Mesoscopic Blood Flow Simulation Considering Hematocrit-Dependent Viscosity*

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Abstract
Blood is a concentrated suspension of blood cells in plasma. Motion and deformation of red blood cells (RBCs) and their mechanical interaction play important roles in determining blood rheology. Here, we propose a computational model of mesoscopic blood flow where the particulate and continuum natures of blood coexist. We modeled blood flow at two different scales, RBC flow at the microscopic level and continuum at the macroscopic level. A hematocrit-dependent viscosity was considered to take account of the effects of the spatial variation of RBC concentrations on the macroscopic flow. Starting with a Poiseuille flow, the blood flow in a cylindrical channel was simulated. Due to fluid shears, RBCs migrated radially toward the center of flow channel, causing a higher fluid viscosity around the central axis than that near the wall of the channel. Such a spatial variation in viscosity altered the velocity profile of macroscopic blood flow and further changed the RBC distribution within the channel. An iterative calculation resulted in a decrease in flow velocity at the center of the flow channel, as observed in vivo and in vitro. These results address the potential of the present computational approach in the analysis of mesoscopic blood flow.

Key words: Mesoscopic Simulation, Blood Flow, Red Blood Cell, Rheology, Hematocrit

1. Introduction
Blood is a concentrated suspension of blood cells in plasma, an aqueous solution that generally follows Newtonian dynamics. Blood cells are primarily red blood cells (RBCs), comprising about one half of the total blood volume. Approximately 5 million RBCs are present in 1 mm$^3$ of blood. At low shear, RBCs stack up, forming rouleaux and aggregations. The particulate nature of RBCs, their inclining and deformability, and physical interactions, such as collisions and contacts, contribute significantly to their behavior as a multiphase suspension, which results in a non-Newtonian nature\(^{(1)}\).

Generally, it is accepted that hemodynamics is related to cardiovascular and cerebrovascular disorders, including arterial sclerosis. For instance, prolonged disturbances of blood flow trigger the formation of a thrombus, which can lead to stroke and thereby cause permanent neurologic and myocardial damage or death\(^{(2)}\). With the Westernization of the Japanese lifestyle, it has become obvious that death from coronary heart disease and cerebral infarction, stemming from atherosclerosis, is increasing. Atherosclerosis is characterized by the accumulation of lipids and macrophages flowing in the bloodstream under the inner walls of arteries, causing stenosis that narrows vessels and impedes normal blood flow. It is thus of central importance to analyze hemodynamics, based on the
discipline of a multi-phase system with internal structures.

Recently, efforts have been made to simulate the rheological behavior of blood by implementing a fluid-structure coupled simulation using the discrete element method\(^{(3)}^{(5)}\), particle method\(^{(6)}^{(7)}\), lattice Boltzmann analysis\(^{(8)}^{(11)}\), immersed boundary method\(^{(12)}^{(13)}\) and immersed finite element method\(^{(14)}\). These fluid-structure-coupled approaches are favorable for analyzing microscopic blood flow, such as a single RBC flowing through a capillary or velocity fields around individual RBCs. However, to express mesoscopic blood flow, it is necessary to simulate at least hundreds of RBCs, which makes the analysis of mesoscopic blood flow quite challenging.

At the mesoscopic level, blood can be regarded as both a particulate flow and a continuum, depending on the scale at which we observe the blood. Microscopically, blood displays a particulate nature because of the RBCs. In contrast, macroscopically, blood behaves like a fluid. Thus, essentially, the mesoscopic nature of blood is a result of the interaction between the particulate nature and the continuum nature of blood flow.

Here, we propose a novel computational model for mesoscopic blood flow. We modeled blood flow at two different scales: RBC flow at the microscopic level and continuum at the macroscopic level. The effects of the macroscopic flow on the microscopic flow were simulated using axial velocity profiles gained from the macroscopic flow in the microscopic simulation. On the other hand, the effects of the macroscopic flow on the microscopic flow were accounted for by considering the spatial variation in viscosity dependent upon local hematocrit on the basis of experimental data\(^{(15)}\).

