such as the hemodynamic resistance and its regulation in the microcirculation, transport of oxygen and nutrients, and immunological and inflammatory responses.

Development of an efficient and accurate RBC model has been a long-standing effort, leading to a number of numerical models of deformable cells which utilize a continuum description [4–7] or a discrete RBC representation at the spectrin molecular level [8,9] as well as at the mesoscopic scale [10–13]. Continuum models often suffer from high computational expense due to non-trivial coupling between nonlinear solid deformations and fluid flow. Similarly, detailed spectrin molecular models of RBCs are very limited by the excessive computational cost. Mesoscopic modeling of RBCs leads to sufficient accuracy at affordable computational cost.

Several mesoscopic RBC models [10,11,13,14] have been developed recently. Most of them employ a similar idea whereby the RBC cytoskeleton and membrane are represented by a network of springs in combination with bending rigidity and constraints for surface-area and volume conservation. Dupin et al. [11] coupled a discrete RBC to a fluid modeled by the lattice Boltzmann method (LBM) [15]. Noguchi and Gompper [10] modeled RBCs and vesicles within the Multiparticle Collision Dynamics framework [16]. Pivkin and Karniadakis [13] employed Dissipative Particle Dynamics (DPD) [17] for a multiscale RBC model, while Fedosov and Karniadakis [14] have extended this model to accurately capture the viscoelastic properties of the RBC membrane and to incorporate the external/internal fluid viscosity contrast, which were not taken into account in most of the previous models. Despite of the current developments of RBC models, all of the methods above still suffer from high computational expense if several thousand RBCs have to be modeled. As a consequence, there have been a few mesoscopic simulations [18,19] of blood flow in large vessels ($D \sim 100 \mu\text{m}$), which employed *two-dimensional* RBC models. Even though two-dimensional models may qualitatively capture the behavior of a RBC suspension, their quantitative predictions have to be considered cautiously, since RBC motion and deformation in flow are inherently three-dimensional.

A more recent development is the use of colloidal particles [20] in constructing red blood cell models leading to a very efficient approach as first demonstrated in [21]. In the current work, we investigate the accuracy of this new low-dimensional RBC (LD-RBC) model, where a RBC is modeled as a ring of 10 colloidal particles connected by the worm-like chain (WLC) springs. Each colloidal particle is represented by a single DPD particle using a new DPD formulation [22], which augments the standard DPD method by introducing non-central dissipative shear interactions between particles, hence conserving angular momentum. In addition, the bending rigidity of RBC is incorporated into the ring model through an angle bending resistance between two consecutive springs. In particular, we

compare the LD-RBC model with the multiscale (MS-RBC) model [14], which accurately captures the RBC's three-dimensional membrane geometry and viscoelastic properties. First, we test the RBC mechanical response of the two models against optical tweezers stretching experiments [23]. Subsequently, we examine the rheological properties of blood modeled as suspensions of MS-RBCs or LD-RBCs by monitoring the blood apparent viscosity and cell-free layer (CFL) and compare against available experimental data. While the MS-RBC model leads to accurate predictions of the dynamic and rheologic properties of blood flow, its applicability is limited by its computational cost. The LD-RBC model is also accurate except in capillaries (below 15 – 20 microns) but it is about two orders of magnitude computationally cheaper than the MS-RBC. Figure 1 shows a schematic diagram of applicability of the two models with respect to characteristic vessel diameters. For the large vessels the use of continuum description leads to even higher computational efficiency. Hence, in this paper we will show that the LD-RBC model is accurate and efficient for the range of the vessel diameters between 50 μm and 200 μm , where the MS-RBC model is very expensive and homogeneous continuum modeling of blood does not provide an adequate description.

The paper is organized as follows. In section 2 we describe both RBC models and the proper scaling between physical and model units; more details are in the supporting material. Section 3 presents a comparison of RBC stretching response of both models and contains the results of blood flow in vessels including flow velocity profiles, blood apparent viscosity, and CFLs. We conclude in section 4 with a brief discussion.

2 Methods

RBCs and their suspending fluid are modeled using the Dissipative Particle Dynamics (DPD) method [17]. DPD is a mesoscopic particle-based method, where each particle represents a *lump* of atoms or molecules rather than an individual atom or molecule. A detailed description of the DPD method can be found elsewhere [17,24] and in the supporting material.

2.1 Low-dimensional RBC model

The detailed derivation of this model as well as the list of all required parameters can be found in [21]. Here we provide a brief review. The LD-RBC is modeled as a ring of 10 colloidal overlapping particles connected by the worm-like chain (WLC) springs. Each colloidal particle is simulated by a single DPD particle using a new DPD formulation [22], where the dissipative forces acting on a particle are explicitly divided into two separate components: *central* and *shear* (non-central) components. It 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 quantitatively correct hydrodynamic characteristics of colloidal suspensions [20]. More details on the new formulation can be found in the supporting material.

