Multiscale Simulations for Fluid Structure Interaction Problems with Biomedical Applications

Shu Takagi, Kazuya Shimizu, Satoshi Ii, Kazuyasu Sugiyama and Kohei Okita

Abstract A numerical method for massively parallel computing to solve fluid-structure interaction problems was developed and the method was employed for solving the multiscale problems in biomedical applications. As one of the examples, a platelet adhesion process to the vessel wall, which occurs at the initial stage of a thrombosis, was analyzed using the multiscale method of coupling continuum scale finite difference method with the molecular scale Monte Carlo method. The platelets adhesion to the injured vessel wall is caused by the protein-protein binding (GP1b-α on the platelet—VWF on the wall.). This protein-protein binding force is evaluated by Monte Carlo simulation, solving the stochastic process of each biding. Adhered platelets also feel the fluid mechanical force from blood flow and this force is affected by the presence of red blood cells, which causes the drastic change to the adhesion process. As another example of multiscale simulations, ultrasound therapy method using microbubbles are also explained.

Keywords Finite difference method · FSI · Protein-protein binding
Full eulerian formulation · Massively parallel computing · Blood flow
Ultrasound · Microbubbles

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1 Introduction

Fluid-Structure Interaction (FSI) phenomena are ofter observed in many situations, e.g., biological systems, and industrial processes. The computational Fluid dynamics is more conventionally described in Eulerian frame, while the computational structure dynamics is more straightforward to be described in a Lagrangian way. The coupling of the Fluid and structure dynamics is not always a easy task due to this difference in the numerical framework. In this paper, a full Eulerian approach for the continuum scale fluid-structure coupling and also fluid-membrane coupling problems is introduced and the method is further extended to multiscale problems such as continuum-molecular coupling ones.

Thinking about the analysis using the voxel data converted from the medical image data of MRI or CT, it is straightforward to develop the full Eulerian finite difference methods, which can directly utilize the voxel data to describe the boundary on the fixed Cartesian meshes and avoid complicated process in mesh generation and reconstruction. Sugiyama et al. [9] developed a novel full-Eulerian FSI solver, and it was extended to a fluid and stiff material interaction and fluid and membrane interaction [4, 5, 11]. The method is also suitable for the massively parallel computation [10] and achieved actual speed of 4.5 peta flops, which was the world-fastest FSI simulation in the year of 2012. The method was used to analyse the platelet adhesion process on the injured vessel wall, which corresponds to the initial stage of thrombosis. To simulate this process, the molecular scale protein-protein binding needs to be considered with the blood flow simulation.

As another example of multiscale problems in the medical applications, high intensity focused ultrasound (HIFU) simulations with the utilization of microbubbles for the ultrasound therapy is introduced. In this method, bubble dynamics equations are coupled as small-scale phenomenon in both space and time with the large-scale fluid mechanical or acoustic field equations. These kinds of multiscale methods developed by the authors are explained in this paper.

2 Multiscale Method for Fluid-Structure-Protein Dynamics Coupling

2.1 Full Eulerian Method for FSI Problems

As is mentioned in Introduction, we have been working on a novel numerical method for fluid structure interaction (FSI) problems, which is available for massively parallel computing. Sugiyama et al. [9] developed a full-Eulerian FSI solver with fixed grid system, which is suitable for introducing the voxel type medical image data. In this method, the concept of well-known VOF method for two-phase flows are introduced for fluid and hyperelastic-materials interaction problems. Since the original VOF method using the one-equation Eulerian formulation cannot keep

the information of the material points to link between the reference and current configurations, a method to quantify the amplitude of deformation is required. For this purpose, we introduced Eq. (1), which gives the advection equation for left Cauchy-Green deformation tensor defined on each grid point, and this equation is temporally updated on the fixed grid system.

$$\partial_t \mathbf{B} + (\mathbf{v} \cdot \nabla)\mathbf{B} = \mathbf{L} \cdot \mathbf{B} + \mathbf{B} \cdot \mathbf{L}^T, \quad \text{where} \quad \mathbf{L} = \nabla \mathbf{v}^T. \tag{1}$$

This full-Eulerian approach method has been reviewed by Takagi et al. [11]. The simulation example of large scale parallel computation with $O(10^6)$ flowing RBC-like hyperelastic particles are shown in Fig. 1.

