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学位論文題目	A Large-Scale Parallel Simulation of Blood Flow in Microvessels （微小血管における血流の大規模並列計算）
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論文内容の要旨

Chapter 1: Introduction

In blood vessels with diameters larger than 300 μm, blood may be modeled as a homogeneous fluid; however, in small vessels, *i.e.* capillaries, arterioles, and venules, the particulate nature of blood becomes more apparent, and individual cell motion affects the blood flow. Red blood cells (RBCs) are the most important constituent of blood, and comprise around 45% volume fraction of blood. In microvessels, the dynamics and deformation of RBCs at physiologically relevant hematocrits are more complex and differ from that in a dilute suspension. Deformation of RBCs leads to interesting features in microcirculation (Fåhræus effect, Fåhræus-Lindqvist effect and formation of a cell-depleted peripheral layer), and plays a very important role in triggering the release of signaling molecules such as adenosine triphosphate (ATP) in physiological processes.

Due to packing of RBCs experimental techniques still encounter difficulties owing to opaque images (light absorption by hemoglobin and light scattering by RBCs). Numerical modeling, however, can further our understanding about many physiological and pathological processes in microcirculation. It is important to simulate blood flow based on cellular scale modeling; hence, we must model RBCs explicitly. 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, exhibiting small resistances to shear and bending. This is a fluid-structure interaction problem, where the solid mechanics of the membrane must be coupled with the fluid mechanics of the cytoplasm (interior liquid) and plasma (exterior liquid). Despite the progress in RBCs modeling and their promising results, high computational expense remains a major problem, particularly for blood flow in vessels with diameters of tens or hundreds of micrometers, involving hundreds or thousands of RBCs. Thus, the dynamics and deformation of RBCs in microvessels is not quantified.

This thesis dealt with the accurate three-dimensional computational modeling and large-scale simulation of RBCs flow in microvessels. The aims of the thesis were:

I. Developing a highly scalable parallel computational framework for large-scale simulations of dense cellular flow.

II. Validating the developed model qualitatively and quantitatively.

III. Quantifying the RBC dynamics and deformation in microvessels for various conditions.

In this thesis, we first explained numerical model based on the particle method and parallel implementation of this method on distributed memory systems. We then demonstrated the accuracy of the developed method by predicting the apparent viscosity, cell-depleted layer thickness and Fåhræus effect from simulations. Finally we quantified RBC deformation and dynamics at dense cellular flow in microvessels. We then concluded this thesis, with discussing ongoing work, and giving some scopes as the future plan of this research.

Chapter 2: Numerical methods

We employed a meshless (particle) method to model microvascular blood flow. Blood was assumed as a dense suspension of initially biconcave RBCs in Newtonian plasma. All the components of blood, including plasma, cytoplasm and membrane were represented by a finite number of particles (Fig. 1). A two-dimensional spring network of membrane particles was constructed to model the deformation of RBCs. The governing equations (the continuity and Navie-Stokes equations) were discretized by using the moving particle semi-implicit method. Forces generated by the stretching/compression and bending of the membrane were substituted into the external force term in Navie-Stokes equations for membrane particles only. Because the membrane motion is tracked directly by membrane particles, the no-slip condition at the membrane is satisfied in this procedure. Boundary conditions were no-slip at the wall and a periodic boundary condition at the inlet and outlet. We confirmed that this model simulated the deformation of single RBCs by optical tweezers stretching and the deformation in shear flow with good accuracy.

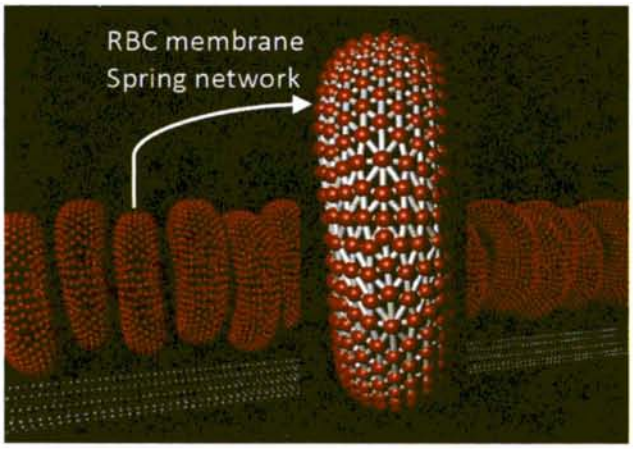

Figure 1: All the components of blood modeled by discretizing them to a finite number of particles.

Chapter 3: Parallel computation for large-scale simulation

In this Chapter, to simulate blood flow in relatively large microvessels with thousands of RBCs, we developed a highly scalable algorithm for parallel computing. The computational domain was 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 were designed in a particular order to minimize communication. For communication between processors we used a message-passing interface (MPI) library, including non-blocking communication. In a strong scaling test, we obtained a linear speedup with the number of CPU cores, and we demonstrated that our model can simulate $O(10^3)$ RBCs at high Hct blood flow (45%) through large microvessels (Fig. 2).

