Particle Modeling for Complex Multi-Phase System with Internal Structures using DEM

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Following the development of a numerical scheme to simulate flowing phenomena of a huge number of red blood cells (RBCs) by the end of 2006, we investigated collective behaviors of RBCs flowing through a stenosed artery. In 2007, modifications were made in the model of RBC such that it could simulate dynamic deformation under not only a low shear flow but a high shear flow. A multi-scale simulation of blood flow was also implemented in order for analyzing mesoscopic phenomena of blood flow.

Keywords: Red blood cell (BRC), Particle, Fluid, Multi-phase system, Internal structure, Discrete Element Method

1. Introduction

The nature of solid and liquid mixture has been of great interest to scientists. In general, those mixed materials exhibit complex rheology, depending on a fraction of solid. The phenomenon becomes significantly complex as the solid forms an internal micro-structure composed of particles. Even with a small fraction of solid, the material shows more or less solid-like behavior. The primary aim of this research project is to understand the nature of fluid-solid mixture where particulate materials exits as a mixture of solid, liquid and gas phases with forming an internal structure such as clustering, and to establish a particle-continuum coupled model based on discrete element method.

The blood consists of a suspension of blood cells in an aqueous solution called plasma. About a half volume of the blood is occupied by red blood cells (RBCs). Approximately 5 million RBCs are present in 1 mm^3 of blood. Thus, blood flow is essentially mixture of solid (RBCs) and liquid (plasma). Under a low shear flow, RBCs agglomerate, forming rouleaux and aggregations which can be called a kind of cluster. The particulate nature of RBCs, their dynamic deformations, and physical interactions significantly contribute to behaving as a multiphase suspension.

Blood flow is believed to be deeply concerned with cardiovascular and cerebrovascular disorders including atherosclerosis. It is therefore important to understand mechanics of blood flow in detail based on the discipline of multi-phase system with internal structures.

2. Computer simulation of RBCs flowing through a stenosed artery

To the end of 2006, we have done computer simulations of RBCs behavior in normal straight arteries. With westernization of the Japanese-style, it has been obvious that death from coronary heart disease and cerebral infarction stemmed from atherosclerosis is increasing. Atherosclerosis is characterized by accumulation of lipids and macrophages flowing in the bloodstream under the inner walls of arteries, causing stenosis that narrows the vessels and impedes normal blood flow.

In order to investigate collective behavior of RBCs flowing through a stenosed blood vessel, computer simulations were performed. An RBC model used is the same as the one that has been used until the last year [1]. In brief, the RBC was modeled as a closed shell membrane consisting of triangular meshes. Neighboring meshes were connected with bending springs to prevent folding of membrane. Nodal points were linked by spring elements to resist to stretching. Fluid forces exerted by blood flow were estimated based on the momentum conservation and Newton's friction law. In order to maintain the volume and surface area of RBC, constraint functions of those were imposed. A mechanical interaction between two RBCs is expressed by a potential function with respect to a

distance between them. A dynamic behavior of RBC in the given flow field was determined toward the minimum energy state. We prepared differently stenosed arteries, namely, a percent stenosis of 10, 30, and 50%, defined as a ratio of the radius at the most stenosed part to that at the entrance. RBCs were distributed evenly within the vessel at hematocrit of 15%. A macroscopic flow field was pre-defined; the axial velocity profile was assumed to be parabolic everywhere whereas the radial velocity was assumed to linearly increase from the central axis to the wall. Simulations were implemented with 256 processors on the Earth Simulator for 12 hrs.

A snapshot of RBCs flowing through a 50% stenosed blood vessel is shown in Fig. 1. As RBCs passed through stenosis, they were enforced centrally to concentrate and agglomerate, developing into a cluster due to tapering of the vessel. This indicates that stenosis potentially contributes to forming a seed of thrombi. It was also observed that, once RBCs were clustered, they had not been disassembled even after RBCs have passed the stenosis. If such a cluster persists and grows, it would develop into a large thrombus that can cause stroke and myocardial infarction. There results indicate that stenosis is risky not only because it narrows a blood vessel and impede blood flow but also seed thrombus formations.

