Multiscale Simulation on the Initial Stage of Thrombus Growth

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Introduction

The fastest supercomputer in Japan, which is called "K", achieved 10 Peta flops speed with LINPACK performance and is now under the development of various kinds of application software. In the present talk, related to this software development, the multiscale modeling of thrombosis simulator is explained and the numerical results of the platelet adhesion on vessel walls, which corresponds to the initial stage of thrombus growth, are discussed.

As is well-known, the top three diseases for the causes of death are cancer, cardiovascular disease and cerebral vessel one. Among these diseases, the myocardial and cerebral infarctions are eventually caused by thrombosis. Therefore, thrombosis is regarded as one of the most important diseases, which cause the death and serious after effect. Thrombosis is, however, very complicated disease which is affected from molecular scale protein-protein interaction to continuum scale in blood flow. Fig.1 illustrates how the heart attack occurs from the viewpoint of multiscale nature of thrombosis. Initially, platelets start aggregate at the injured wall, where von Willebrand Factor (vWF) is attached. The Glycoprotein, GP1b-α, on platelet membrane starts showing ligand-receptor interaction with this vWF and platelets start aggregating 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 they end up with the blockage of the vessels.

In this study, we develop the numerical model of the initial stage of thrombus formation and discuss the simulation results. Fig.2 is the schematic figure to illustrate the idea of current approach; the continuum scale blood flow containing RBCs and platelets is coupled with the molecular scale ligand-receptor biding effects between the platelets and vessel walls. First, the continuum scale modeling is explained as a macroscopic modeling. Then, the molecular interaction between GP1b-α on a platelet and vWF on the vessel wall is explained as a microscopic modeling. Finally, the coupling effect is discussed.

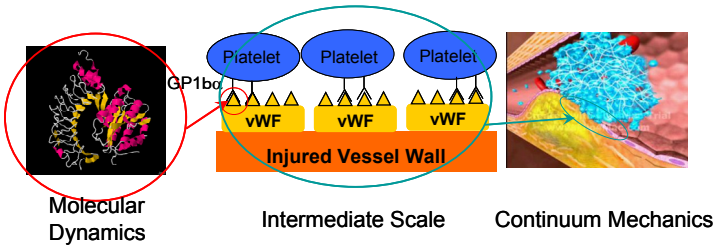


Fig. 1 Multiscale phenomena related to thrombosis

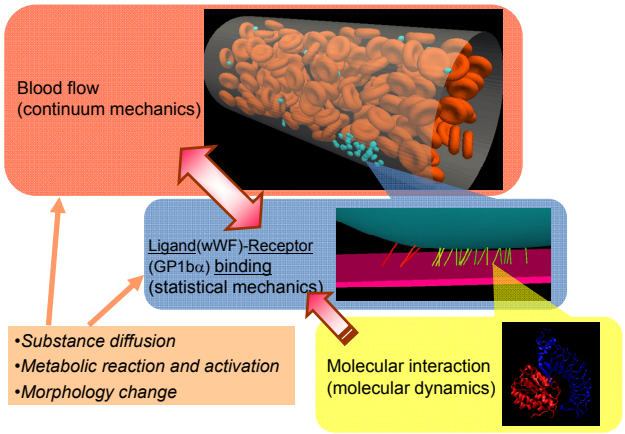


Fig.2 Multiscale modeling on the platelets adhesion

Macroscopic Modeling: Continuum Scale

A blood is a suspension flow which includes bio-membrane vesicles such as red-blood-cell (RBC), platelet and leucocyte. Especially, the RBCs mainly occupy the human blood approximately 45% of its volume. Due to the high concentration of the RBCs and their movement in the core region of the vessels,, the platelets tend to move near the vessel wall and to immediately aggregate on the injured wall. To analyze these phenomena, in the continuum scale, the coupling method with the blood flow and membrane motion is an important issue.

Here, we have developed the full Eulerian fluid-membrane coupling method [1], which is a further extension of the full Eulerian fluid-structure coupling method [2] suitable for massively parallel computation. Assuming that the fluid (i.e. blood plasma) is incompressible and Newtonian, the mixture Navier-Stokes equations including a closed membrane are given with one equation formula using VOF function to express the stress jump on the membrane, where the following advection equation of surface left Cauchy-Green deformation tensor $\mathbf{G}_s$ is additionally solved to calculate the stress on hyperelastic membranes.

$$\frac{D\mathbf{G}_s}{Dt} = \nabla \mathbf{v}^T \cdot \mathbf{G}_s + \mathbf{G}_s \cdot \nabla \mathbf{v} \tag{1}$$

The equations are solved on the fixed Cartesian mesh and obtained with the standard finite difference/volume method. We also consider the molecular scale ligand-receptor binding force which adhere the platelet on injured wall. The force is evaluated using stochastic Monte-Carlo simulation as explained below.