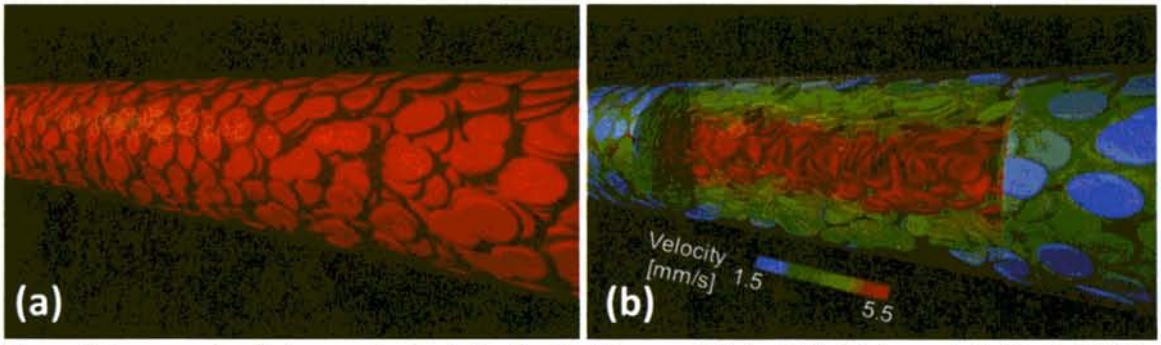

Figure 2: An example of a large-scale simulation for $D = 50$ μm and $Hct = 45\%$: (a) A snapshot of typical RBCs. (b) The domain is cut in the central plane of the vessel, and colors represent the local velocity in flow direction.

Chapter 4: Dense cellular flow simulation with accurate dynamics and rheology

In Chapter 4, the results of numerical simulation were qualitatively and quantitatively investigated and carefully compared with experimental results. Several simulations of blood flow in microvessels, typical of microcirculation and microfluidic devices were performed. The tube Hct was ranged from 20 to 45%, and the microvessel diameters were in the range from 9 to 50 μm. We visualized simulated blood flow in microvessels. In qualitative comparisons with available experimental images, our model reproduced RBCs configuration successively. For the first time, the dynamic of individual RBCs including tank treading and tumbling behavior at dense (45%) cellular flow was investigated. The membrane particles displacement for RBCs close to the vessel wall exhibited a different motion from those far from the wall, suggesting the occurrence of the swinging motion. The swinging frequency of RBCs decreased with increasing the distance from vessel wall. A tumbling-like or semi flipping motion was observed in the intermediate region *i.e.*, $R/4 < r < R/2$, where R is the vessel radius. This behavior of RBCs disappeared in the near centerline region as RBCs formed a parachute shape. The prominent tank treading and tumbling almost disappeared with decreasing the vessel size to capillaries whose diameters is in the order of an RBC diameter.

For quantitative validation, we focused on collective dynamics of many RBCs. Analysis of the simulation results was performed to study the interesting features of the blood flow in microcirculation arising from RBC deformation, *i.e.* Fåhræus-Lindqvist effect, Fåhræus effect, and the formation of a cell depleted peripheral layer. First, the Fåhræus effect (narrow tube hematocrit < discharge hematocrit) was considered. Our simulations yielded very good agreement with empirical expressions for various vessel sizes and tube Hcts. To study the Fåhræus effect, the local Hct and velocity profile were analyzed. The radial variation of the local Hct demonstrated high concentration near the vessel centerline with a

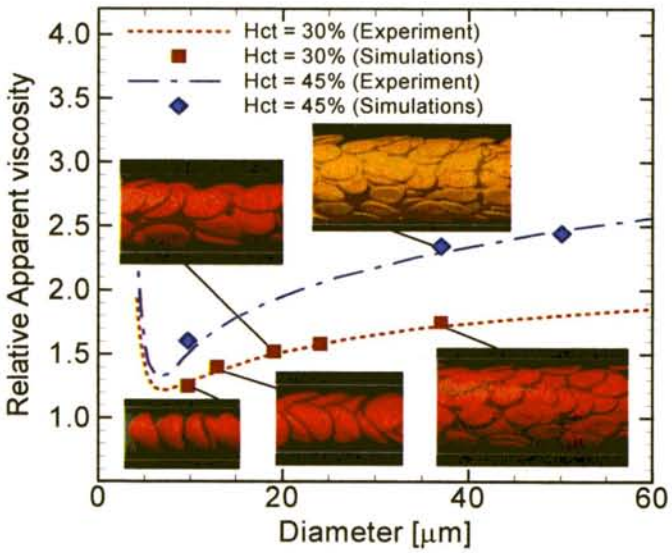

Figure 3. The relative apparent viscosity as a function of vessel diameter and Hct. Simulated results (symbols) are compared with experimental results by Pries *et al.* (1992).

sharp drop near the wall due to the RBCs migration and the formation of cell-depleted peripheral layer (CDPL). The velocity profiles near the center of the vessel seemed a nearly flat (plug flow) profile, but the velocity near the wall had a steep gradient, which matched the velocity gradient of Poiseuille flow. Velocity profile bluntness was increased with increasing Hct values. For further validation, the CDPL formation was analyzed. Our numerical results were in good agreement with the previous experimental data. Finally, the apparent viscosity of blood flow in microcirculation, which is refered as Fåhræus-Lindqvist effect, was calculated from the simulations. Our results were in excellent agreement with an empirical description of experimental results and reproduced a nonlinear increase in the apparent viscosity with the increase in the vessel diameter and Hct (Fig. 3). We further illustrated how the apparent viscosity varied as the shear rate was increased. We found that the sensitivity of shear rate to the apparent viscosity enhanced with increasing the Hct. These quantitative validations supported our model being an efficient tool for large scale simulations with realistic prediction capability.