We also simulated flowing behaviors of pathologically stiffened RBCs in a stenosed artery. As an RBC loses its elasticity, it tends to take a capped shape rather than a biconcave shape at a natural state as illustrated in Fig. 2. The aim of this simulation is to see the influence of stiffening of an RBC membrane on the collective behavior of RBCs. The simulation was implemented at the Reynolds number of 0.015 and hematocrit of 11.4. Figure 3 plots a temporal variation of the drag force caused by RBCs. In this figure, a red line represents stiffened RBCs and a black line normal RBCs. As obvious, a flow resistance is larger for stiffened RBCs. This simulation results clearly demonstrate that stiffening of an RBC may consequently lead to hypertension.

Fig. 2 Snapshot of an RBC whose membrane is pathologically stiffened.

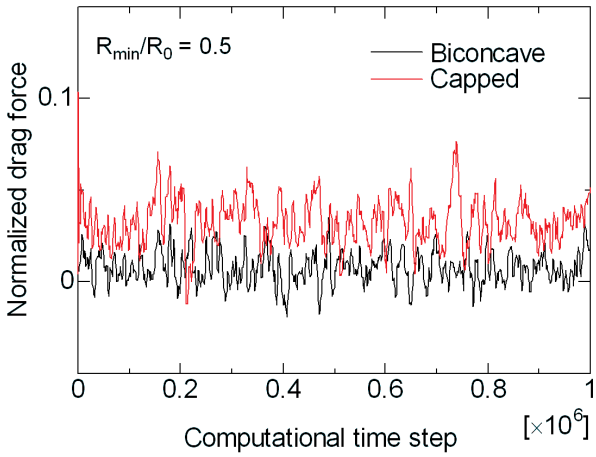

Fig. 3 Time variation of the drag force obtained by the simulation of RBCs flowing through a stenosed artery. A red line represent pathologically stiffened RBCs and a black line normal RBCs.

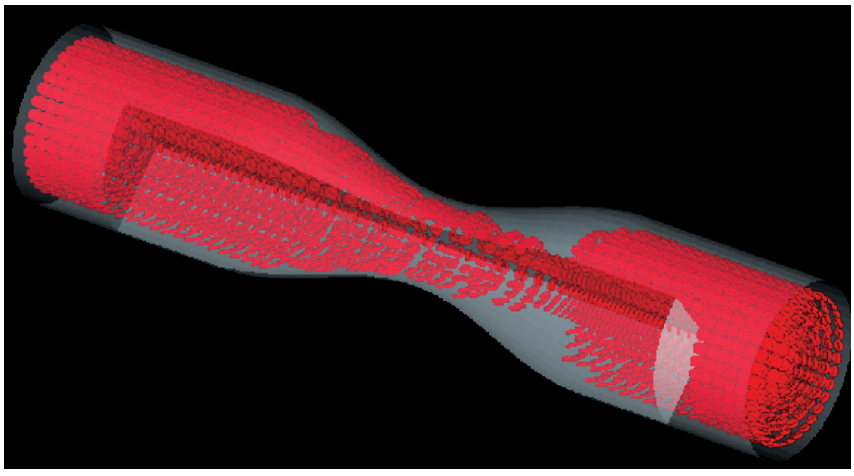

Fig. 1 A snapshot of RBCs flowing through a stenosed artery.