2. Methods

2.1 RBC flow

A microscopic blood flow is modeled by the RBCs’ flow. We adopted the RBC model developed by Wada and Kobayashi\(^{(16)}\). Briefly, the RBC was modeled as a closed shell membrane consisting of triangular meshes, as depicted in Figure 1(a). As seen in Figure 1(b), the neighboring meshes were connected with bending springs to prevent folding of the membrane. Nodal points were linked by spring elements to resist stretching. Because of deformation, elastic energies are generated and stored in RBCs. The stretching energy, \(W_s\) and bending energy, \(W_b\) were modeled as

\[
W_s = \frac{1}{2} k_s \sum_{i=1}^{N_s} (L_i - L_{i0})^2, \quad (1)
\]

\[
W_b = \frac{1}{2} k_b \sum_{i=1}^{N_b} \tan^{-1}\left(\frac{\theta_i}{2}\right), \quad (2)
\]

where \(k_s\) and \(k_b\) represent spring constants, \(N_s, N_b\) are the number of stretching springs and bending springs, \(L_{i0}\) and \(L_i\) are the length of the spring in the natural state and after deformation, and \(\theta_i\) is the contact angle between neighboring elements. The resistance to area changes of the RBC membrane was considered at both global and local levels, since this RBC model should express nature of both lipid bilayer and spectrin networks\(^{(16)}\). Letting the total area of the RBC membrane \(A\) and the area of each element \(A_e\), the penalty functions \(W_A\) was introduced as

\[
W_A = \frac{1}{2} k_A \left(\frac{A - A_0}{A_0}\right)^2 + \frac{1}{2} k_a \sum_{e=1}^{N_e} \left(\frac{A_e - A_{e0}}{A_{e0}}\right)^2 A_{e0}, \quad (3)
\]

where the subscript 0 denotes the natural state, \(N_e\) is the number of elements consisting of RBC membrane, and \(k_A\) and \(k_a\) are coefficients for global and local area constraints. The volume energy was introduced to express a change in transmural pressure across the RBC membrane which is generated to balance out elastic forces of the RBC membrane. Given
volume $V$, the volume energy $W_V$ is described as

$$W_V = \frac{1}{2} k_V \left( \frac{V - V_0}{V_0} \right)^2 V_0$$

(4)

where $k_V$ is volume elasticity. Note that $k_V$ is not the volume elasticity of internal fluid, but is the parameter to describe the allowance of RBC volume change in relation to elastic forces of the RBC membrane. As stated in Wada and Kobayashi (2003), physically, equation (4) represents the volume elastic energy generated by a change in RBC volume under transmural pressure $p$ ($p > 0$ when external pressure > internal pressure):

$$p = k_V \left( \frac{V_0 - V}{V_0} \right)$$

(5)

where $k_V$ denotes the volume elastic modulus if we regard an RBC as an elastic body.

Fluid forces act on the RBC membrane externally from plasma. Here, we neglected the internal fluid force generated by the movement of hemoglobin. The modeling of the fluid forces has been described in detail by Nakamura et al. (17). In brief, the fluid force was estimated for each element of the RBC, and modeling of an external fluid force $f^e_{\text{out}}$ was made separately for $f^e_{\text{n out}}$ and $f^e_{\text{t out}}$ which represent the normal and tangential forces, respectively. For modeling of the normal force, we supposed the situation where fluid with velocity $U_f$ and density of $\rho$ impinges on a small element $e$ on the RBC element that moves at the velocity of $U_e$. In this situation, a flow rate $Q$ passing through element $e$ is

$$Q = A_e \Delta u_{\text{n out}}$$

(6)

