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MULTISCALE ANALYSIS OF BLOOD FLOW: MODELING AND SIMULATION OF MULTIPLE RED BLOOD CELL FLOW

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ABSTRACT: *In order to simulate red blood cell (RBC) behaviors in a flowing blood, we developed a mathematical model of an elastic RBC and their multi-body interaction based on the minimum energy principle. The results showed realistic behavior of multiple RBCs in a straight artery as well as single RBC behavior in a uniform shear flow including tumbling and tank treading motion observed in experiments. Non-Newtonian fluid property of blood was demonstrated by a novel simulation method to interactively repeat the macro-scale analysis of blood flow and the micro-scale analysis of RBC flow.*

1. INTRODUCTION

Blood is an inhomogeneous fluid consisting of blood cells suspended in a liquid component called plasma. About a half volume of the blood is occupied by red blood cells (RBCs), and thereby the blood flow dynamics in microcirculation depends strongly on the motion, deformation and interaction of RBCs and the viscosity of plasma [1]. Further, the biological reactions which induce thrombosis and hemolysis are sometimes triggered by mechanical interactions of multiple RBCs, resulting in failure of blood circulation. In order to understand blood rheology, multi-scale modeling and simulation of blood flow, including both microscopic RBC behavior and macroscopic fluid properties, is essential. In this study, we developed a three-dimensional model of an elastic RBC based on the minimum energy principle, and simulated the dynamical behavior of multiple RBCs in flowing blood.

2. METHODS

2.1 Single RBC Model

The RBC was modeled as a closed shell membrane which surrounds the internal liquid of RBC. The RBC membrane consisting of a lipid bilayer and an underlying skeletal network has elastic resistances to stretching, bending and area expansion of the membrane [2]. We represented those elastic properties by a spring network which was constructed by dividing the membrane into small triangular elements and linking the nodal points and neighboring elements with springs [3, 4] (Fig. 1). The elastic energies generated by stretching, W_s, and bending, W_b, of the membrane were expressed as

$$W_s = \frac{1}{2} k_s \sum_{l=1}^{N_l} (L_l - L_{l0})^2 \tag{1}$$

$$W_b = \frac{1}{2} k_b \sum_{l=1}^{N_l} L_l \tan^2\left(\frac{\theta_l}{2}\right) \tag{2}$$

where subscript 0 denotes the natural state, k_s and k_b are stretching and bending spring constants, respectively, L_l is a length of spring l, θ_l is a contacting angle between neighboring elements. Taking the local and global area change in the membrane, the elastic energy by area expansion was defined as

$$W_A = \frac{1}{2} k_A \left(\frac{A - A_0}{A_0}\right)^2 A_0 + \frac{1}{2} k_a \sum_{e=1}^{N_e} \left(\frac{A_e - A_{e0}}{\mathrm{A}_{e0}}\right)^2 A_{e0} \tag{3}$$

where k_A and k_a are a global and a local area expansion modulus, A and A_e are area of the whole membrane and the element e, respectively. The constraint of a RBC volume, V, was imposed by a penalty function;

$$W_V = \frac{1}{2} k_v \left(\frac{V - V_0}{V_0}\right)^2 V_0 \tag{4}$$

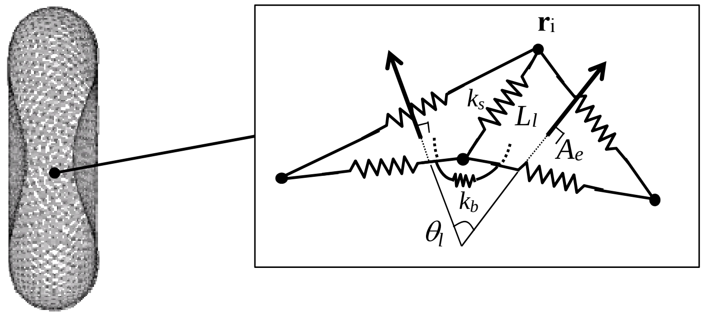


Fig. 1 Spring network model of RBC

where k_V is a constant equivalent to a bulk modulus of RBC. Based on the minimum energy principle, the problem to determine the shape of RBC can be written as

$$\text{Minimize } W = W_s + W_b + W_A + W_V \text{ with respect to } \mathbf{r_i} \qquad (5)$$

where $\mathbf{r}_i$ is a position vector of the nodal point on the membrane.