Chapter 5: Quantification of red blood cell deformation at high-hematocrit blood flow in microvessels

Experiments have failed to observe RBC behavior at the center of microvessels for a dense suspension of RBCs, owing to the light scattering by RBCs and light absorption by hemoglobin. Instead, our method could be applied to study the deformation and interaction of RBCs in microcirculation. Hence, in Chapter 5 we quantified the deformation of RBCs in microvessels. 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 regions: near-center, middle, and near-wall regions. The influence of these factors varied with vessel diameter, hematocrit, and shear rate. To investigate the effect of the shear rate on deformation, the stretching ratio was compared among γ = 20, 95, and 150 s^{-1} for D = 37 μm and Hct = 30%. A nonlinear response to the shear rate was observed. A change from 20 to 95 s^{-1} caused a large increase in the stretch, whereas the difference in the stretch between 95 and 150 s^{-1} was small, even near the wall. We also examined the effect of the Hct on the RBCs deformation. The stretch ratio did not differ significantly among the Hct values in the near-center region. The stretch was slightly greater at higher Hcts, particularly in the near-wall region. This effect explained by the velocity profile and CFL thickness. Analyzing the stretching in smaller vessels with D = 19 and 24 μm, revealed that the near-center region was not found and almost all the parachute-shaped RBCs disappeared. To the best of our knowledge, this was the first quantitative study of the deformation of RBCs in vessels with a few tens of micrometers in diameter. These results could help for further understanding of the mechanics of blood flow and mass transport in microvessels, for example ATP release, which induces by the deformation of RBCs.

Chapter 6: Conclusions

As a brief conclusion, a large-scale parallel simulation of dense cellular flow in microvessels with accurate dynamics and rheology was developed. For the first time, we succeeded to quantify the RBC dynamics and deformation in blood flows with high Hct. The use of computational biomechanics to study blood flow especially in diseases is still in its infancy, and there are many outstanding questions that need to be addressed. The possible uses of this method include the study of blood disease in complex networks of microvasculature, the design of microfluidic devices for blood diagnosis, and to predict the diffusion of solute and drug particles. Same approaches may be applicable to studies on the behavior of other cells in microcirculation, platelets, WBCs, cancer cells, etc.

論文審査結果の要旨

血液は赤血球の懸濁液であり，血流の力学特性および物質輸送特性を理解するためには，まず，流動する赤血球の挙動を解明する必要がある．数値計算はこのための有効な方法論となるが，膨大な計算負荷のため，血管径 10 μm 程度までしか計算ができないことが課題であり，大規模計算を可能とする新しい計算手法が必要である．本論文は，これらの研究成果をまとめたものであり，全編 6 章からなる．

第 1 章は，序論であり，本研究の背景，目的を述べている．

第 2 章では，基礎となる支配方程式および離散化手法について説明しており，血漿，赤血球膜，赤血球内部流体を連成計算するための粒子法について述べている．

第 3 章では，領域分割法に基づく並列化手法を提案し，プロセッサの台数にほぼ比例する高速化を達成し，64 プロセッサのシステムでも血管径 50 μm 程度の計算が可能であることを示している．この並列化手法は，粒子懸濁液の流動計算に対し，幅広く応用できる重要な成果である．

第 4 章では，開発した計算手法の実現象の再現性について詳細に検討している．微小血管内の血流の特徴量である，みかけの粘度や血漿層厚さなどについて，過去に報告されている実験値と比較し，非常に良い一致が得られることを示している．これは，計算手法の妥当性を明らかにした重要な成果である．

第 5 章では，微小血管を流動する赤血球の変形量を定量化することに初めて成功している．局所的なせん断応力分布および壁の影響により，管軸近傍，管壁近傍およびその中間領域では変形が異なり，また，管径，流量および赤血球体積率によって変化することを明らかにしている．これは，赤血球の変形能が低下するマラリアなどの疾患や変形能に伴う膜からの ATP 放出などを理解する上で，基礎的な知見となる重要な成果である．

第 6 章は結論である．

以上要するに本論文は，微小血管における血流の大規模並列計算手法を開発し，実際の赤血球流動現象の再現性を示すとともに，微小血管を流動する赤血球の運動および変形を解明したものであり，医工学及び計算力学の発展に寄与するところが少なくない．

よって本論文（医工学）の学位論文として合格と認める．