where $A_e$ is the area of element $e$, and $\Delta u_{\text{n out}}$ is the velocity difference between external fluid and element $e$ in a direction normal ($n_e$) to element $e$. Note that such a velocity jump at the RBC membrane does not physically occur since the fluid velocity coincides with the RBC membrane velocity, but it is considered for modeling of fluid forces. Considering the conservation of fluid momentum at element $e$, we gain the fluid force acting normal to the element of the RBC membrane as

$$f^e_{\text{n out}} = \rho Q \Delta u^e_{\text{n}}$$

In contrast, the tangential force $f^e_{\text{t out}}$ was estimated from a situation where a sphere with a radius of $a$ falls at velocity $\Delta u^e_{\text{t}}$ in a quiescent flow field. From Newton’s viscosity law, the tangential force $f^e_{\text{t out}}$ was modeled as

$$f^e_{\text{t out}} = \frac{\mu_{\text{out}} \cdot A_e \Delta u^e_{\text{t}}}{\delta}$$

(7)

where $\Delta u^e_{\text{t}}$ is the velocity difference tangent to element $e$, $\mu_{\text{out}}$ is the viscosity of external fluid. $\delta$ is the equivalent boundary layer thickness, which was estimated as $\delta = 4a/9$ where $a$ is the radius of RBC at a fully expanded state, based on Stoke’s theory (17). Note that, in the actual simulation, fluid velocity was assessed at the centroid of each element. Because $f^e_{\text{out}}$ is defined for a triangular element $e$, its contribution to a node is $\frac{1}{3}$ of it. Moreover, because a node is associated with more than one element, the fluid force acting on the node is the sum of all fluid forces of the surrounding elements. Thus, the fluid force $\mathbf{f}_i$ at node $i$ is given by

$$\mathbf{f}_i = \frac{1}{3} \sum_{N_i} f^e_{\text{out}}$$

(8)

where $N_i$ is the number of elements that adopt node $i$ as a vertex.

A repulsive force working between two RBCs is expressed by a potential function $\Phi_{ij}$. From a physical point of view, this function represents a pressure elevation between two RBCs when they are in close proximity. Suppose the situation in Figure 2, where RBC 1 comes closer to RBC 2. We defined the potential function that works between node $i$ of RBC 1 and node $j$ of RBC 2 to express the pressure elevation as

$$\Phi_{ij} = k_r \left( \frac{\pi \rho_{ij}}{2} - \tan \left( \frac{\pi \rho_{ij}}{2} \right) \right)$$

(9)
where $z_{ij} = d_{ij}/\lambda -1$, $d_{ij}$ is the distance between nodal points $i$ and $j$, and $\lambda$ is the equilibrium distance. It is assumed that this potential function works for $-1 \leq z_{ij} \leq 0$. In the current simulation, the equilibrium distance $\lambda$ was set to $L_0$, which is the natural length of a spring such that a repulsive force acts only when RBCs come very close. A summation of the potential function $\Phi$ that works in the system of interest is expressed by

$$\Phi = \sum_i \sum_j \Phi_{ij}$$ (10).

A repulsive force working between a wall and RBC is also modeled by using the potential function like eq. (9). The potential function $\Omega_i$ for nodal point $i$ is expressed by

$$\Omega_i = k_w \left( \frac{\pi y_i}{2} - \tan \left( \frac{\pi y_i}{2} \right) \right)$$ (11)

where $y_i = \Delta_i/\lambda_w -1$, $\Delta_i$ is the distance between nodal point $i$ and the wall, $k_w$ is a parameter to express the magnitude of a repulsive force, and $\lambda_w$ is an equilibrium distance. Here, $\lambda_w$ was set the same as $\lambda$. As is the same as eq. (9), we assumed that this works at $-1 \leq y_i \leq 0$.