3. Computer simulation of an RBC in a high-shear flow

Quantitative evaluation of hemolysis, the breaking open of RBCs, is essential in designing artificial organs. Recently, numerical methods to quantify hemolysis from a measured or calculated macroscopic flow velocity field have been proposed. Nevertheless, their predictive accuracy has not reached a satisfactory level required in practice. This would be because the conventional methods evaluate just a macroscopic flow field and have not well considered deformation of RBCs. For further amelioration of the predictive accuracy, it would be necessary to take into account motion and dynamical deformation of individual RBCs in a flow field. For this purpose, we need to have an elastic RBC model that can express its deformation not only in a physiological shear range but also in a high shear flow which can occur in artificial organs.

We made modifications in modeling of shear resistance of the RBC membrane by introducing a nonlinear spring in which the spring constant increases as it is more stretched. Mathematically, it is defined by

$$k_s^i = k_{s0} \exp\{\alpha(\lambda^i - \beta)\}, \quad (1)$$

where k_s^i is a spring constant of line element i, k_{s0} = 15 μN/m and α, β are parameter constants. Parameters α and β are determined by numerical experiments of RBC where a deformation index of RBC embedded in a steady parallel shear flow is compared with experimental data. Figure 4 is a schematic drawing of the experiment. Figure 5 shows the relationship between fluid shear stress τ and L/W. Here, L and W are the length of long and short axes when the RBC shape is approximated as an ellipsoid. For comparison, the simulation results, obtained when a linear spring model (α = 0) is used, are also presented (empty marks). As seen, qualitatively good match with experimental data was obtained when a non-linear spring model was adopted. An acceptable match was obtained when α = 3, β = 1.35.

Using this parameter set, dynamic deformation of an RBC under a cyclically reversing shear flow at the frequency f of 3 Hz was also analyzed. Figure 6 shows the temporal variations of L/W and fluid shear stress τ. Again, the improvement was achieved by using a non-linear spring model.

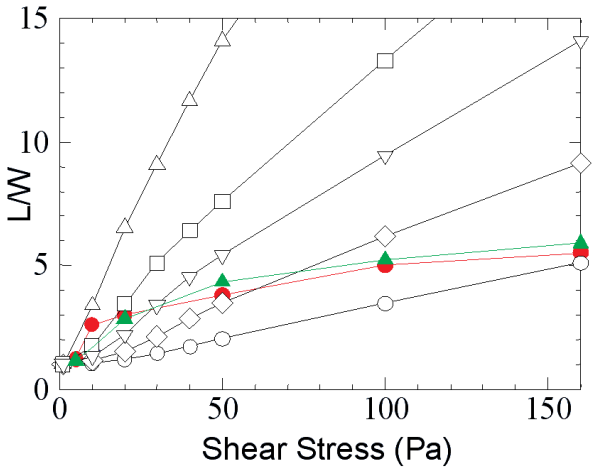

Fig. 5 Relationship between τ and L/W. Green marks represent the simulation results obtained with a non-linear spring model, red marks the experimental results [2, 3], empty marks the simulation results with a linear spring model.

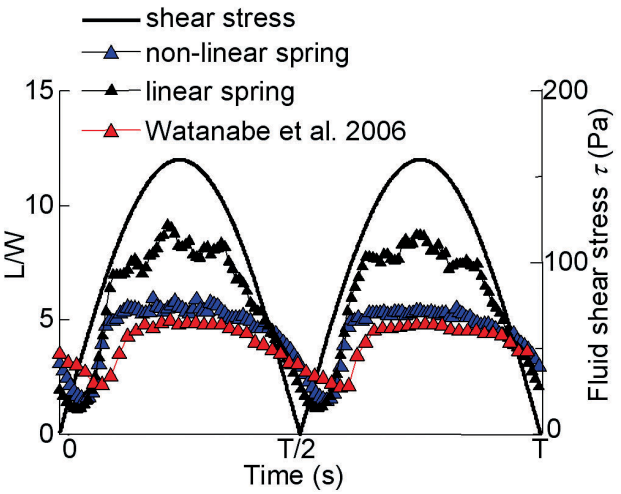

Fig. 6 Time variation of τ and L/W obtained by the simulation of an RBC in an unsteady parallel flow. Experimental results were from Watanabe et al. [3].