2.2 *Full Eulerian Method for Fluid-Membrane Interaction Problems*

The above-mentioned method was further developed for fluid-membrane interaction problems and applied to the blood flows containing Red Blood Cells and platelets. Ii et al. [4, 5] developed a full Eulerian fluid–membrane interaction method as an extension of the concept proposed by Sugiyama et al. [9]. In this method, a smoothed volume fraction (VOF) function is introduced to express a material phase describing each fluid. This VOF function ϕ chages the value from 0 to 1 within a few computational meshes. A membrane transition region Γ is

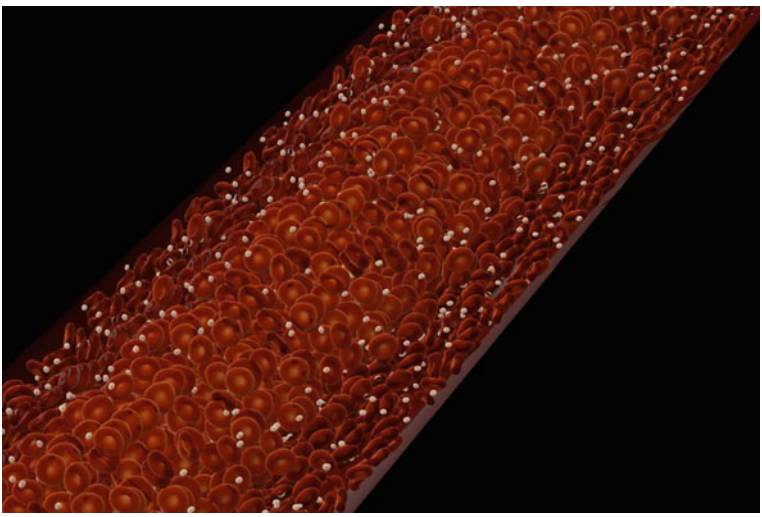


Fig. 1 Large scale parallel computation with $O(10^6)$ deformable hyper elastic particles

expressed as $|\nabla\phi| \leq \varepsilon$, where $|\nabla\phi|$ corresponds to a smoothed Delta function (e.g. [2] and ε is an arbitrarily value depending on the mesh size.

Introducing a basic theory on the finite deformation [1, 8], a set of governing equations with a one equaion formulation for the mixture is given in the Eulerian frame. The discretization of a set of PDEs is given in the finite difference/volume manner, and the SMAC algorithm is employed for the coupling of the pressure and velocity fields using the staggered arrangement. More detailed description on the numerical methods is given in [4, 5].

As one of the examples for the numerical simulations, the flows containing many RBCs and some platelets in an capillary tube are shown in Fig. 2. Snapshots of numerical results at $t = 7.5$, 30 and 75 ms are shown. It is found that the initially-distributed RBCs interact and are mixed in time. Each RBC has a different shape of a parachute type or slipper one reported in both experiment [3] and a numerical simulation [12]. The deformed RBCs tends to flow near the axial center due to a hydrodynamic effect, causing a plasma phase near the wall, so-called the cell-free layer.

2.3 *Multiscale Coupling Method for Simulating the Platelet Adhesion Process*

Thrombosis is one of the most important diseases causing the myocardial and cerebral infarctions. This disease is caused with a very complicated mechanism

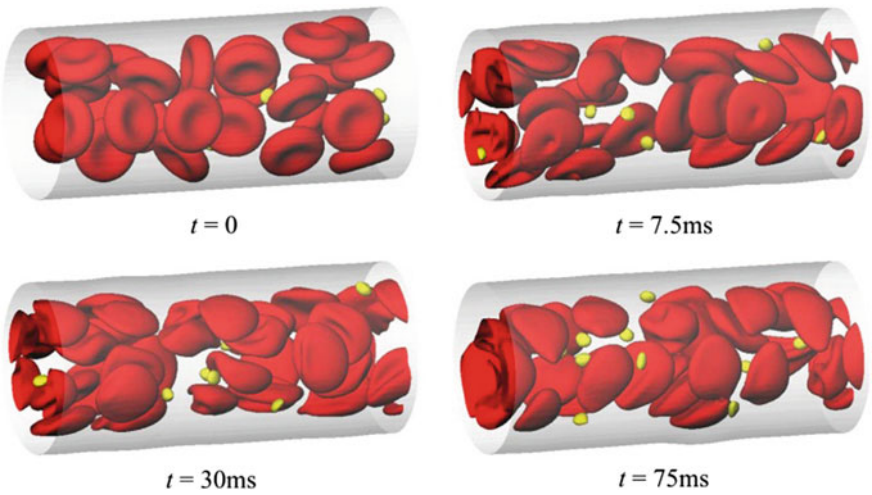


Fig. 2 Simulated results of flowing RBCs and platelets. Reproduced from Ii et al. [4]

affected from molecular scale protein-protein interaction to continuum scale fluid mechanical interaction in blood flow. In the initial stage, platelets start showing the aggregation at the injured wall, where von Willebrand Factor (VWF) is attached. The Glycoprotein, GPIb-α, on the platelet membrane shows ligand-receptor type interaction with this VWF. Through the binding force between GPIb-α and VWF, platelets start showing adhesion around this spot. From this stage, very complicated activated process of platelets and interactions with blood, vessel walls red blood cells, fibrin etc. occur. And, finally, they end up with the occlusion of the vessels.