Given elastic energies, fluid forces and potential energies, the motion of nodal point $i$ placed on the RBC membrane was determined from

$$m \ddot{r}_i = F_i + \bar{F}_i$$ (12)

where a dot indicates a time derivative, $r_i$ is the position vector of nodal point $i$, $m$ is the mass of the nodal point, $F_i$ is the sum of membrane elastic forces, repulsive forces from other RBCs and those from the wall. Based on the virtual work theory, $F_i$ is given by

$$F_i = -\frac{\partial(W + \Phi + \Omega_i)}{\partial r_i}$$ (13)

where $W = W_k + W_h + W_d + W_f$.

Figure 1. (a) Red blood cell model and (b) a schematic representation of a mechanical model of the membrane.

Figure 2. An image of the physical interaction between neighboring RBCs.
2.2 Continuum blood flow

A macroscopic blood flow is modeled as a continuum, described by a continuity equation and the Navier-Stokes equations

$$\frac{\partial u_i}{\partial x_i} = 0 \quad (14)$$

$$\rho u_j \frac{\partial u_i}{\partial x_j} = -\frac{\partial p}{\partial x_i} + \frac{\partial}{\partial x_i} \left( \mu \left( \frac{\partial u_i}{\partial x_i} + \frac{\partial u_j}{\partial x_j} \right) \right) \quad (15)$$

where $i$ and $j$ represent the Einstein summation convention, $u_i$ is a flow velocity vector in the $i^{th}$ direction, $p$ is pressure, $\rho$ is the density of fluid, and $\mu$ is the viscosity of fluid. In general, the fluid viscosity is assumed to be spatially constant for the analysis of arterial blood flow; however, this is not true in small arteries due to the spatial variation of RBC concentration. In the current study, we introduced a hematocrit (Hct) function $F(Hct)$ to the viscous term of the Navier-Stokes equation to express a local viscosity that is dependent on the local hematocrit concentration.

Non-Newtonian nature of blood is often represented by the Casson model. Shiga et al.\textsuperscript{(15)} obtained an empirical formula of the relationship between Casson viscosity, $\mu_c$ and hematocrit, Hct as

$$\ln \left( \frac{\mu_c}{\mu_p} \right) = k \cdot Hct \quad (16)$$

where $\mu_p$ represents the plasma viscosity and $k$ is a constant. Based on this equation, we express the hematocrit function $F$ as

$$F = \frac{\mu_c}{\mu_p} = \exp \left[ k \cdot Hct \right], \quad (17)$$

whereby the Navier-Stokes equation (15) can be rewritten as

$$\rho u_j \frac{\partial u_i}{\partial x_j} = -\frac{\partial p}{\partial x_i} + \frac{\partial}{\partial x_i} \left( \mu_p \exp \left[ k \cdot Hct \right] \left( \frac{\partial u_i}{\partial x_i} + \frac{\partial u_j}{\partial x_j} \right) \right) \quad (18).$$

In the actual simulation, we solved Eqs. (14) and (18) by a finite volume method using STAR-CD (CD Adapco, Japan).

2.3 Evaluation of local hematocrit

To link the microscopic blood simulation with the macroscopic one, the cross-sectional distribution of local hematocrit was evaluated. Given the spatial distribution of RBCs within a flow channel, we counted the number of RBCs in region $\Gamma$ that subdivides a cross-section of the flow channel, as exemplified in Figure 3. Each region is a hexahedral bin consisting of a series of computational meshes, used for the macroscopic blood flow simulation, concatenated in the axial direction of the channel. The presence of each RBC inside or outside the region is judged based on the location of its centroid. This method does not provide the local hematocrit accurately, however, statistically, it suffices as an estimate. The local hematocrit was then evaluated by

$$Hct_\Gamma = \frac{N_r \times V_r}{V_\Gamma} \quad (19)$$

where $N_r$ is the number of RBCs in region $\Gamma$, $V_r$ is the volume of one RBC and $V_\Gamma$ is the volume of region $\Gamma$. 
2.4 Simulation procedure

A flowchart of the simulation is presented in Figure 4. Assuming Poiseuille flow as the initial macroscopic flow, the microscopic blood flow for a period of 0.05 s was simulated. From the RBC distributions obtained by the microscopic flow simulation, we evaluated the cross-sectional distribution of local hematocrit, and calculated the local viscosity for each mesh. Using the local viscosity in the Navier-Stokes equation, the macroscopic flow was calculated. The velocity profile at the outlet of the flow channel was employed as a new velocity profile to calculate RBC behaviors in the microscopic flow. This process was repeated until no substantial change was observed in the axial velocity profile.

