A Thrombus Growth Model Based on Level Set Methods

Chaoqing Ma, Oubong Gwun

Abstract

In this paper, a multi-scale model is applied to the simulation of thrombus growth. This model includes macroscale model and microscale model. The former is used to model the plasma flow with Navier-Stokes equations, and the latter is used to model the platelets adhesion and aggregation, thrombus motion, and the surface expansion of thrombus. The force acting on platelets and thrombus from plasma is modeled by the drag force, and the forces from biochemical reactions are modeled by the adhesion force and the aggregation force. As more platelets are merged into the thrombus, the thrombus surface expands. We proposed a thrombus growth model for simulating the expansion of thrombus surface and tracking the surface by Level Set Methods. We implemented the computational model. The model performs well, and the experimental results show that the shape of thrombus in level set expansion form is similar with the thrombus in clinical test.

Keywords : thrombosis | computational model | Level Set Methods

I. INTRODUCTION

Thromboembolism is a life-threatening disorder with high morbidity, disability and death rate. The causes of thrombosis are endothelial injured, abnormal blood flow, and hypercoagulability. The thrombus is the product of thrombosis which is a blood clot containing blood cells and fibrous proteins. The crumbling thrombus and large thrombus may cause myocardial infarction and stroke. For this reason, the research of thrombosis prevention and treatment become important in which the clinical tests and experiments carried out in laboratory are required.

In recent years, the simulation of thrombosis becomes a new research trend because of cost saving and easy operate. In the simulation, the computational model describes the process of thrombosis, and computer technology implements the simulation. Numerous computational models have been proposed in the papers of thrombosis simulation. Since the blood clotting is a multi-scale phenomenon, the multi-scale models are the most-used model style. It combines macroscale model which models the blood flow with macroscopic properties such as velocity and viscosity, and microscale model which models the biochemical reactions among microscopic bodies such as blood cells and fibrin. Z. Xu et al. proposed a multi-scale model in which the blood flow is described through continuum Navier-Stokes equations in macroscale model and the interaction between blood cells and fibrinogen is described through an extended stochastic discrete cellular Potts model [1]. H. Kamada et al. also proposed a multi-scale model. The particles semi-implicit method is used to model blood flow in macroscale and a spring force is used to model the interactions between platelets and injured vascular wall in microscale [2]. Both of the models are well used in researches about thrombus development [3-6]. The common point of these models is that the thrombus is in the form of particles aggregation, because the blood cells and fibrinogen are all particles. It raises the problem that the surface and the shape of thrombus are not accurate which affects the accuracy of the impact of thrombus

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growth to blood flow. In the paper of A. L. Fogelson et al. [7] and the paper of F. F. Weller [8], the thrombi in their models is continuum. Although the surfaces of thrombin are continuum and smooth curves, without platelets, the process of platelets adhesion and aggregation are not intuitive.

In this paper, we proposed a multi-scale model for thrombus growth containing both particles and smooth thrombus surface. In this model, the macroscale model is used to model plasma flow based on Navier-Stokes equations, and the microscale model is used to model platelet adhesion and aggregation, and thrombus growth. To keep the thrombus surface smooth and continuum, we proposed a thrombus growth model for surface expansion. The thrombus surface expands by the growth model, and is tracked by Level Set Methods.

II. LEVEL SET METHODS

Level Set Methods introduced by S. Osher and J. A. Sethian are numerical techniques for interface tracking using level sets [9]. One of the advantages of Level Set Methods is that it is easy to follow the object shapes that change topology. The level sets are described through level set function ϕ, and signed distance function is most-used as shown equation (1) and (2):

$$\phi(\vec{x}) = \begin{cases} \text{distance}(\vec{x}) & : \vec{x} \text{ is outside} \\ -\text{distance}(\vec{x}) & : \vec{x} \text{ is inside} \end{cases} \quad (1)$$

$$\text{distance}(\vec{x}) = \min_{\vec{p} \in \text{Surface}} \|\vec{x} - \vec{p}\| \quad (2)$$

where $\vec{p}$ is the closest point on the surface to $\vec{x}$. The point on the object surface has the level set $\phi = 0$. The point inside the object has the level set $\phi < 0$, and that outset the object has the level set $\phi > 0$.

If the surface moves under a speed $\vec{F}$, the level set equation describes the time evolution of the level set function ϕ shown as below:

$$\phi_t + \vec{F}|\nabla\phi| = 0 \quad (3)$$

$$\text{given } \phi(\vec{x}, t = 0) \quad (4)$$

where t is time. The speed $\vec{F}$ has three terms [10]:

$$\vec{F} = \vec{F}_{\text{prop}} + \vec{F}_{\text{curv}} + \vec{F}_{\text{adv}}$$

where $\vec{F}_{\text{prop}}$ is the propagation expansion speed, $\vec{F}_{\text{curv}}$ is the speed depend on the curvature, and $\vec{F}_{adv}$ is the advection speed. By defining different speed function, Level Set Methods can be applied to various fields.

