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Quantification of red blood cell deformation at high-hematocrit blood flow in microvessels

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ABSTRACT

The deformation of red blood cells in microvessels was investigated numerically for various vessel diameters, hematocrits, and shear rates. We simulated blood flow in circular channels with diameters ranging from 9 to 50 μm, hematocrits from 20% to 45%, and shear rates from 20 to 150 s^{-1} using a particle-based model with parallel computing. The apparent viscosity predicted by the simulation was in good agreement with previous experimental results. We quantified the deformation of red blood cells as a function of radial position. The numerical results demonstrated that because of the shape transition in response to local shear stress and the wall effect, the radial variation of red blood cell deformation in relatively large microvessels could be classified into three different regions: near-center, middle, and near-wall regions. Effects of the local shear stress and wall varied with vessel diameter, hematocrit, and shear rate.

1. Introduction

Blood is a dense suspension of highly deformable red blood cells (RBCs) in plasma. An RBC is a biconcave cell with a high surface-to-volume ratio, in which a Newtonian solution of hemoglobin is enclosed by a thin membrane. The membrane consists of a lipid bilayer underlined by a spectrin network (Mohandas and Evans, 1994), exhibiting small resistances to shear and bending (Evans, 1983, 1989). Hence, RBCs deform significantly in blood flow. The deformation of RBCs greatly affects the mechanics of blood flow, especially in the microcirculation. Interesting features of blood flow include the Fåhræus effect (Fåhræus, 1929), Fåhræus–Lindqvist effect (Fåhræus and Lindqvist, 1931), and formation of a cell-free layer (CFL) (Goldsmith, 1971; Tateishi et al., 1994; Kim et al., 2007). Recently, it was found that RBC deformation triggers the release of adenosine triphosphate (ATP) (Fischer et al., 2003; Moehlenbrock et al., 2006; Wan et al., 2008; Forsyth et al., 2011), which acts as a signaling molecule in various physiological processes. Some diseases such as malaria (Cooke et al., 2001; Dondorp et al., 2000; Suresh, 2006), type II diabetes (Tsukada et al., 2001), and sickle cell anemia (Higgins et al., 2007) are also linked to RBC deformability. Hence, to better understand the physiological and pathological conditions of the cardiovascular system, it is crucial to quantify the deformation of RBCs.

Recent confocal microscopy with microfluidics has improved experimental measurements of the behavior of RBCs in microvessels. For example, studies have examined the dispersion of RBCs (Lima et al., 2009) and tracer particles (Saadatmand et al., 2011) in 50- to 100-μm vessels using confocal micro-particle tracking velocimetry (Lima et al., 2007). However, owing to light scattering by RBCs and light absorption by hemoglobin, RBCs can be observed only at hematocrits (Hcts) of $<20\%$ with this method (Lima et al., 2009; Saadatmand et al., 2011). Thus, previous experiments have failed to quantify the deformation of RBCs in blood flow at physiologically relevant Hcts.

Numerical modeling can provide information for various Hcts. However, numerical simulations of blood flow in microvessels are challenging because of problems related to coupling membrane mechanics and fluid mechanics as well as computational costs. A few studies have examined three-dimensional simulations of blood flow with multiple RBCs. Zhao et al. (2010) developed a numerical model based on a boundary integral method and analyzed the shapes of RBCs and viscosity for vessels up to 16.9 μm in diameter, involving $O(10^1)$ RBCs. Freund and Orescanin (2011) further investigated the deformation and motion of RBCs, the blood viscosity, and the local Hct in an 11.3-μm vessel using this method. Dupin et al., (2007) proposed a lattice-Boltzmann-based method and simulated $O(10^2)$ RBCs in a rectangular channel. Clausen et al. (2010) developed a lattice-Boltzmann method for simulating $O(10^3)$ RBCs on the IBM Blue Gene/P, but they focused on the performance of their method. Dissipative particle dynamics has also been applied successfully to investigate the apparent viscosity and CFL for vessels up to 40 μm in diameter (Fedosov et al., 2010, 2011a, 2011b).