2.5 Simulation conditions

The present study solved hemodynamics in a cylindrical channel having a diameter of 105 µm and a length of 100 µm.

In the microscopic simulation, 1472, 2416, or 3417 RBCs were placed randomly within the channel.
the channel, resulting in a global hematocrit of 0.15, 0.24, and 0.35, respectively. A Cartesian coordinate \((x, y, z)\) was instituted at the center of the inlet of the flow channel with the \(x\)-axis lying along the center line of the channel. A periodic boundary condition was assumed for the inlet and outlet of the channel. Table 1 summarizes the parameters of the microscopic flow. The parameters were determined on the basis of experimental data. Please see Wada and Kobayashi\(^{16}\), Tsubota and Wada\(^{18}\) and Appendix for details of determining parameters. Note that the value of \(k_b\) is dependent on the number of meshes. Values of parameters \(k_e\) and \(k_w\) used to represent the interaction with other RBC or the wall are set arbitrarily to avoid overlapping of RBCs and penetrations of an RBC into the wall for numerical stabilities. The parameter \(k\) in Eq. (18) was set to 2.85, based on the viscosity of the whole blood being 4.55 mPa·s and that of the plasma being 1.33 mPa·s, a shear rate of 230 s\(^{-1}\), and temperature of 37°C.

For the analysis of macroscopic simulation, the channel was divided into computational meshes. First, the channel was divided into 31 along the \(x\)-axis. In each cross-section perpendicular to the central axis of the channel (\(x\)-axis), 192 meshes with 209 nodes were created. Hexahedral meshes were then made by connecting corresponding nodal points between adjacent cross-sections. The boundary conditions for the macroscopic simulation included a Poiseuille flow with a Reynolds number of 0.1 at the inlet, a traction-free condition of \(p = 0\) at the outlet, and zero velocity with non-slip at the wall. Note that, for this Reynolds number, the channel is long enough for the macroscopic blood to fully develop by the outlet.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tr>
<td>Number of nodes, (N)</td>
<td>175</td>
</tr>
<tr>
<td>Number of elements, (N_e)</td>
<td>346</td>
</tr>
<tr>
<td>Mass of each node of RBC, (m)</td>
<td>(2.0 \times 10^{-13}) kg</td>
</tr>
<tr>
<td>Spring constant for stretching, (k_e)</td>
<td>(1.5 \times 10^{-6}) N/m</td>
</tr>
<tr>
<td>Spring constant for bending, (k_b)</td>
<td>(2.5 \times 10^{-12}) N</td>
</tr>
<tr>
<td>Spring coefficient for global area, (k_d)</td>
<td>(4.5 \times 10^{-3}) N/m(^2)</td>
</tr>
<tr>
<td>Spring coefficient for local area, (k_v)</td>
<td>(5.0 \times 10^{-4}) N/m</td>
</tr>
<tr>
<td>Spring coefficient for volume, (k_v)</td>
<td>50 N/m(^2)</td>
</tr>
<tr>
<td>Coefficient of the repulsive force between the RBCs and wall, (k_v) and (k_w)</td>
<td>(2.0 \times 10^{-13}) N</td>
</tr>
<tr>
<td>Density of fluid, (\rho)</td>
<td>(1.0 \times 10^{3}) kg/m(^3)</td>
</tr>
<tr>
<td>Initial volume of RBC, (V_r)</td>
<td>87.51 µm(^3)</td>
</tr>
</tbody>
</table>