Here, the numerical model for conducting the initial stage of thrombus formation is explained. To analyze this process, we used the above-explained the full Eulerian fluid-membrane coupling method. The method is further coupled with the stochastic Monte Carlo method for the interactions between GPIb-α and VWF molecules. The basic concept of this multiscale thrombosis simulator is given in Fig. 3.

Using this simulator, the influence of RBCs on the platelets adhesion process was investigated. It was shown from the simulation that the adhesion of platelets does not occur without the presence of RBCs. The velocity fluctuation in the wall-normal direction caused by the presence of RBCs plays an essential role to have the platelets adhesion. The snapshot of the platelet adhesion in the presence of RBCs are shown in Fig. 4.

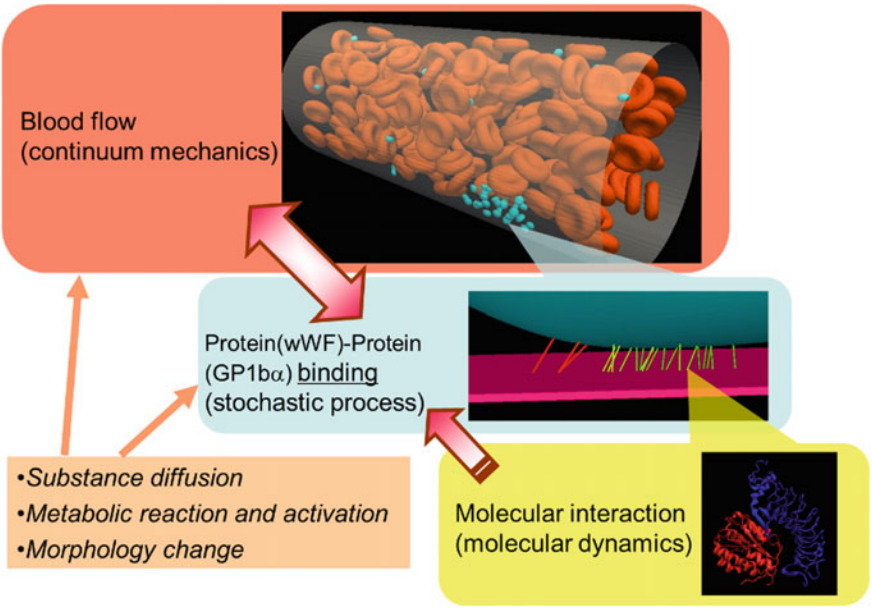


Fig. 3 Concept of multiscale modeling of thrombosis

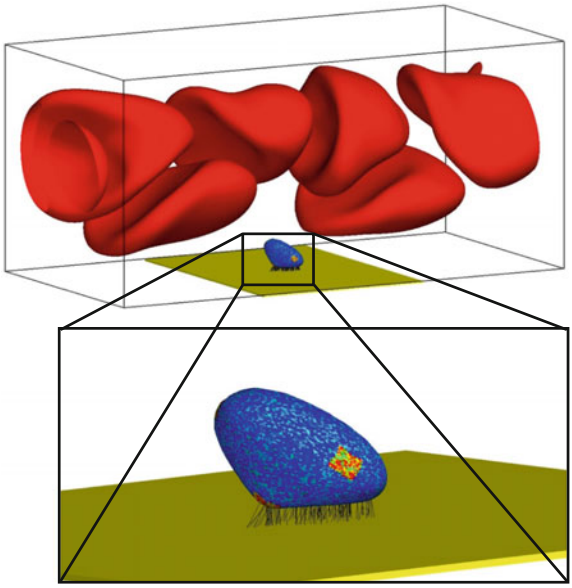


Fig. 4 Simulation result of platelet adhesion in the presence of RBCs

3 Multiscale Simulations of HIFU with Microbubbles

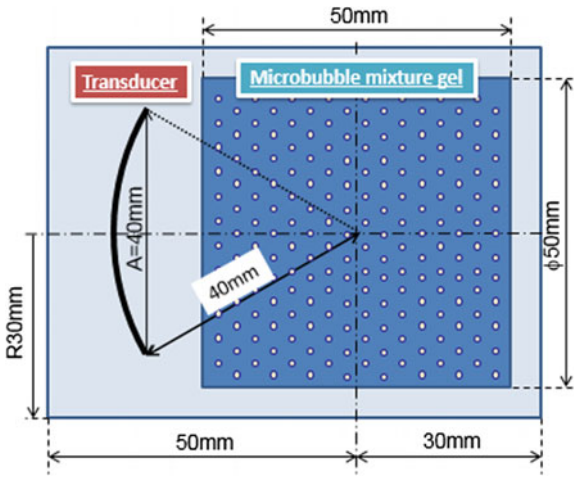
3.1 Microbubble Enhanced HIFU

Ultrasound therapy is a rapidly growing technique, which is expected to be one of the minimally-invasive methods. In ultrasound therapy, High Intensity Focused Ultrasound (HIFU) is used to achieve the local treatment with the high energy deposition. This treatment is known to be enhanced using the ultrasound contrast agent microbubbles [6]. That is, the heat generated by the bubble motion contributes an enhanced localized heating effect, via volume oscillation of bubbles. The behavior of microbubbles in a focused ultrasound field is not well investigated due to the complex interactions between the oscillating bubbles and the ultrasound. Here, as another example of the multiscale coupling method, the simulation method for microbubble-enhanced HIFU is introduced.

3.2 Simulation Model

Numerical simulations were conducted for the focused ultrasound in microbubble mixture gel shown in Fig. 5. For ultrasound propagation, bubbly flow mixture equations are solved as large-scale equations. The basic equations are discretized by a sixth-order finite difference scheme in space and are developed temporally on the basis of the finite-difference time-domain (FDTD) method with orthogonal mesh.

Fig. 5 Simulation Setup