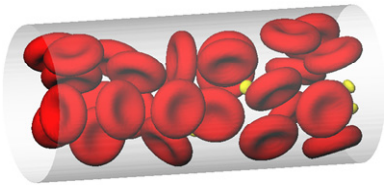
Microscopic Modeling: Molecular Scale

Stochastic Monte Carlo (SMC) simulation[3] and Molecular Dynamics (MD) simulation is conducted in order to evaluate the adhesion force between a platelet and vessel wall in the phenomenon of the primary aggregation of platelets. When the endothelial-cells on the vascular surface get damaged, von Willebrand factor (vWF) instantly binds to exposed subendothelial tissues. Platelets can adhere to the vessel wall through the interaction between vWF A1 domain (vWFA1) and platelet glycoprotein Ibα (GPIbα). vWFA1 – GPIbα bond has a short life-time and by itself cannot make irreversible adhesion. The number of bonds is stochastically estimated by SMC simulation and the total adhesion force of a platelet, which has 15000 – 20000 GPIbα on its surface, is obtained. This force is coupled with continuum scale simulations through the source term in Momentum equation, i.e., Navier-Stokes equation.

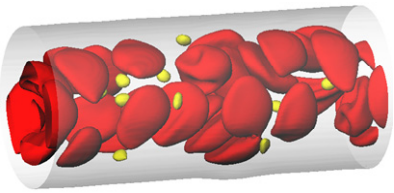
Results and Discussion

The pressure driven flows including the multiple RBCs and platelets in a circular tube were carried out. Fig.3 illustrates the time evolution of the shape of RBCs and platelets, and Fig.4 does the time evolution of platelets location. It is well-known that, in actual blood flows, RBCs tends to flow in the center of vessels with large deformation constructing so-called blood plasma layer, and that small platelets tends to flow in this plasma layer. From Fig.4, it is observed that, once the platelets are coming closer to the vessel wall, they stays there and it is rarely observed that they go back to the center region of vessels.

Next, the effect of RBCs on the adhesion of platelets is shown in Fig.5. It is very interesting to see that platelet which is initially located slightly away from the vessel wall does not come to adhere on the wall without RBCs. This is because the platelets flow with the plasma and it has a low probability to come close to the vessel wall. On the other hand, in the presence of RBCs, platelets are much easier to adhere on the wall because RBCs produce the velocity fluctuation in the normal direction of the wall. This simulation results support the fact that thrombus does not glow without the presence of RBCs. We are also developing the method to include the bio-chemical reactions caused after the activation of platelets triggered by the GP1bα-vWF binding. These results will be also presented in the talk.



(a) t= 0.0 [s]



(b) t= 75.0 [ms]

Fig. 3 Time evolution of RBCs shape and location

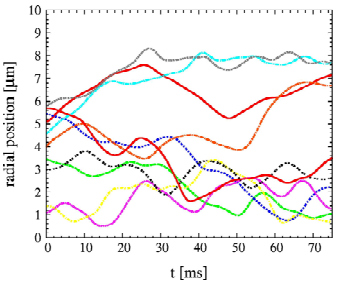


Fig. 4 Time evolution of platelets location

Summary

The novel fluid-membrane interaction method was developed using full-Eulerian formulation with finite difference discretization. The method also introduces the molecular scale ligand-receptor binding effect between platelets and vascular endothelium through the coupling with the stochastic Monte Carlo method. The results illustrate that platelets are much easier to aggregate on the vessel wall in the presence of red blood cells and the effect of red blood cells and molecular interaction force is quantitatively discussed using the present method

Aknowledgement

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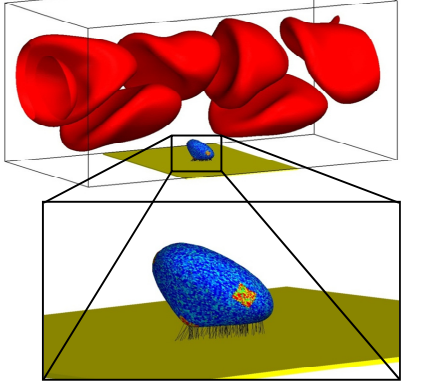
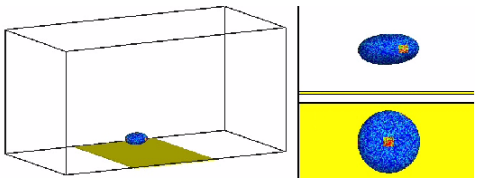
References

[1] S. Ii *et al.*, *Communication in Computational Physics*, **12** , 544 (2012).
[2] K. Sugiyama *et al.*, *J. Comput. Phys.* **230**, 596 (2011).
[3] M. Dembo *et al.*, *Proceeding of the Royal Society B* **234**, 55 (1988).



(a) with RBCs



(b) without RBCs (no adhesion)

Fig.5 Effect of RBCs on platelet adhesion