3. Results

Our results showed a drastic change in the RBC distributions and flow velocities with progress of the simulation. Regardless of the global hematocrit, simulations qualitatively followed the same fashion. Initially, RBCs were distributed randomly within the flow channel. Given a Poiseuille flow, RBCs inclined against fluid shear and migrated radially toward the center of flow channel while traveling downstream. Although collisions with other RBCs flowing more inside the channel somehow hindered the migration toward the center of channel, RBCs became more dense at the center of the channel and sparse near the wall, demonstrating a higher hematocrit at the center of the flow channel. Correspondingly, the viscosity became higher at the center of the flow channel. Such a spatial variation in viscosity resulted in a decrease in the velocity of macroscopic blood flow at the center of the channel and an increase near the wall. Also, such a change in the velocity profile of macroscopic flow caused a re-distribution of RBCs within the channel, thereby varying the
spatial distribution of local hematocrit again. An iterative calculation resulted in a progressive decrease in the flow velocity at the center of the channel.

As representative simulation results, the spatial distributions of RBCs for Hct 0.15 at steps 1, 6, 11, and 16 are displayed in Figure 5 as a contour plot of hematocrit. Initially, the RBCs were distributed randomly within the flow channel (Fig. 5(a)). With flowing, RBCs migrated radially toward the center of the channel. As a result, the contour plot in Figure 5(b) shows a concentric pattern of hematocrit distribution, in which a higher hematocrit was observed at the center compared to that near the wall. The overall appearance of the hematocrit distribution remained the same with subsequent simulations (Fig. 5(c, d)).

A series of the axial velocity profiles along the \( y \)-axis at steps 1, 6, 11, and 16 for Hct 0.15 are presented in Figure 6. Here, the velocity was normalized with the central velocity in the first step. Initially, the velocity profile was parabolic; however, as the simulation progressed, the velocity at the center of the channel showed a decreasing trend.

Presented in Figure 7 is the change in the axial velocity at the center of channel with the progress of mesoscopic simulation for global hematocrit of 0.15, 0.24, and 0.35. Here, the axial velocity at each step was normalized with that at the first step or Poiseuille flow. A comparison of the results at various hematocrit values showed that the axial velocity at Hct 0.35 decreased more dramatically than the others, but at the converged state, the normalized velocity at Hct 0.35 was almost the same as that at 0.24. The velocity observed at Hct 0.15 was larger than that at 0.24 and 0.35 at the final step; however, the declining tendency may last until the normalized velocity becomes equal to that at 0.24 and 0.35. This would be due to the limited number of RBCs that can exist at the center of the channel.

In order to investigate the effects of hematocrit on the mesoscopic flow, we assessed the degree of fluctuation in flow velocity, because this may reflect motions and interactions of RBCs while flowing. Here, we calculated the root mean square (RMS) of RBC velocities. Given the simulated results, we sorted RBCs at one instant in time according to their radial position in a cylindrical channel. Then, we divided the radial positions into 10 sections, and calculated RMS the axial velocity in each section by

\[
RMS = \sqrt{\frac{\sum (U_i / U_p - 1)^2}{N - 1}}
\]  

where \( U_i \) is the \( x \)-axial velocity of RBC \( i \) (averaged velocity of all nodal points) and \( U_p \) is the mean velocity of macroscopic axial flow. Note that \( U_i \) was normalized with \( U_p \) to compare the results between different flow conditions. The calculated RMS for Hct 0.15, 0.24 and 0.35 is given in Fig. 8. As seen, each RMS curve is almost flat up to the normalized radius of 0.6. Nevertheless, beyond the normalized radius 0.6, RMS significantly elevated towards the wall. On comparing the RMS values between different hematocrits we found that there is an increase in RMS as the hematocrit becomes larger.

![Figure 5. Contour plots of the hematocrit obtained for a global hematocrit of 0.15 at steps (a) 1, (b) 6, (c) 11, and (d) 16.](image-url)
Figure 6. Comparison of the velocity profile of an axial flow obtained for the global hematocrit of 0.15. Note that the velocity was normalized with the central velocity at the first step.