To construct the cell model we allow colloidal particles in the same RBC to overlap, i.e., the colloidal particles in the same cell interact with each other through soft conservative forces. The radius of each colloidal particle is chosen to be equal to the radius of the ring, and hence the configuration of a RBC is approximately a closed-torus as shown in Figure 2 (left).

Neighboring colloidal particles in the LD-RBC construction are connected by the WLC attractive springs with the following forces

$$F_{wlc} = \frac{k_B T}{\lambda_p} \left[\frac{1}{4(1-x_j)^2} - \frac{1}{4} + x_j \right], \quad (1)$$

where $x_j = l_j/l_m$ with l_j being the length of the spring j and l_m is the maximum spring extension, λ_p is the persistence length, and $k_B T$ is the energy unit. Since the RBC membrane has bending resistance, the LD-RBC model also incorporates the bending resistance between two consecutive springs. The bending forces are derived from the cosine (COS) bending potential given by

$$U_{ijk}^{COS} = k_b [1 - \cos(\theta_{ijk})], \quad (2)$$

where k_b is the bending stiffness and θ_{ijk} is the angle between two consecutive springs.

Here, λ_p mainly determines the Young's modulus. However, to match both axial and transverse RBC deformations under stretching with the experimental data [23], k_b is adjusted to reach a good agreement, which also gives some contribution to the Young's modulus. The LD-RBC model does not have the membrane shear modulus.

Since the thickness of LD-RBC model is constant, we estimate the variations of the RBC volume and surface area under stretching by calculating the relative change of the area formed by the ring under stretching. For healthy RBCs we find that it varies within only 8% in the range of all stretching forces [21]. Therefore, the surface-area and hence, the volume of RBCs remain approximately constant in the LD-RBC model. The volume of a LD-RBC is equal to approximately $158 \mu m^3$, which is about 50% larger than that of a MS-RBC. The LD-RBC appears to be thicker than a MS-RBC, while the cell radius is the same for both models.

Furthermore, we examine the effect of coarse-graining on stretching response by varying the number of particles (N_c) to model the RBC. We find that an increase in the number of particles making up the RBC results in a smoother RBC surface [21]. In comparison with the optical tweezers data [23], again we find that an increase of N_c results in better agreement, but for $N_c \geq 10$ the differences in model predictions become negligible [21]. Thus, to gain sufficiently good agreement and keep the computation cost low, we choose $N_c = 10$ for all simulations; this is an accurate minimalistic model that we will employ in our studies.

2.2 Multiscale RBC model

The membrane of MS-RBC is constructed by N_v DPD particles with coordinates $\{\mathbf{x}_{i=1 \dots N_v}\}$, which are vertices of a two-dimensional triangulated network on the RBC surface [8,14], see figure 2 (right). The surface area and volume of the MS-RBC are equal to $135 \mu m^2$ and $94 \mu m^3$, respectively. The network nodes are connected by N_s springs with potential energy

$$V_s = \sum_{j \in 1 \dots N_s} \left[\frac{k_B T l_m (3x_j^2 - 2x_j^3)}{4\lambda_p (1-x_j)} + \frac{k_p}{(n-1)l_j^{n-1}} \right], \quad (3)$$

where l_j is the length of the spring j , l_m is the maximum spring extension, $x_j = l_j/l_m$, λ_p is the persistence length, $k_B T$ is the energy unit, k_p is the spring constant, and n is a power. The above equation includes the attractive worm-like chain potential and a repulsive potential for $n > 0$ such that a non-zero equilibrium spring length can be imposed. The RBC membrane

viscosity is incorporated into the RBC model through a dissipation added to each spring. Following the general framework of the fluid particle model [25] a combination of dissipative and random forces [14] is added to each spring that satisfies the fluctuation-dissipation balance providing consistent temperature of the RBC membrane in equilibrium.

The bending resistance of the RBC membrane is modeled by the COS potential as in the case of the LD-RBC, i.e.,

$$V_b = \sum_{j \in 1 \dots N_t} k_b [1 - \cos(\theta_j - \theta_0)], \quad (4)$$

where k_b is the bending constant, θ_j is the instantaneous angle between two adjacent triangles having the common edge j , and θ_0 is the spontaneous angle.

The MS-RBC model also includes the area and volume conservation constraints, which mimic area-incompressibility of the lipid bilayer and incompressibility of the interior fluid, respectively. The corresponding energy is given by

$$V_{a+v} = \sum_{j \in 1 \dots N_t} \frac{k_d (A_j - A_0)^2}{2A_0} + \frac{k_a (A - A_0^{tot})^2}{2A_0^{tot}} + \frac{k_v (V - V_0^{tot})^2}{2V_0^{tot}}, \quad (5)$$

where N_t is the number of triangles in the membrane network, A_0 is the triangle area, and k_d , k_a and k_v are the local area, global area and volume constraint coefficients, respectively. The terms A and V are the total RBC area and volume, while A_0^{tot} and V_0^{tot} are the specified total area and volume, respectively. More details on the RBC model can be found in [26,14].