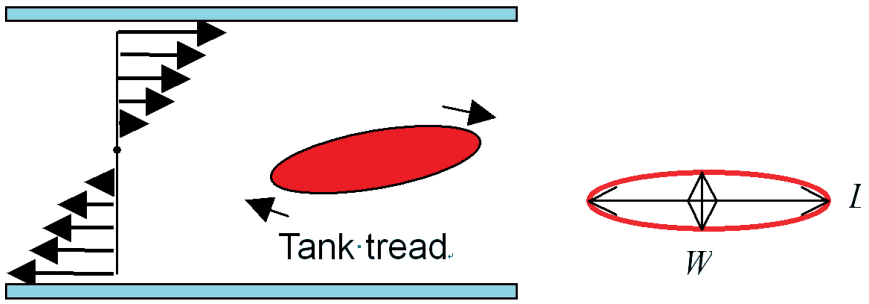

Fig. 4 Schematic drawing of an experiment where an RBC is embedded in a steady shear-flow. The deformation of an RBC is assessed by L and W which are the length of a long axis and a short axis when the RBC is approximated as an ellipsoid.

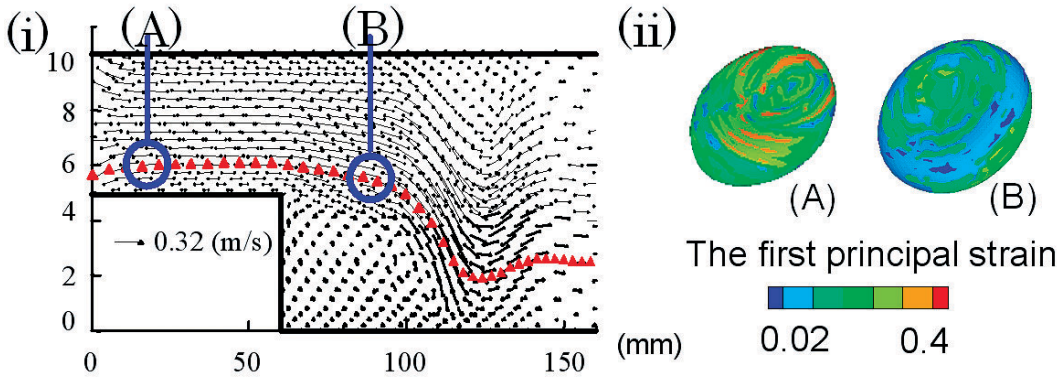

Fig. 7 (i) Vector plots of flow in a back-step flow, (ii) contour plots of the first principal strain in (A), (B).

Given this modified RBC model, its dynamic behavior in a back-step flow at the Reynolds number of 1000 was simulated. Figure 7 (i) plots velocity vectors of the back-step flow, showing a vortex formation behind the step. Figure 7 (ii) shows contour plots of the first principal strain ε on the RBC membrane in region (A) and (B) encircled in Fig. 7 (i). Although the conventional hemolysis index *SS* that is scalar value of an instantaneous fluid stress tensor at each location was almost the same in (A) and (B), the distribution and magnitude of the first principal strain ε were quite different. Along the flow trace of an RBC (red dots in Fig. 7 (i)), the maximum of the first principal strain ε_{max} over the membrane was calculated and plotted against *SS* in Fig. 8 As seen in Fig. 8, no consistent tendency was found between ε_{max} and *SS*. This was due to fluid viscous forces. Because the RBC flowing in the back-step flow was exposed to dynamically changing fluid mechanical environment as it moved, the viscous force was exerted from the interaction with surrounding fluid forces. As a consequence, viscous effects appear in deformation behavior of RBC. Note that a viscosity was not considered in the membrane of the present model. In essence, the RBC shape was not determined solely from fluid forces which instantaneously act on it. These results address the necessity to consider dynamic deformation of RBCs for better evaluation of hemolysis and the utility of the current RBC model for building an RBC-based hemolysis simulator. The computer simulation of two and more RBCs in a high-shear flow is underway.