III. COMPUTATIONAL MODEL OF THROMBUS GROWTH

In our simulation, we assume that only platelets and plasma are in the vessel. The thrombosis is caused by injured vascular wall, and the thrombus is the primary thrombus which contains platelets only. In the model, plasma flow is an incompressible viscous Newton fluid, and the flow of plasma is modeled in macroscale. Platelets are small solids which get the motion from plasma, but not affect the plasma flow. Platelet adhesion and aggregation are two phases of thrombosis, and they are modeled in microscale. Thrombus is a big solid which as same as vascular wall, affects the plasma flow. The growth of thrombus is modeled in microscale, too. The level sets of the model are defined as Fig. 1.

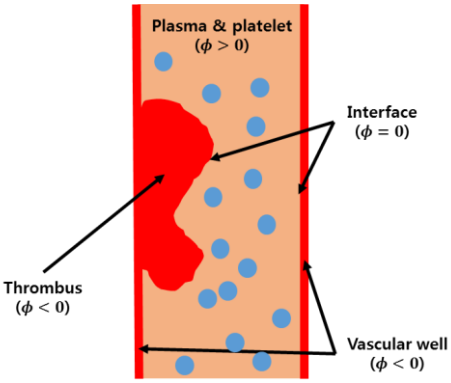

Fig. 1. Illustration of the level sets in the model.

1. Model of plasma

The motion of plasma flow is generated by the continuum Navier-Stokes equations as following:

$$\frac{\partial \vec{u}}{\partial t} + \vec{u} \cdot \nabla \vec{u} + \frac{1}{\rho} \nabla p = \vec{a} + \nu \nabla \cdot \nabla \vec{u} \quad (5)$$

$$\nabla \cdot \vec{u} = 0 \quad (6)$$

Equation (5) is the momentum equation showing how the fluid flows under the influences of pressure p, acceleration $\vec{a}$, and kinematic viscosity ν. In the equation, $\vec{u}$, t, and ρ are the fluid velocity, time, and fluid density, respectively. Equation (6) shows the incompressibility condition ensuring the fluid is incompressible.

All the parameters in Navier-Stokes equations and the level set function ϕ for plasma are stored in a Marker-and-cell (MAC) grid [11] as shown in Fig. 2.

The plasma flow supplies the basic motion of

platelets and has interaction effects with thrombus.

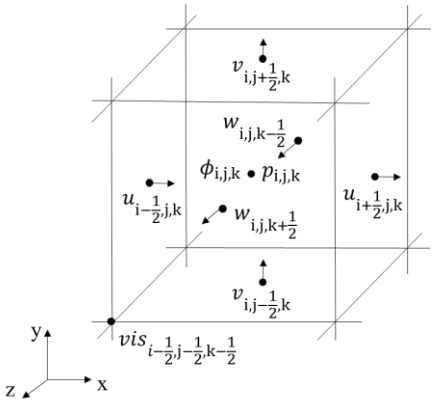

Fig. 2. An example of MAC grid cell.

2. Model of platelets

The motion of platelets is under three force, drag force from plasma flow, adhesion force and aggregation force caused by blood clotting mechanism.

According to one-way coupling, Platelets get drag force from plasma to keep moving, but they do not give any force to plasma in turn. The drag force is calculated as below:

$$\vec{F}_{dr\_p} = \iint_{S_p} D(\vec{u}_{plasma} - \vec{u}_{platelet})\, dS \quad (7)$$

where S_p is the platelet surface, and $\vec{u}_{platelet}$, $\vec{u}_{plasma}$ are the velocity of platelet, the velocity of plasma surrounding the platelet each. D is a coefficient proportional to the plasma viscosity.

Platelet adhesion and aggregation are two important biochemical reactions. Platelet adhesion is the reaction between platelets and injured vascular wall and platelet aggregation occurs between platelets and platelets having adhered or aggregated which can be seen as the thrombus. We defined radius R_{ad} and radius R_{ag} to judge if a platelet has adhesion force and aggregation force. If the distance between a platelet and the injured vascular wall is smaller than R_{ad}, the platelet has adhesion force calculated as below:

$$\vec{F}_{ad\_p} = \iint_{S_{ad}} F_{ad\_max} \frac{R_{ad} - \|\vec{x} - \vec{p}\|}{R_{ad}} \hat{i}\, dS \quad (8)$$

where S_{ad} is the surface of injured vascular wall inside R_{ad}, $\hat{i}$ is a unit vector pointing from the platelet $\vec{p}$ to the point $\vec{x}$ on S_{ad}, and F_{ad_max} is the maximum of the adhesion force.