Extension of the linear analysis of [27] for a regular hexagonal network allows us to uniquely relate the model parameters to the network macroscopic elastic properties, bending rigidity, and membrane shear viscosity, see [26,14] for more details. In practice, the macroscopic membrane properties serve as an input to be used to calculate the necessary model parameters without any manual adjustment. The membrane network that assumes the same equilibrium lengths of all tethers may develop local “bumps” due to stress anomalies in a membrane triangulation since a network on a closed surface cannot consist of triangles whose edges have the same lengths. Such local stress artifacts depend on the network regularity and the ratio of the membrane elastic and bending contributions. To eliminate the stress artifacts we employ a “*stress-free*” model obtained by computational annealing. Thus, the equilibrium length l_0^i of each spring is set to the edge length after triangulation. This modification provides a network free of local stress anomalies.

Both internal and external fluids are simulated by a collection of free DPD particles and are separated by the cell membrane through bounce-back reflections of them at the membrane surface. Moreover, a dissipative force between fluid particles and membrane vertices is set properly to account for the no-slip boundary conditions at the membrane surface.

2.3 Scaling to physical units

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

$$r_c = \frac{D_0^P}{D_0^D} [m], \quad (6)$$

where the superscript D denotes “DPD”.

Due to the fact that we will perform RBC stretching simulations to obtain the mechanical properties of the models, it is natural to involve the Young’s modulus Y into the scaling as the main parameter. Hence, energy and force scales are given by

$$(k_B T)^D = \frac{Y^P}{Y^D} \left(\frac{D_0^P}{D_0^D} \right)^2 (k_B T)^P, \quad N^D = \frac{Y^P}{Y^D} \frac{D_0^P}{D_0^D} N^P, \quad (7)$$

where “N” denotes Newton. In addition, we define the time scale as follows

$$\tau = \frac{D_0^P}{D_0^D} \frac{\mu_p^P}{\mu_p^D} \frac{Y_0^D}{Y_0^P} s, \quad (8)$$

where τ is the model time, μ_p is the plasma viscosity, and s denotes seconds.

3 Results

In this section the LD-RBC and MS-RBC models are compared through a number of tests. First, single RBCs of both models are subjected to stretching deformation and are compared against experimental data from optical tweezers. This is an important first step serving two objectives: (i) to extract the important mechanical parameters of the model (e.g. shear modulus); and (ii) to validate the single RBC model under large nonlinear deformation conditions. Subsequently, these validated single RBC models are used to create suspensions in order to evaluate the dynamic and rheologic response of blood flow in microvessels. To this end, we compare against available experimental data for corresponding flow velocity profiles, blood apparent viscosities, and cell-free layers for different vessel diameters and hematocrit values. The implicit assumption made here is that the small fraction of white cells and platelets in whole blood will not affect its dynamic and rheologic behavior; indeed, the results presented here validate this assumption. A complete set of simulation parameters for the both RBC models can be found in the supporting material.

3.1 RBC stretching test

The RBC mechanical response of both models is probed by subjecting a single RBC to stretching deformation analogously to the optical tweezers experiments [23]. Figure 3 shows a sketch of both RBC models under stretching deformation. The stretching force f is applied in opposite directions to a set of particles drawn as black spheres in case of the MS-RBC model and to two particles separated by the distance of one diameter of the ring in case of the LD-RBC model. Note that the viscous properties of the cell and suspending media do not affect the final stretching since RBC deformations are measured after the equilibrium stretched state is achieved for a given force. Figure 4 presents as points experimental axial and transverse RBC diameters under deformation [23] for a healthy RBC and for a RBC at the latest stage (schizont) of intra-erythrocytic parasite development in malaria disease. Simulation results of both the MS-RBC and LD-RBC models are depicted by lines. The simulated curves are in excellent agreement with the experimental data for both RBC models. The RBC Young’s modulus is found to be $18.9 \mu\text{N/m}$ and $180.0 \mu\text{N/m}$ for healthy

RBC and at the schizont stage, respectively, in case of the MS-RBC model, while the LD-RBC model yields the values of $20.0 \mu N/m$ and $199.5 \mu N/m$, respectively. Note that the LD-RBC model captures the linear as well as the non-linear RBC elastic response.