Thus, the deformation of RBCs in microvessels is not well understood. Given that RBCs are approximately 8 μm in diameter, their flow characteristics in vessels with a few tens of micrometers in diameter may differ from those in smaller microvessels. To efficiently

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simulate blood flow in large microvessels, thousands of RBCs must be involved. Previously, we developed a numerical model of micro-scale blood flow based on a particle method (Kondo et al., 2009; Imai et al., 2010). This method has been applied successfully to study the microcirculation in malaria infection (Kondo et al., 2009; Imai et al., 2010, 2011) and thrombogenesis (Kamada et al., in press). More recently, we have developed a highly scalable parallel implementation of this method for large-scale studies and we confirmed that our model predicted well the CFL thickness and Fåhræus effect (Alizadehrad et al., 2012). The objective of the present paper was to investigate the deformation of RBCs in microvessels for a variety of vessel diameters, Hcts, and shear rates. We simulated blood flow in circular channels for diameters of 8–50 μm, Hcts of 20–45%, and shear rates of 20–150 s^{-1}. First, our model was further validated by comparing the apparent viscosities between our simulation and experimental results. Then, we quantified the deformation of RBCs for these conditions.

2. Methods

2.1. Numerical model

The details of the model can be found in Imai et al. (2010), and we provide a brief review here. All blood components, including plasma, cytoplasm, and membranes, are modeled using a finite number of particles. Assuming that plasma and cytoplasm are incompressible viscous fluids, the motion of particles is governed by the conservation laws of mass and momentum as

$$\frac{D\rho}{Dt}=0, \tag{1}$$

$$\rho\frac{D\mathbf{u}}{Dt}=-\nabla p+\mu\nabla^2\mathbf{u}+\mathbf{f}, \tag{2}$$

where t refers to the time; ρ, the density; $\mathbf{u}$, the velocity; p, the pressure; μ, the dynamic viscosity; D/Dt, the Lagrangian derivative; and $\mathbf{f}$, the external force. We used the moving particle semi-implicit method (Koshizuka and Oka, 1996) to discretize the governing equations. The RBC is modeled as an initially biconcave cell, consisting of membrane particles and cytoplasm particles. A triangular network of membrane particles is constructed, where neighboring particles are connected by a linear spring to represent the elastic property of RBCs. Bending resistance is also considered between neighboring triangles. Forces generated by the stretching/compression and bending are substituted into the external force term in Eq. (2) for membrane particles only. Note that although membrane viscosity is not explicitly modeled, viscous effects in the membrane are naturally included due to the viscous term of Eq. (2). Because the membrane motion is tracked directly by membrane particles, the no-slip condition at the membrane is satisfied in this procedure. In the previous study (Imai et al., 2010), we confirmed that this model simulates the deformation of single RBCs by optical tweezers stretching (Suresh et al., 2005) and the deformation in shear flow (Cranston et al., 1984) with good accuracy. Note that the deformation of RBCs presented in this paper was within the range validated by these single cell tests. Although aggregation of RBCs is expected to be significant at low shear rates (Reinke et al., 1987), the aggregation was not modeled in the present study to concentrate on the effects of mechanical factors on the deformation.

2.2. Parallel computing

To simulate blood flow in relatively large microvessels with thousands of RBCs, we developed a highly scalable algorithm for parallel computing (Alizadehrad et al., 2012). The computational domain is divided into several sub-domains and distributed among the processors of concurrent parallel processing systems. In this model, the numbering of membrane particles and their network connections are designed in a particular order to minimize communication. Local communication between neighbor processors uses a message-passing interface (MPI) library, including non-blocking communication. In a test for strong scaling, the resulting speed-up increased almost linearly with the number of processors, in which the code was run on Quad-Core Xeon clusters connected with a Gigabit Ethernet.

2.3. Analysis

Consider a straight, circular microvessel with diameter D and length L. The boundary conditions are the no-slip condition at the wall and a periodic boundary condition at the channel inlet and outlet. To drive the flow in the channel, the pressure difference Δp is given between the inlet and the outlet. To avoid the effect of periodic boundary condition, the length is set to be long enough, at least $L/D>2$ and $L/d_{RBC}>8$, where d_{RBC} is the diameter of RBCs, and specifically, $L=66$, 120, 79, and 113 μm for $D=19$, 24, 37 and 50 μm, respectively. The parameters of plasma and RBCs are listed in Table 1. Each simulation is run for sufficient time to remove the effects of the initial transition and data are analyzed over the time at almost quasi-steady state. The flow is characterized by the pseudo-shear rate $\gamma=U/D$, where U is the mean velocity of blood including both plasma and RBCs for the quasi-steady state. Because the velocity of blood is fluctuated in time even at the quasi-steady state, we averaged the velocity for approximately 0.3 s to have the mean velocity U.