As similar as adhesion force, if the distance between a platelet and the thrombus is smaller than R_{ag}, the platelet has aggregation force:

$$\vec{F}_{ag\_p} = \iint_{S_{ag}} F_{ag\_max} \frac{R_{ag} - \|\vec{x} - \vec{p}\|}{R_{ag}} \hat{i}\, dS \quad (9)$$

where S_{ag} is the surface of thrombus inside R_{ag}, and F_{ag_max} is the maximum of adhesion force.

3. Model of thrombus

When a platelet is stuck on the thrombus or the injured vascular wall, we think it as a new part of the thrombus and merge it into the thrombus. In the previous works shown in the introduction part, the growth of thrombus is just particles aggregation. In this paper, the growth of thrombus is the expansion of thrombus surface by Level Set Methods.

To construct the speed we need to consider the size of platelets and the deformation of platelets in the merging. There are two conditions for the surface expansion. One is the curve of deformation is a bell-shape curve, and the other one is the volume of the expansion is equal to the platelet volume. Therefore, we choose 2D Gauss function (equation (10)) to define the speed function.

$$f(x,y) = A \exp\left(-\left(\frac{x^2}{2\sigma^2} + \frac{y^2}{2\sigma^2}\right)\right) \quad (10)$$

The speed function of thrombus expansion is defined as below:

$$\vec{F}(\vec{x}) = f(\text{distance}(\vec{x},\vec{p}))\hat{n} \quad (11)$$

where $\vec{x}$ is the point on the thrombus surface, $\vec{p}$ is the touch point of the stuck platelet and thrombus, and $\hat{n}$ is the normal of thrombus surface. $f(\text{distance}(\vec{x},\vec{p}))$ is the 2D Gauss function in which $x = y$ using the distance as the parameter. So the highest value occurs in the touch point $\vec{p}$, and the values decrease with $\vec{x}$ far from $\vec{p}$. Because the value of the point $\vec{x}$ very far from $\vec{p}$ is almost zero, we use the distance to decide if this surface point has speed. By adjusting the value of A and σ, we can control the high and the width of the expansion. But the volume of the area under the Gauss curve should equal to the platelet volume.

The thrombus is a big solid inside the vessel. Plasma flow acts force on the thrombus and is affected by the thrombus at the same time. The drag force on thrombus from plasma flow is as below:

$$\vec{F}_{dr\_t} = \iint_{S_{tp}} D\vec{u}_{plasma}\, dS \quad (12)$$

where S_{tp} is the interface of thrombus and plasma. Another force which keep the thrombus sticking to the injured vascular wall is the adhesion force, and it is calculated as:

$$\vec{F}_{ad\_t} = \iint_{S_{tv}} \vec{F}_{ad\_max}\hat{n}\, dS \quad (13)$$

where S_{tv} is the interface of thrombus and injured vascular wall, and $\hat{n}$ is the normal of the interface. The thrombus will break off from the vascular wall if the drag force $\vec{F}_{dr\_t}$ becomes larger than the adhesion force $\vec{F}_{ad\_t}$. Then the thrombus flows under the drag force only.

IV. EXPERIMENTAL RESULTS

We implemented the proposed multi-scale model and visualized the process of thrombus growth by the Visualization Toolkit (VTK).

We test the model in a part of virtual vessel as shown in Fig 3. The virtual vessel is a straight tube, and outside the vessel, we define a MAC grid box to build the MAC grid. Platelets distribute uniformly in the vessel, and the platelets positions are randomly assigned. The direction of blood flow is the positive direction of x axis. To keep the number of platelets in the vessel is fixed, a number of platelets are added from the vessel entry as platelets flow out the vessel. A part of injured vascular wall is located near the vessel exit.

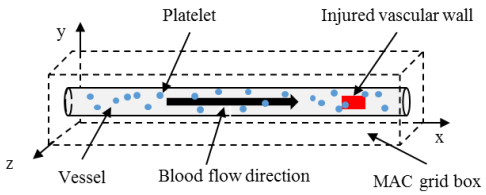

Fig. 3. Illustration of the virtual vessel.

The parameter values of the simulation are shown in Table 1. We assumed the virtual vessel is venule.

Table 1. The values of parameters used in the simulation.