3.2 Blood flow

Blood is modeled as a suspension of RBCs and simulations are performed for two tube hematocrit values of 30% and 45%, and for various tube diameters within the range from $10 \mu m$ to $120 \mu m$. Blood flow in a tube is sustained by subjecting the mixture of RBCs and solvent particles to a body force, which is equivalent to a constant pressure gradient in Poiseuille flow. The no-slip boundary conditions on the tube wall are imposed using frozen wall particles in combination with an adaptive wall shear force and bounce-back reflection of the solvent and RBC particles at the fluid-solid interface. In a pre-processing stage, the wall particles are allowed to move until the equilibrium state is reached. Then, the particles, which occupy the region of solid walls, are frozen in order to model the wall. This allows us to have a nearly uniform fluid density next to the tube wall. More details on the adopted no-slip boundary conditions can be found in [28,29]. The thickness of the wall is equal to one r_c which is the DPD cutoff radius. The wall particles have the same density as that of the solvent particles.

3.2.1 Velocity profiles—The simulations presented here include two tube hematocrits and several tube diameters between $10 \mu m$ and $120 \mu m$. The blood flow is driven by a uniform body force per unit mass (f) applied to both solvent and RBC particles in the flow direction. It is equivalent to the pressure gradient $\Delta P/L = \rho f$, where ΔP is the pressure drop over the tube length L and ρ is the suspension's mass density. Figure 5 compares the velocity profiles of blood flow ($u(r)$) and the flow of pure plasma ($u_p(r)$) under the same pressure drop ΔP for different hematocrits and tube diameters. The blunt velocity profiles for different RBC models are in good agreement for a larger tube diameter. For small tube diameters ($D \sim 10 \mu m$) and high hematocrit ($H_t = 45\%$) the LD-RBC model significantly underpredicts the development of the velocity profile since it does not accurately represent the three-dimensional RBC shape and structure, which are of importance for tube diameters comparable with the RBC size.

Figures 6 and 7 show the corresponding sample snapshots of blood flow for different models and hematocrits for the tube diameters $D = 10 \mu m$ and $D = 40 \mu m$, respectively. RBCs in Poiseuille flow migrate towards the tube center resulting in the formation of a core of the flow consisting mainly of RBCs. A RBC core is visually observed with a thin plasma layer or cell-free layer near the tube walls. The cell core of the flow results in plug-like velocity profiles shown above in figure 5.

3.2.2 Relative apparent viscosity—Fahraeus and Lindqvist [30] found that the apparent viscosity of blood increases as the tube hematocrit increases (more cell crowding in the tube results in a higher resistance, and hence higher macroscopic viscosity) and/or as the tube diameter increases. RBCs migrate to the tube center yielding the formation of the CFL near the wall, which serves as an effective lubrication for the viscous blood flow core. In small tubes the CFL thickness is comparable with the tube diameter resulting in a lower apparent viscosity of blood in comparison with large tubes, where the CFL becomes negligible. The work of Pries et al. [31] provides a comprehensive database for the description of relative apparent blood viscosity as a function of tube diameter and hematocrit. They compiled various viscosity measurements in tubes with diameters ranging from 3.3 to $2000 \mu m$ with hematocrits of up to 60% and at high shear rates ($\dot{\gamma} > 50 s^{-1}$). They also fitted experimental viscosity data with the empirical equations, which predict relative apparent blood viscosity for a fixed tube diameter and hematocrit value.

In this work the average shear rate ($\dot{\gamma}$) is varied from 30 to 70 s^{-1} . The relative apparent viscosity μ_{rel} is defined as

$$\mu_{rel} = \frac{Q_p}{Q}, \quad (9)$$

where Q is the volumetric flow rate of blood defined as $Q = 2\pi \int_0^R ru(r)dr$ and Q_p is the volumetric flow rate of the pure plasma flowing in the same tube with the same pressure drop ΔP . Figure 8 shows the computed relative apparent viscosity as a function of both tube diameter and tube hematocrit in comparison with the empirical formula by Pries et al. [31]. Good agreement between simulations (LD-RBC and MS-RBC) and experiments in most cases confirms that the LD-RBC model is able to capture realistic blood flow properties and rheology. In case of small tubes ($D \sim 10 \mu m$) and large hematocrit ($H_t = 45\%$) the values obtained with LD-RBC model are significantly higher than the empirical predictions and the MS-RBC results. This discrepancy is caused by the simplified representation of the RBC structure, which becomes essential for blood flow behavior in tubes of a small diameter.