Figure 7. Change in the axial velocity at the center of the flow channel. Note that the velocity value for each hematocrit (Hct) was normalized with that at the first step.

Figure 8. RMS values of the axial velocity of RBCs for Hct 0.15, 0.24 and 0.35.
4. Discussion

Blood flow properties in a small vessel were analyzed by interactively simulating macro- and microscopic blood dynamics. The results of the microscopic flow simulation demonstrated that RBCs gathered around the center of the flow channel, whereas a plasma layer developed near the wall, as observed in vivo\(^{(19)}\). Additionally, the macroscopic flow showed a decrease in the axial flow velocity at the center of the flow channel. These flow features are also qualitatively similar to in vivo data\(^{(20),(21)}\). It is therefore considered that the simulation results represent the mesoscopic behavior of blood flow.

The simulation results might be compared with Lima et al.\(^{(22)}\) who performed micro-PIV measurements of flow of pure water and in vitro blood (hematocrit up to 17\%) in a rectangular PDMS channel (100-\(\mu\)m square in cross-section). Note that flow conditions including the cross-sectional geometry of flow channel are slightly different from Lima et al.\(^{(22)}\), but comparisons with Lima et al.\(^{(22)}\) would be still important to discuss the validity of present simulations. According to Lima et al.\(^{(22)}\), the ensemble-averaged velocity profile of in vitro blood with hematocrit up to 17 \% did not change significantly from a parabolic profile. In contrast, we found that there was a slight decrease in the velocity with an increase in hematocrit. By scanning their data, it was revealed that the velocity at 5 \(\mu\)m from the center (width 100 \(\mu\)m) for the case of 17 \% hematocrit is 95 \% of that of pure water (zero hematocrit). It was quantitatively agreed with our simulated results (Fig. 7) where the velocity at the center of channel tended to converge to 94-95 \% of the Poiseuille flow in Hct 0.15.

When a RBC is placed alone in the same flow channel as that used in this simulation and subjected to a shear flow, like Poiseuille flow, it elongates and aligns at a constant angle to the direction of flow with the membrane undergoing tank-tread motion. Additionally, it migrates toward the center of the channel along a shear gradient, so-called “axial migration”\(^{(23)}\). Such behaviors of a RBC are slightly depressed in multiple RBCs flow by collisions with other RBCs that flow more inside at a higher velocity. Around the center of the channel, RBCs become packed and develop into agglomerates.

The value of parameter \(k_s\) actually affects the degree of stretching of RBC membrane, and whereby exerts effects on its various behaviors such as the rate of tank-treading and tumbling. However, since the degree of RBC deformation is relatively small in the present simulation conditions, a variation in the value of \(k_s\) in a physiological range would not give rise to a substantial change in the simulation results, in particular collective behaviors of RBCs. Since a macroscopic blood flow is determined by the collective behaviors of RBCs, the mesoscopic nature of blood flow would remain almost the same even if parameter \(k_s\) is changed.

Parameters \(k_r\) and \(k_w\) are used to represent the interaction with other RBC or the wall. Since, to our best knowledge, no quantitative data for the physical interaction between RBCs and between one RBC to the wall has been published yet, the value of those parameters as well as potential functions (9) and (11) was set arbitrarily. However, note that the potential functions work only in a close distance with other RBCs or a wall. In fact, these functions work when a distance between two RBCs or a RBC and the wall is smaller than 1.12 \(\mu\)m. Actually, the aim of the potential functions is not to express the physically real interaction, but to avoid overlapping of RBCs or penetration of RBCs into the wall. Thus, the values of \(k_r\) and \(k_w\) are set to be small such that they minimally affect the behaviors of RBCs. As far as the values of \(k_r\) and \(k_w\) are set in such a way, changes in the values of \(k_r\) and \(k_w\) may not bring about collective behaviors of RBCs from a macroscopic point of view.