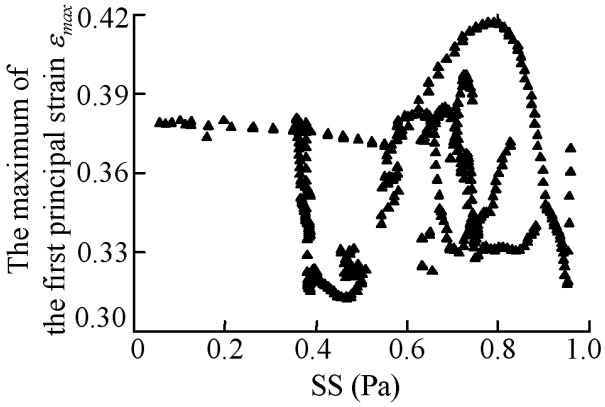

Fig. 8 Relationship between *SS* and ε_{max}.

4. Mesoscopic blood flow simulation by multi-scale modeling

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. We therefore investigated the rheological properties of blood at a meso-scale by interactively carrying out the micro-scale simulation of RBCs' flow and the macro-scale simulation of the blood flow. A micro-scale flow was simulated by solving multiple RBCs flow by using the same technique described in section 2. 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.

Although the calculation is still underway, 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 depicted in Fig. 9. As a consequence, the velocity profile at the central axis decreased (Fig.10), which seemed 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.

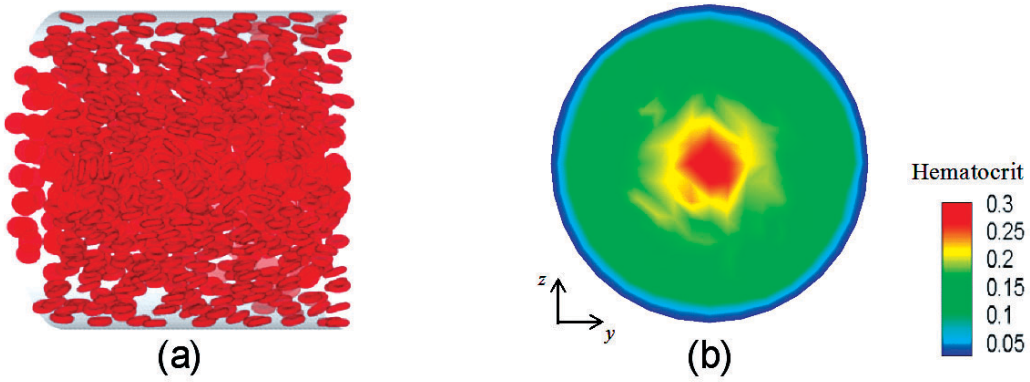

Fig. 9 (a) Snapshots of RBCs flow in a microscopic blood flow simulation at hematocrit of 0.15 at the 35th step of interaction. (b) Contour plot of hematocrit.

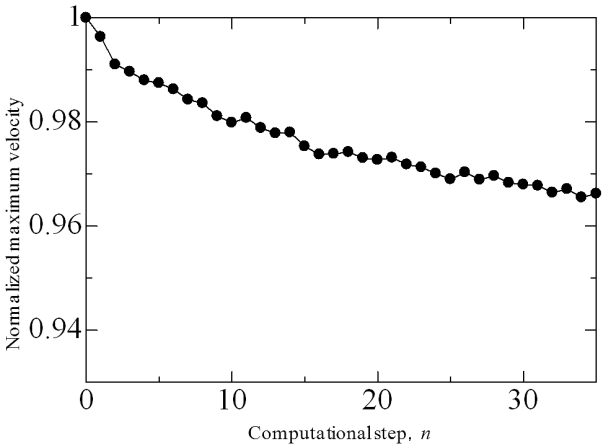

Fig.10 Change in the normalized maximum velocity during the mesoscopic blood flow simulation at hematocrit of 0.15.