Table 1
Parameters for numerical model.

Density of plasma:	ρ_p	1.0×10^3 kg/m^3
Density of cytoplasm:	ρ_c	1.0×10^3 kg/m^3
Viscosity of plasma:	μ_p	1.3×10^{-3} Pa s
Viscosity of cytoplasm:	μ_c	8.0×10^{-3} Pa s
Initial length of spring:	l_0	4.6×10^{-7} m
Stretching spring constant:	k_s	1.0×10^{-5} N/m
Bending spring constant:	k_b	2.4×10^{-11} N

Previously, we confirmed that this model simulated well the thickness of CFL and Fåhræus effect (Alizadehrad et al., 2012) for vessels up to 50 μm. To further validate the numerical results, the apparent viscosity was compared with experimental data. The apparent viscosity of blood in microvessels depends on the vessel diameter and the Hct, which is referred to as Fåhræus–Lindqvist effect (Fåhræus and Lindqvist, 1931). The apparent viscosity is calculated relative to the viscosity of plasma as

$$\frac{\mu_b}{\mu_p}=\frac{Q_p}{Q_b}, \tag{3}$$

where μ_b is the apparent viscosity, and Q_p and Q_b are the respective flow rates for plasma only (without RBCs) and blood. For given values of D, L, μ_p, and Δp, the flow rate Q_p is obtained analytically. The value of the relative apparent viscosity is averaged over the time for a quasi-steady state.

To quantify the deformation of RBCs, the gyration tensor of an RBC is calculated as

$$\mathbf{G}=\frac{1}{M}\sum_{m=1}^{M}(\mathbf{x}_m-\mathbf{x}_g)\otimes(\mathbf{x}_m-\mathbf{x}_g), \tag{4}$$

where $\mathbf{x}_m$ is the position vector of the m-th membrane particle of the RBC, and $\mathbf{x}_g$ is the center of gravity of the RBC (Noguchi and Gompper, 2005; McWhirter et al., 2009; Pan et al., 2010). The gyration tensor is a symmetric 3×3 matrix with three eigenvalues, $\lambda_1\geq\lambda_2\geq\lambda_3$. Assuming that the shape of a stretched RBC is an ellipsoid, the eigenvalues correspond to the diameters, and the stretching ratios can be obtained from

$$s_i=\frac{\sqrt{\lambda_i}-\sqrt{\lambda_i^0}}{\sqrt{\lambda_i^0}}, \tag{5}$$

where λ_i^0 is the i-th eigenvalue at the reference state, and $\lambda_1^0=\lambda_2^0>\lambda_3^0$ for the initial biconcave shape. To study the radial variation in the stretch, $S_i(r)$, the value of s_i is averaged over the space and time, for the RBCs whose center of gravity is located at a radial position within $r\pm1$ μm. We also measure the orientation of the RBCs, where the inclination angle θ is determined by the angle between the eigenvector associated with the eigenvalue λ_3 and the flow direction, *i.e.*, $\theta/\pi=0$ for the orientation perpendicular to the flow and $\theta/\pi=0.5$ for the orientation parallel to the flow.

3. Results and discussion

3.1. Apparent viscosity

The relative apparent viscosity obtained from the simulations is shown in Fig. 1 for vessel diameters ranging from 9 to 50 μm and Hcts of 20%, 30%, and 45%, with a pseudo-shear rate of around 90 s^{-1}. Pries et al. (1992) provided an empirical description of *in vitro* experimental data for the apparent viscosity as a function of the diameter and Hct. Our results agreed very well with their description. Our model correctly reproduced a nonlinear increase in the apparent viscosity with increases in vessel diameter and Hct. While the description by Pries et al. (1992) was based on an averaged apparent viscosity for pseudo-shear rates >50 s^{-1}, it is