3.2.3 Single cell in Poiseuille flow—Next, we examine a single RBC in a very narrow tube, where experiments [32–34] show that a RBC transits from its biconcave shape to a stable parachute-like shape. The inset plots in figure 9 illustrate RBC shapes for the MS-RBC and LD-RBC models. LD-RBC simulations reveal that a RBC does not necessarily retain the parachute-like shape. It may flip in the flow with several intermediate positions which correspond to a RBC aligned along the flow direction and a RBC across the flow. This erroneous behavior may enhance the apparent blood viscosity for small vessels as shown in figure 8. To quantify the RBC behavior in tube flow for different models we employ the gyration tensor, which characterizes the RBC shape. It is defined as follows

$$G_{mn} = \frac{1}{N_c} \sum_i (r_m^i - r_m^C)(r_n^i - r_n^C), \quad (10)$$

where r^i are the cell particle coordinates, r^C is the RBC center-of-mass, N_c is the total number of particles in a cell, and m, n represent different components of coordinates. For the LD-RBC model with an initial flat-ring shape the gyration tensor has the minimum eigen-value equal to zero, while the other two large eigen-values correspond to the ring diameter. The transition to the parachute-like shape is then characterized by the minimum eigen-value as it increases starting from zero. For the MS-RBC model the biconcave-to-parachute transition can be also characterized by the minimum eigen-value of the gyration tensor as it increases from its lowest value which corresponds to the equilibrium RBC shape. Figure 9 shows the variation of the minimum eigen-value of the gyration tensor for the LD-RBC and MS-RBC models. The minimum eigen-value for the MS-RBC model increases from its equilibrium value to that of the parachute shape and remains virtually constant. This indicates that the parachute shape is stable in agreement with experimental observations. In the case of LD-RBC model the minimum eigen-value does not remain constant indicating that the LD-RBC model cannot reproduce stable RBC parachute shape in Poiseuille flow in very small capillaries, i.e., below 15 – 20 μm .

3.2.4 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 to 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 δ we measured the outer edge of the RBC core similarly to CFL measurements in experiments [35–37]. Figure 10 shows a snapshot of the outer edge of the RBC core as well as the measurement of the CFL thickness as the average distance from the core edge to the tube wall. The edge of RBC core is determined by the position of outermost RBCs, and is averaged over all the snapshots taken after the flow has reached steady state. Discrete samples of δ from the obtained curves were taken every $0.5 \mu\text{m}$ along the flow direction. Varying this resolution yields slightly different values of δ , with the standard deviation ranges from 0.1 to $0.3 \mu\text{m}$ in all runs.

Figure 11 presents CFLs for different tube diameters and tube hematocrits using the LD-RBC and MS-RBC models in comparison with in vitro [35,38] and in vivo experiments [36,37]. We find that the simulated CFLs are consistent with the predictions of Fahraeus and Fahraeus-Lindqvist effects [39,30]. CFLs are wider for lower H_t values and larger tube diameters indicating migration of RBCs to the tuber center. It appears that CFL thicknesses calculated from different models (LD-RBC and MS-RBC) agree well in general. However, we have to point out that for the same aforementioned reason, in case of a small tube diameter ($D = 10 \mu\text{m}$) the CFL thickness predicted by the LD-RBC model is slightly larger than that obtained with the MS-RBC model. For high hematocrit ($H_t = 0.45$) the calculated CFL thickness for the tube diameter $D = 10 \mu\text{m}$ is even larger than the value at $D = 20 \mu\text{m}$, which is obviously inconsistent with the predictions of Fahraeus and Fahraeus-Lindqvist effects [39,30]. The previously described flipping of RBCs in tube flow for the LD-RBC model results in a slight enhancement of CFL in small diameter tubes.

Comparison of the simulated CFLs and those obtained in experiments [35–38] in figure 11 shows partial agreement. Several differences between simulations and experiments may contribute to the discrepancies. Note that the simulations mimic blood flow in rigid and infinitely-long tubes, while experiments employ finite tube or vessel length. Thus, the CFL measurements in simulations are carried out after the steady state is reached and further cell migration can be neglected. Bugliarello et al. [38] and Reinke et al. [35] 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 [39], which predicts that H_t should be lower than H_d , our simulation results show a good agreement with their results.

CFLs from in vivo experiments plotted in figure 11 show satisfactory agreement with simulations for high hematocrit values ($H_t = 0.3 - 0.45$), whereas for low H_t the agreement is rather poor. In fact, available in vivo measurements [36,37] of CFLs show a significant scatter in the results. Yamaguchi et al. [40] found the CFL in cat cerebral microvessels to be approximately $4 \mu\text{m}$ (not shown in figure 11) and independent of the vessel diameter. Maeda et al. [36] reported CFLs in the range $1-2 \mu\text{m}$ for the vessel diameters $25-35 \mu\text{m}$ at $H_t = 0.45$, where the rabbit mesentery was perfused. Kim et al. [37] obtained CFLs in the range of $0.8-3 \mu\text{m}$ increasing from the diameter of $10 \mu\text{m}$ to $50 \mu\text{m}$ 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 figure 11 may be due to several reasons 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, and spatial resolution of the measurements [35–38].