Hematocrit affects the behaviors of RBCs at the microscopic level and thus the velocity fluctuation of blood flow at the macroscopic level. Lima et al.\(^{(22)}\) assessed the velocity fluctuation in in vitro blood flow in the rectangular PDMS channel by calculating the root
mean square of velocity at one site over time. However, as we assume a steady flow for a macroscopic velocity field, it is difficult to make a direct comparison with their data. Instead, here we evaluated RMS of RBC velocities as presented in Fig. 8. The simulated results are qualitatively in good agreement with Lima et al.\textsuperscript{(22)} who showed drastic elevation in the RMS value near the wall and larger RMS for higher hematocrit. The value of RMS would reflect motions such as tumbling and translations of RBCs and their interactions while flowing. With an increase in Hct, RBCs tend to collide more frequently, which resulted in larger RMS for higher Hct. Although detailed investigations on the behaviors of each RBC remain as a future work, the present simulation could capture such Hct-dependent nature of blood flow.

It is quite obvious that RBC behavior induced a change in the macroscopic velocity profile, and \textit{vice versa}. With the axial migration of RBCs, the RBC concentration became higher around the center of the channel while that near the wall became lower, bringing about an increase in blood viscosity around the center and decreased viscosity near the wall, respectively. As a consequence, the flow velocity in the center of the channel decreased and that near the wall increased, developing into a blunt kind of velocity profile. These results address the potential of the present computational approach in the analysis of the rheology of blood in small vessels where the particulate and continuum natures of blood coexist.

The results showed that convergence of the flow velocity was faster for larger Hct (Fig. 7). For higher Hct, RBCs were tightly packed within a flow channel. As a consequence, a spatial distribution of RBCs did not change so much with progress of the simulation. Note that this does not retard convergence. Rather, it simply means that the spatial distribution did not vary from the initial state because of a limited room within the flow channel. In contrast, for lower Hct, RBCs could relatively freely flow in a radial direction. As a result, the simulation for lower Hct required more computational steps to gain convergence of the flow.

In addition to hematocrit, the viscosity of blood is dependent on the shear rate\textsuperscript{(24),(25)}. A decrease in shear rate causes a progressive increase in the viscosity. In normal RBCs, a significant increase in viscosity occurs when the shear rate is less than 1 s\textsuperscript{-1}\textsuperscript{(25)}. If we calculate a radial distribution of the shear rate under the present simulation, we find that such a low shear rate region (\(\gamma < 1\) s\textsuperscript{-1}) is confined to the central part of flow channel (approximately \(r < 1.5\) µm for global Hct = 0.15), which is actually smaller than one RBC (~8 µm). This means that even if we include the shear rate-dependent viscosity in the present simulation, the results are not expected to be very different. Indeed, the effects of shear rate-dependent viscosity would be more pronounced for larger arteries or low flow velocities.

\textbf{5. Conclusions}

A novel computational scheme for the analysis of mesoscopic blood rheology is proposed. The scheme was applied to the analysis of blood flow in a small blood vessel. The simulated flow dynamics were in good agreement with \textit{in vivo} observations. These results address the potential application of the present computational approach to the analysis of mesoscopic blood flow where particulate and continuum natures of blood coexist.

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Appendix

Parameters $k_a$ and $k_d$ are estimated by a comparison with Evans et al. (1976) who carried out a micro-aspiration experiment for a fully expanded RBC and reported the area modulus of $K$, which should be equal to $k_a+k_d$, as 0.5 N/m. However, this value of $k_a+k_d$ brought a significant resistance to even a small change in the membrane area, inducing numerical instabilities. Thus, in the present simulation, we used one-hundredth-fold value for $k_a+k_d$ which is 0.005 N/m. A distribution ratio of $k_d$ to $k_a$ was arbitrarily determined such that $k_d$ accounts for 90% of $K$ based on the assumption that the global constraint of area would be much larger than the local constraint.

References