The signed distance function is employed for the shape representation of a transducer in the computational domain. Ultrasound irradiations are represented as the sound source or sink corresponding to the volume fraction of transducer. The perfectly matched layer (PML) is employed to represent the nonreflecting boundary.

For the small-scale bubble behaviors to resolve the rebound of bubble collapse, the bubble dynamics equation given by Eq. (2) is integrated in adaptive time increments that are consistently smaller than the time increment for the integration of the basic equations for the mixture. Bubbles are described by the representative bubble at the Lagrange point x_B and coupled with the mixture phase by the Euler–Lagrange method, which requires the interpolation of physical values between Euler and Lagrange points.

More detail description for the numerical method is given in [7].

$$\rho_L\left[\left(1-\frac{\dot{R}}{c}\right)R\ddot{R}+\left(1-\frac{1}{3}\frac{\dot{R}}{c}\right)\frac{3}{2}\dot{R}^2\right]=\left(1+\frac{\dot{R}_2}{c}\right)\left[P_G-P_S-\frac{2\sigma}{R}-4\mu\frac{\dot{R}}{R}-\frac{4}{3}G\left[1-\left(\frac{R_0}{R}\right)^3\right]\right]$$
$$+\frac{R}{c}\left[\frac{dP_G}{dt}-\frac{dP_S}{dt}+\frac{2\sigma}{R}\frac{\dot{R}}{R}+4\mu\left(\frac{\dot{R}}{R}\right)^2-4\mu\frac{\ddot{R}}{R}-4G\left(\frac{R_0}{R}\right)^3\frac{\dot{R}}{R}\right] \tag{2}$$

3.3 Numerical Results

Numerical simulations were conducted for the different microbubble concentrations. The comparison between numerical results and experimental results are shown in Fig. 6. Both results show good agreements and indicate that the higher

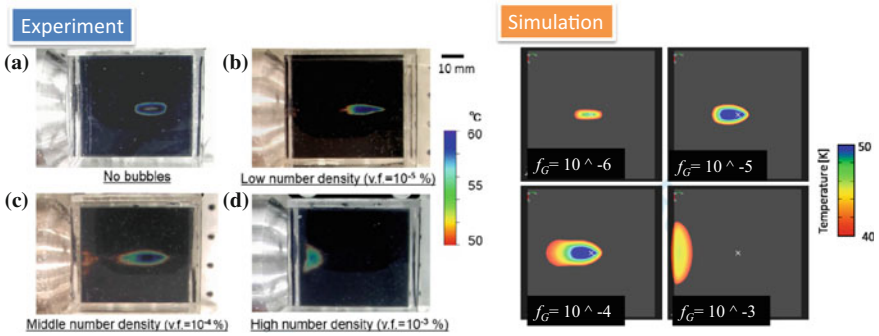


Fig. 6 Temperature rise distribution of HIFU for different bubble concentrations

concentration give the temperature rising spot coming closer to the transducer. This interesting behaviour comes from the fact that each bubble dissipates the energy due to bubble oscillation, and this gives the shielding effect of pressure wave propagating in bubbly liquid mixture with the increase of bubble concentration.

4 Conclusions

In this paper, 2 types of multiscale simulations have been briefly introduced. The present simulation results support some experimental results and help us to understand what is going on in the microscale phenomena. The concept of the present methods is available for many other problems. More detail discussion for the limitation of the methods will be important for the wide area of the applications.

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