4 Discussion

We have presented a comparison of mechanics, dynamics, and rheology of blood flow in capillaries and arterioles modeled as a suspension of RBCs represented by a multiscale (MS-RBC) and a low-dimensional (LD-RBC) network-spring type descriptions. The two models were compared in identical flow conditions, i.e. at the same pressure drop. The MS-RBC model incorporates the viscous dissipation of lipid bilayer into the membrane whereas the LD-RBC model does not. The solvent in both cases is also simulated explicitly using the DPD approach. The MS-RBC has been extensively validated in reproducing accepted experimental results for both tumbling and tank-treading responses [14]. However, since the LD-RBC model does not include the membrane properties, only tumbling is observed but not tank-treading. Both models are able to predict accurately in shear flows the viscoelastic behavior of RBC suspensions, and even the formation of RBC aggregates.

In the current work we performed cell stretching simulations for healthy RBCs and infected cells in malaria. The results from both models are in excellent agreement with the optical tweezers experiments; the LD-RBC model yields the Young's modulus of 20.0 and 199.5 $\mu\text{N/m}$ for healthy RBCs and infected RBCs at the schizont stage of parasite development, respectively, which is in close agreement with the corresponding MS-RBC values. This demonstrates that the LD-RBC model is able to capture linear as well as non-linear RBC elastic response. In the LD-RBC model, the parameter λ_p of the WLC spring and the parameter k_b of the bending force determine the Young's modulus. We found that the number of particles $N_c = 10$ in the LD-RBC model is enough to yield sufficiently accurate RBC representation; this is the most accurate minimalistic model that we employ in blood flow modeling. In the MS-RBC model, besides the Young's modulus, other parameters are the area-compression (K) and membrane shear (μ_0) moduli, which are related to the Young's modulus. The modeling parameters also include k_d , k_a and k_v , in addition to the WLC spring and bending resistance parameters used in the LD-RBC model. The number of vertices on each RBC (N_v) is varied from 100–27344, and it is found that $N_v = 500$ is enough to gain sufficiently good agreement.

Furthermore, we modeled blood flow in tubes where blood was simulated as a suspension of RBCs. The tube hematocrit H_t was varied between 0.3 and 0.45, while the tube diameters were in the range from 10 to 120 μm . The majority of the LD-RBC model simulations showed very good agreement with the simulations by the MS-RBC model, the experimental data, and empirical predictions. However, when the tube diameter becomes comparable with the RBC size, significant discrepancies appear especially at high hematocrit ($H_t = 0.45$). In particular, an “artificial tumbling” of the RBC that the model exhibits periodically tends to increase significantly the apparent viscosity that the LD-RBC predicts in tubes of diameter 10 microns or less. This is likely to be the result of an erroneous representation of the three-dimensional structure and shape of RBCs in the LD-RBC model.

However, in comparison with the multiscale RBC model, the LD-RBC model is much cheaper computationally. In particular, in LD-RBC model each RBC consists of only 10 DPD particles, while in MS-RBC model 500 DPD particles are used to represent a RBC. Furthermore, the diameter of LD-RBC is about half of that of MS-RBC resulting in computational cost reduction by approximately 2^3 times. As a result, the computational cost can be reduced by about two orders of magnitude. This allows us to simulate blood flow in large (several hundred microns) and long vessels under healthy conditions and in various diseases (e.g., malaria, sickle-cell anemia, etc.).

Despite the success of the LD-RBC model, it has several limitations. As mentioned above, it is unable to reproduce the exact three-dimensional RBC structure, which voids its

applicability to model blood flow in vessels of a small diameter below approximately 20 μm . Also, unlike the MS-RBC model, the LD-RBC model does not capture the rheological properties of RBC membrane, which may be of importance under certain flow conditions in pathological cases.

Taken together the comparisons in accuracy and efficiency of the two RBC models we presented here and in conjunction with existing modeling practices for blood flow suggest a *new* hierarchical multiscale approach as we demonstrate in figure 1. For capillaries and arterioles up to about 100 μm in diameter the use of the MS-RBC would provide the best accuracy. For arterioles from about 25 μm to about 325 μm the use of LD-RBM would provide good accuracy combined good efficiency of the atomistic simulation. For larger arterioles and for arteries, using the Navier-Stokes equation to model blood flow as a homogeneous single-phase fluid is valid and hence standard computational fluid dynamics (CFD) methods can be employed.