2.2 Mechanical Interaction between RBCs

The mechanical interaction between multiple RBCs was represented by a potential function assigned at each nodal point on the membrane, mathematically defined as

$$\Phi_{ij} = \begin{cases} k_r\left(\pi z/2 - \tan \pi z/2\right) & \text{for } -1 \le z < 0 \\ k_a\left(1 - \cos \pi z\right) & \text{for } 0 \le z < 1 \\ 2k_a & \text{for } 1 \le z \end{cases} \qquad (6)$$

where $z = d_{ij} / \delta - 1$, d_{ij} is a distance between two nodal points of different membrane, δ is the equilibrium distance, and k_r and k_a are coefficients to determine the intensity of the reaction and attraction forces, respectively.

2.3 Estimation of Fluid Force

The fluid force acting on the RBC membrane was estimated from the difference in the velocity, $\Delta\mathbf{u}^e$, between the external fluid (plasma) and RBC membrane at each element. From Newton's viscosity law and conservation of the fluid momentum the forces normal and tangent to the membrane were obtained as

$$\mathbf{f}_n^e = \rho A_e \left|\mathbf{\Delta u}_n^e\right| \mathbf{\Delta u}_n^e \qquad (7)$$

$$\mathbf{f}_t^e = \mu A_e \mathbf{\Delta u}_t^e / \delta \qquad (8)$$

where subscripts n and t denote a normal and a tangent component, ρ and μ are a density and a viscosity of the external fluid, respectively, and δ is an equivalent boundary layer thickness.

2.4 Solving Method

The motion and deformation of RBCs were obtained by solving the motion equations of mass points assigned at all of the nodal points of the membrane;

$$m\ddot{\mathbf{r}}_i = \mathbf{F}_i + \mathbf{f}_i \qquad (9)$$

where a dot means a time derivative, m is a mass of the nodal point, and the fluid force $\mathbf{f}_i$ is given by

$$\mathbf{f}_i = \frac{1}{3}\left(\mathbf{f}_n^e + \mathbf{f}_t^e\right) \qquad (10)$$

From virtual work theory, an elastic force $\mathbf{F}_i$ is given by

$$\mathbf{F}_i = -\partial W / \partial \mathbf{r}_i \qquad (11).$$

A set of the motion equations (9) was explicitly solved step by step using finite difference scheme.

2.5 Parameters

Parameters used in the following simulations are encapsulated in Table. 1.

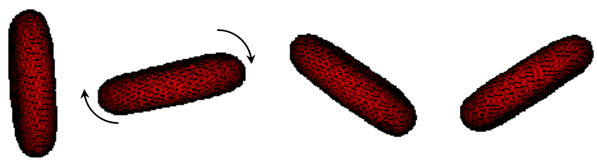
Table 1 Parameters used for the simulation

Number of nodes, N	175	Mass, m	1.0×10^{-13} kg
Number of elements, N_e	346	Coef. of repulsive force, k_r	2.0×10^{-13} N
Spring constant for stretching, k_s	1.0×10^{-6} N/m	Coef. of attractive force, k_a	0 N
Spring constant for bending, k_b	2.5×10^{-6} N	Density of plasma, ρ	1.0×10^{3} kg
Local area expansion modulus, k_a	5.0×10^{-4} N/m	Viscosity of plasma, μ	1.0×10^{-3} Pa.s
Global area expansion modulus, k_A	4.5×10^{-3} N/m	Time step, Δt	1.0×10^{-6} s

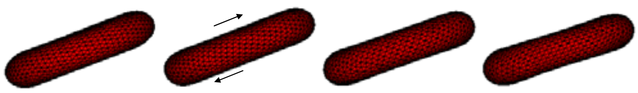
3. RESULTS AND DISCUSSION

3.1 Single RBC Behavior in a Uniform Shear Flow

In order to validate our model, the behavior of a single RBC in a uniform shear flow was investigated. The initial biconcave discoid shape of RBC was obtained by decreasing the volume of a swollen spherical RBC (146 μm^3) to that of a normal RBC (87.6 μm^3). As shown in Fig. 1, the RBC rotated as a rigid body at a shear rate less than 20 s^{-1}, while it orientated at a constant angle (18 deg) with rotating its membrane at a higher shear rate. These characteristic behaviors of a single RBC are known as tumbling and tank treading motion, respectively, and the transition shear rate was quantitatively consistent with experimental results [6].