5. Conclusion

This year, we studied collective behaviors of RBCs flowing in a stenosed artery. From the results, we found that stenosis jeopardizes a man not only because it obstructs blood flow but also because it may seed thrombus formations by enhancing agglomeration of RBCs. Using pathologically stiffened RBCs, we found that stiffening of RBCs may contribute to causing hypertension.

We made some modifications in modeling of an RBC membrane such that it could simulate its deformation behavior even in a high shear flow. A reasonably good match with experimental data was achieved in both steady and unsteady parallel flow. An RBC in a back-step flow was simulated to see how the RBC behaves in a complex flow field. The results demonstrated that a conventional hemolysis index is not always indicative of RBC deformation. Although further studies are requisite, this model would be useful to build an RBC-based hemolysis simulator.

A multi-scale simulation of blood flow was also implemented in order for analyzing mesoscopic phenomena of blood flow. Since this method is very time-consuming, we have not obtained a converged-state yet. Nevertheless, it is quite obvious even from the results that have been obtained to date that this method provides valuable information to understand the mechanism to induce non-Newtonianity of blood flow.

Toward the year 2009, we will continue to implement a multi-scale simulation of blood flow. At the same time, we will perform some experiments to corroborate our simulations results that have been obtained.

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DEM による内部構造を持つ複雑多相系の粒子モデル

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本プロジェクトは粒子系離散モデルに基づいて、液相（血漿）と固相（赤血球）が混在する血液の複雑な流動現象を解明することを目的としている。2007年度は①狭窄部を有する血管内を流れる赤血球動態の解析、②高せん断流れ下における赤血球変形の解析と膜面力学パラメータの同定、③血流マルチスケール計算による血液流動のメゾスコピック解析を行なった。以下にその詳細について示す。①直円管で模擬した血管の中央付近に狭窄を作成し、そこに赤血球を流す計算を行った。結果より赤血球は狭窄部において凝集塊を形成し、狭窄部を過ぎてもその塊は瓦解せずに下流に流れていたことから、血管に狭窄部があることで瞬間的に高赤血球濃度になり、これが急性心筋梗塞や脳梗塞などを引き起こす血管塞栓の形成を促進しているのではないかということが示唆された。また、赤血球が正常な状態と病的に硬くなった状態である状態（片凹型）を模擬して、狭窄血管での流動について検討したところ、赤血球が病的に硬くなることで、血流抵抗が大きく増加することがわかった。これより、赤血球が病的に硬くなるということは、単に個々の赤血球の問題ではなく、循環器系全体の問題になりうるということが示唆された。②高せん断流れ下における赤血球の変形動態を定量的に評価できるように、赤血球モデルの改良を行なった、具体的にはせん断流に対する抵抗力が非線形的に増加するようなモデルを開発した。この改良によって、低せん断流中だけでなく、非生理学的な高せん断流中においても変形動態をほぼ正確に再現できるモデルとなった。2008年度はこのモデルを用いて、過剰変形に起因する機械的溶血現象の解明に取り組む予定である。③血流を微視的な立場から見た赤血球流動と巨視的な立場から見た流体運動という2つの異なるスケールでモデル化し、それらを相互に関連づけて繰り返す血液流動のマルチスケール計算を行なった。繰り返し計算を行なった結果、微視的レベルでは赤血球は管中央付近に移動してクラスタを形成するとともに、巨視的レベルでは血流が管軸中央でほぼ平らになるような速度分布を取るようになった。計算で得られた巨視的血流の速度分布は生体内で観察されるようなものに類似しており、本計算手法は血液の流動特性を検討するのに有効であることが示唆された。

キーワード：赤血球, クラスタ形成, 流体, 多相系, 離散要素法