Highlights

1. We compare RBC simulated stretching with optical tweezers
2. We predict the apparent viscosity accurately at two different hematocrit values.
3. We model the cell free layer as a function of vessel diameter.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Mchedlishvili G, Maeda N. Blood flow structure related to red cell flow: a determinant of blood fluidity in narrow microvessels. *Japanese Journal of Physiology*. 2001; 51:19–30. [PubMed: 11281993]
2. Popel AS, Johnson PC. Microcirculation and hemorheology. *Annual Review of Fluid Mechanics*. 2005; 37:43–69.
3. Maeda N. Erythrocyte rheology in microcirculation. *Japanese Journal of Physiology*. 1996; 46:1–14. [PubMed: 8743714]
4. Fung, YC. *Biomechanics: Mechanical properties of living tissues*. 2nd Edition. New York: Springer-Verlag; 1993.
5. Evans, EA.; Skalak, R. *Mechanics and thermodynamics of biomembranes*. Boca Raton, Florida: CRC Press, Inc; 1980.
6. Pozrikidis C. Numerical simulation of cell motion in tube flow. *Annals of Biomedical Engineering*. 2005; 33(2):165–178. [PubMed: 15771270]
7. Eggleton CD, Popel AS. Large deformation of red blood cell ghosts in a simple shear flow. *Physics of Fluids*. 1998; 10(8):1834.
8. Discher DE, Boal DH, Boey SK. Simulations of the erythrocyte cytoskeleton at large deformation. II. Micropipette aspiration. *Biophysical Journal*. 1998; 75(3):1584–1597. [PubMed: 9726959]
9. Li J, Dao M, Lim CT, Suresh S. Spectrin-level modeling of the cytoskeleton and optical tweezers stretching of the erythrocyte. *Biophysical Journal*. 2005; 88:3707–3719. [PubMed: 15749778]
10. Noguchi H, Gompper G. Shape transitions of fluid vesicles and red blood cells in capillary flows. *Proceedings of the National Academy of Sciences USA*. 2005; 102(40):14159–14164.

11. Dupin MM, Halliday I, Care CM, Alboul L, Munn LL. Modeling the flow of dense suspensions of deformable particles in three dimensions. *Physical Review E*. 2007; 75(6) 066707.
12. Dzwinel W, Boryczko K, Yuen DA. A discrete-particle model of blood dynamics in capillary vessels. *Journal of Colloid and Interface Science*. 2003; 258(1):163–173. [PubMed: 12600784]
13. Pivkin IV, Karniadakis GE. Accurate coarse-grained modeling of red blood cells. *Physical Review Letters*. 2008; 101(11) 118105.
14. Fedosov DA, Caswell B, Karniadakis GE. A multiscale red blood cell model with accurate mechanics, rheology, and dynamics. *Biophysical Journal*. 2010; 98(10):2215–2225. [PubMed: 20483330]
15. Succi, S. *The Lattice Boltzmann equation for fluid dynamics and beyond*. Oxford: Oxford University Press; 2001.
16. Malevanets A, Kapral R. Mesoscopic model for solvent dynamics. *Journal of Chemical Physics*. 1999; 110(17):8605–8613.
17. Hoogerbrugge PJ, Koelman JMVA. Simulating microscopic hydrodynamic phenomena with dissipative particle dynamics. *Europhysics Letters*. 1992; 19(3):155–160.
18. Bagchi P. Mesoscale simulation of blood flow in small vessels. *Biophysical Journal*. 2007; 92:1858–1877. [PubMed: 17208982]
19. Zhang J, Johnson PC, Popel AS. Effects of erythrocyte deformability and aggregation on the cell free layer and apparent viscosity of microscopic blood flows. *Microvascular Research*. 2009; 77:265–272. [PubMed: 19323969]
20. Pan W, Caswell B, Karniadakis GE. Rheology, microstructure and migration in brownian colloidal suspensions. *Langmuir*. 2010; 26(1):133–142. [PubMed: 20038167]
21. Pan W, Caswell B, Karniadakis GE. A low-dimensional model for the red blood cell. *Soft Matter*. 2010; 6:4366–4376.
22. Pan W, Pivkin IV, Karniadakis GE. Single-particle hydrodynamics in dpd: A new formulation. *Europhysics Letters*. 2008; 84(1) 10012.
23. Suresh S, Spatz J, Mills JP, Micoulet A, Dao M, Lim CT, Beil M, Seufferlein T. Blood viscosity in tube flow: dependence on diameter and hematocrit. *Acta Biomaterialia*. 2005; 1:15–30. [PubMed: 16701777]
24. Groot RD, Warren PB. Dissipative particle dynamics: Bridging the gap between atomistic and mesoscopic simulation. *Journal of Chemical Physics*. 1997; 107(11):4423–4435.
25. Espanol P. Fluid particle model. *Physical Review E*. 1998; 57(3):2930–2948.
26. Fedosov DA, Caswell B, Karniadakis GE. Systematic coarse-graining of spectrin-level red blood cell models. *Computer Methods in Applied Mechanics and Engineering*. 2010; 199:1937–1948.
27. Dao M, Li J, Suresh S. Molecularly based analysis of deformation of spectrin network and human erythrocyte. *Materials Science and Engineering C*. 2006; 26:1232–1244.
28. Fedosov DA, Pivkin IV, Karniadakis GE. Velocity limit in DPD simulations of wall-bounded flows. *Journal of Computational Physics*. 2008; 227(4):2540–2559.
29. Fedosov DA, Karniadakis GE. Triple-decker: Interfacing atomistic-mesoscopic-continuum flow regimes. *Journal of Computational Physics*. 2009; 228(4):1157–1171.
30. Fahraeus R, Lindqvist T. The viscosity of the blood in narrow capillary tubes. *American Journal of Physiology*. 1931; 96:562–568.
31. Pries AR, Neuhaus D, Gaehtgens P. Blood viscosity in tube flow: dependence on diameter and hematocrit. *American Journal of Physiology*. 1992; 263:H1770. [PubMed: 1481902]
32. Tsukada K, Sekizuka E, Oshio C, Minamitani H. Direct measurement of erythrocyte deformability in diabetes mellitus with a transparent microchannel capillary model and high-speed video camera system. *Microvascular Research*. 2001; 61(3):231–239. [PubMed: 11336534]
33. Faivre, M. PhD thesis. Marseille, France: Red blood cells and vesicles.
34. Tomaiuolo G, Simeone M, Martinelli V, Rotoli B, Guido S. Red blood cell deformation in microconfined flow. *Soft Matter*. 2009; 5:3736–3740.
35. Reinke W, Gaehtgens P, Johnson PC. Blood viscosity in small tubes: effect of shear rate, aggregation, and sedimentation. *AJP - Heart and Circulatory Physiology*. 1987; 253:H540–H547.