(a) Shear rate: 10 s^{-1}

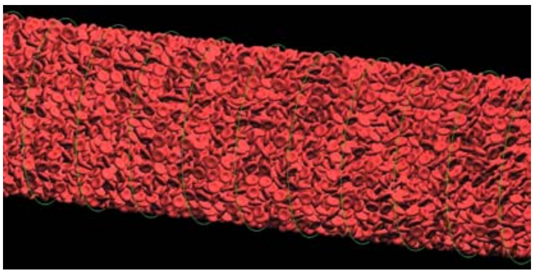


(b) Shear rate: 200 s^{-1}

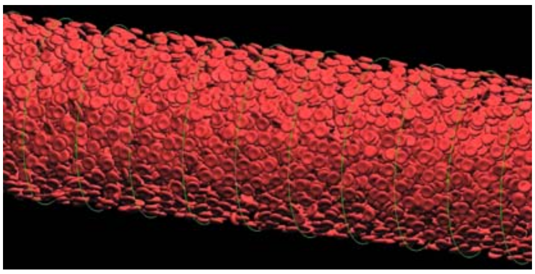
Fig. 2 A single RBC behavior in a uniform shear flow

3.2 Multiple RBC Behavior in a Straight Artery

The behavior of multiple RBCs in a small artery was simulated using the Earth Simulator—a highly parallel vector supercomputer. We used 64 nodes each of which has 8 CPUs. Thus, in total, 256 CPU processors are used for the present simulation. We placed 16,256 RBCs spatially at random in a straight artery with a diameter of 106 μm and a length of 1024 μm as an initial condition (Fig. 3 (a)). A fully-developed parabolic velocity profile with a mean velocity of 0.5 mm/s was assumed. The results showed the RBCs aligned in the flow direction all at once immediately after the simulation was commenced (Fig. 3(b)). Then, while flowing downstream, they tumbled around the central axis of a flow channel and exhibited tank-treading near the wall, depending on the shear rate of the flow. These behaviors are similar to a experimental study where RBC behaviors were observed by means of a micro-PIV [7], demonstrating that our model is capable of representing the characteristics of multiple-RBC flows.



(a) Initial state



(b) After 0.7 sec

Fig. 3 Multiple RBC behavior in a straight artery with a diameter of 106 μm.

3.3 Multiscale Analysis of RBC Flow

Approximately half volume of blood is composed of RBCs which are believed to strongly influence blood flow properties. Non-Newtonian properties of blood are basically derived by the collective behaviors of RBCs [1]. We therefore carried out the micro-scale simulation of RBCs' flow and the macro-scale simulation of the blood flow in order for investigating the rheological properties of blood at a meso-scale by interactively. A micro-scale flow was simulated by solving multiple RBCs flow by using the same technique described above. Flow at a macro-scale was modeled as a continuum expressed by the equations of continuity and Navier-Stokes. The interaction between the micro and macro-scale simulation was achieved through the exchange of the axial velocity profile gained from the macro simulation and a local viscosity estimated from a local concentraiton of RBCs from the micro simulation. General concept of this simulation is schematically shown in Fig. 4.

The results demonstrated that the RBCs tended to migrate axially towards the central axis of af flow channel, causing higher fluid viscosity around the central axis than that near the wall of the flow channel. As a consequence, the velocity profile at the central axis decreased, which seems to be finally converged to that of non-Newtonian blood flow where a velocity profile is flat around the central axis of the channel. These results addressed the potential of the present computational approach to the analysis of the rheology of blood in small vasculatures where non-Newtonian property of blood is not negligible.

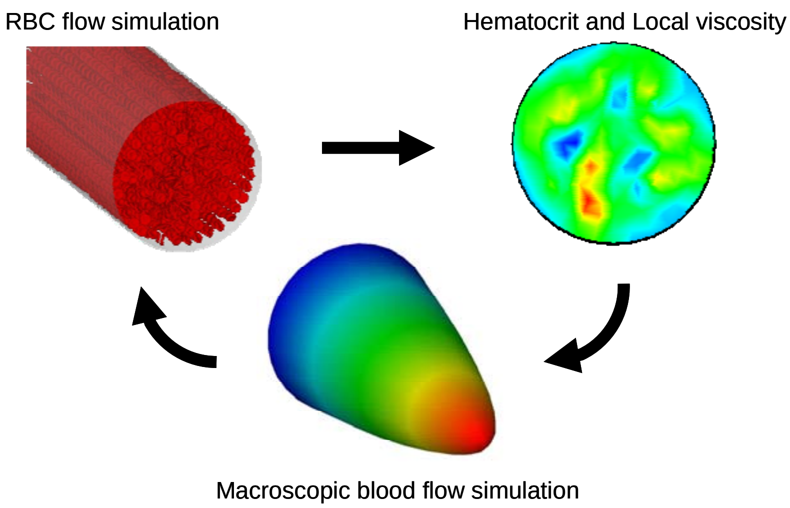


Fig.4 Schematic drawing of a concept of mesoscopic blood flow simulation by multi-scale analysis

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