	Parameter	Value
Parameters of venule	Reynolds Number	0.01
	Velocity of blood flow	2 mm/s
	Reynolds Number	0.02 mm
Parameters of model	Resolution of MAC grid	$30 \times 60 \times 30$
	R_{ad}	0.725×10^{-2} mm
	R_{ag}	0.725×10^{-2} mm
	F_{ad_max}	0.025N
	F_{ag_max}	0.0125N
	D	ν
	ν	0.000345 pa·s
	Diameter of platelet	0.29×10^{-2} mm

The experimental results are shown in Fig. 4 and Fig. 5. There are two tests, and in every test we give the thrombus in level set expansion form and particle aggregation form. Fig. 4(a) and Fig. 5(a) are the whole vessels in the process of thrombus growth. Fig. 4(b) and Fig. 5(b) are the enlarged drawing of the thrombus in particle aggregation form. Fig. 4(c) and Fig. 5(c) are the level set expansion form of the thrombus. Because different methods are used in thrombus growth, the difference between the shapes of two kinds of thrombi is significant. Compared with the thrombus modeled by particle aggregation, the thrombus modeled by level set expansion is much more similar to the real primary thrombus in dialysis venous tubing [12] shown in Fig. 6.

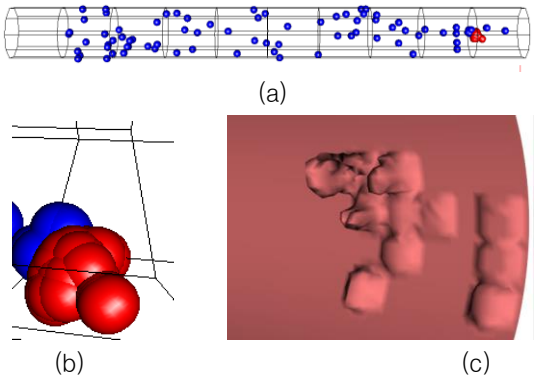

Fig. 4. The experimental results of test 1. The time is 0.2s and the number of platelets in thrombus is 97.
(a) is whole vessel in thrombus growth simulation. (b) is thrombus in particle aggregation. (c) is thrombus in level set expansion.

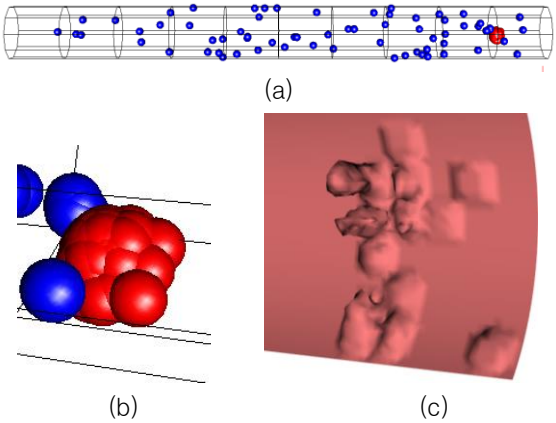

Fig. 5. The experimental results of test 2. The time is 0.6s and the number of platelets in thrombus is 733. (a) is whole vessel in thrombus growth simulation. (b) is thrombus in particle aggregation. (c) is thrombus in level set expansion.

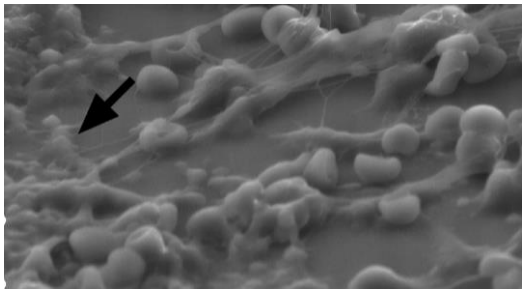

Fig. 6. Electron micrograph of platelets adherent to the lumenal surface of the dialysis venous tubing which is pointed by the black arrow.

V. CONCLUSION

A model for thrombus growth is proposed in this study. The plasma flow which brings platelets to thrombus growth is modeled by Navier-Stokes equations in the macroscale model with viscosity and velocity as the variables. The platelets adhesion an aggregation, the process of thrombus surface expansion, and thrombus motion are modeled in the microscale model. The motion of platelets and the motion of thrombus are controlled by forces from plasma flow and biochemical reactions. The growth of thrombus is described as the thrombus surface expansion and is tracked by Level Set Methods. We implemented and tested the proposed model, the results show that the thrombus modeled by Level Set Method is more similar to the real thrombus in clinical study.

Since the primary thrombus is the starting of the mixed thrombus, the shape of primary thrombus affects not only the blood flow, but also the aggregation of red blood cell in next step. The surface of primary thrombus obtained in the proposed model can be applied to the prediction of thrombosis. With any particular hemodynamic data, the chance and severity of thrombosis can be predicted; furthermore, the changes of blood flow caused by thrombosis are obtained from the model, and these changes can be taken as a quantitative indicator of thrombosis.

This study still has much scope to be improved. By improving and completing the speed function of thrombus surface expansion, the accuracy of thrombus growth will be increased, and this will be our future works of this study.

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