36. Maeda N, Suzuki Y, Tanaka J, Tateishi N. Erythrocyte flow and elasticity of microvessels evaluated by marginal cell-free layer and flow resistance. *American Journal of Physiology*. 1996; 271:H2454. [PubMed: 8997305]
37. Kim S, Kong RL, Popel AS, Intaglietta M, Johnson PC. Temporal and spatial variations of cell-free layer width in arterioles. *AJP - Heart and Circulatory Physiology*. 2007; 293:H1526–H1535. [PubMed: 17526647]
38. Bugliarello G, Sevilla J. Velocity distribution and other characteristics of steady and pulsatile blood flow in fine glass tubes. *Journal of Biorheology*. 1970; 7:85–107.
39. Fahraeus R. The suspension stability of the blood. *Physiological Reviews*. 1929; 9:241–274.
40. Yamaguchi S, Yamakawa T, Niimi H. Cell-free plasma layer in cerebral microvessels. *Biorheology*. 1992; 29:251–260. [PubMed: 1298443]

Fig. 1. Applicability of different models with respect to a characteristic vessel size (diameter). MSM denotes the multiscale model (MS-RBC in the text); LDM denotes the low-dimensional model (LD-RBC in the text); “continuum” refers to using the Navier-Stokes equations for single-phase flow.

Fig. 2.
Schematic of the LD-RBC (left) and MS-RBC (right) models.

Fig. 3.

A sketch of the stretched LD-RBC (left) and MS-RBC (right) models.

Fig. 4. RBC axial and transverse diameters under deformation for a healthy RBC and a RBC at schizont stage in malaria in comparison with experiments [23].

Fig. 5. Velocity profiles of blood flow relative to those of plasma under the same pressure drop for different hematocrits and RBC models. Left: $D = 40 \mu m$; Right: $D = 10 \mu m$.

Fig. 6. Blood flow in a tube of $D = 10 \mu m$: LD-RBC (left) and MS-RBC (right) for $H_t = 30\%$ (upper) and $H_t = 45\%$ (lower). Solvent particles are not drawn.

Fig. 7.
Blood flow in a tube of $D = 40 \mu m$: LD-RBC (left) and MS-RBC (right) for $H_t = 30\%$ (upper) and $H_t = 45\%$ (lower). Solvent particles are not drawn.

Fig. 8.

Blood apparent viscosity as a function of tube diameter and hematocrit. Simulation data are plotted with symbols, while the lines are the empirical correlation by Pries et al. [31].

Fig. 9. Minimum eigen-value of the gyration tensor for different RBC models in tube flow of diameter $D = 9 \mu m$. In case of the MS-RBC model the minimum eigen-value is normalized by subtracting its lowest value of the equilibrium RBC shape.

Fig. 10.

A sketch of a RBC core edge and measurement of cell-free layer thickness for $H_t = 0.3$ and $D = 20\mu\text{m}$.

Fig. 11.
Cell-free layer thicknesses for different tube diameters and hematocrit values in comparison with available experiments.