Application of Immersed Boundary Method in Modelling of Thrombosis in the Blood Flow

Saule Maussumbekova(✉) and Assel Beketaeva

Al-Farabi Kazakh National University, av. al-Farabi, 71, 050008 Almaty, Kazakhstan
saulemaussumbekova@gmail.com, azimaras@mail.ru
http://www.kaznu.kz

Abstract. Thrombosis occurrence is associated with hemodynamics instability. For prediction of it various experimental and numerical methods are developed. However, the greatest interest is mathematical methods for computing the hemodynamic parameters in thrombus formation. The model is possible to calculate the basic hemodynamic parameters of blood flow and the development of stenosis as a result of thrombosis. To describe the two dimensional blood flow in vessels with complex geometry as incompressible Newtonian fluid was used the conservation momentum law. Changing the shape of the vascular bed is considered in connection with possible biochemical processes like blood clots. It was assumed that convective flows do not have significant changes with the growth of blood clots, however, it is not conclusive with respect to real systems. Thrombus growth entails a change in the flow region, which is taken into account in this study using the immersed boundary method. The presence of the immersed boundary is taken into account by adding a special function in the equation of motion, allowing you to accurately represent streamlined border area. Unknown special function determined at the numerical solution stage of the problem, thus removing the requirement elastic boundaries. Also model consists from the equations describing the dynamics of the distribution of the main metabolites of blood clotting. For the numerical solution of the problem the method of splitting into physical parameters was used. To approximate the convective terms were used the quasi monotone high-order schemes. As a result of numerical experiments it was found that the use of the immersed boundary method qualitatively describes the dynamics of the stenosis as a result of thrombosis.

Keywords: Hemodynamics · Incompressible newtonian fluid · Navier-stokes equations · Complex geometry · The immersed boundary method · Numerical solution · Thrombus

1 Introduction

Modern medicine is essentially an experimental science with great empirical impact experience on the course of disease by various means. Experimental study

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is limited for a detailed study of the processes in biological media and the mathematical modeling is the most effective method for their research. Statements of the biological and medical problems that lead to the need for the numerical solution of systems of partial differential equations appeared relatively recently. They are presented in [1]. For the numerical solution of these problems were used methods previously used for solving fluid physics [2]. The rheological relations for the biological mechanics are developed in [3]. Description of the simplest mathematical model of the circulatory of heart can be found in [4]. The functions of the circulatory system of humans, which consists of small and large circles, are very important and diverse, so their modeling, both in normal and pathological conditions, is one of the biggest challenges of medicine. The dynamic model of pulsating fluid flows in the expandable tubes is the most adequate. Quasi-one dimensional - hydraulic model of an incompressible fluid in a deformable blood vessel, in the case of a generalized to hierarchical branching of factorial structured blood vessels were used in [5]. Another approach of modeling the functioning of the circulatory system based on a quasi three-dimensional circulatory system was proposed in [6]. In this case, The change of all parameters which can be output is a subject to simulation, for example, the concentration of active substances in the blood and the pressure on different parts of the circulatory system, as well as the velocity of blood flow. Normal functioning of the blood coagulation system provides liquid flow state of blood. The ability to provide a rapid local reaction of the body in response to the local disruption of normal flow conditions is a feature of the blood coagulation system. Maintaining the integrity of the circulatory system is provided by high speed of activation reactions of the coagulation system. Cascading biochemical mechanisms of signal amplification from of the lesion of the vascular wall provide speed of these reactions [7]. To date, the number of mathematical models describing the kinematics of the activation of key metabolites of the blood coagulation system were developed [8–11]. Interaction processes of blood coagulation with mass transfer are given in [25]. Effect of convective transport in the distribution of the factors of the coagulation system in space, affecting the growth of the thrombus is analyzed in [26], but the effect of a growing thrombus on flow around it was not taken into account. In this paper we formulate a mathematical model describing the production of the main metabolites of the coagulation system, their transport and distribution of the flow by diffusion. The qualitative dependences of activation thrombotic conditions in blood flow were investigated from its properties such as viscosity, flow conditions as pressure drop and chemical composition.

2 Mathematical Model

The formation of a dense fibrin polymer which prevents substance migration is a blood thrombus in the vessel. The flow is not only involved in the transfer of key metabolites of blood clotting in the space, but also has a direct effect on blood clot, deforming it. The transition from one type of spatial temporal behavior to a qualitatively different type is of great interest in the study of the dynamics

of growth of blood clots in the bloodstream, it means to define the conditions under which the activation coagulation system is associated by damage involve the formation of a blood clot, and in which they are not sufficient to stimulate thrombus formation. The flow of blood is described by the equations of a viscous incompressible fluid. As a place of activation of a cascade of biochemical reactions will be the portion of the surface of the local damage to the vessel wall. The size of the damage and the intensity of activation of coagulation in this area are free parameters of the problem. Viscous flow described by non-stationary Navier-Stokes equations.

$$div\boldsymbol{V} = 0 \tag{1}$$

$$\frac{\partial \boldsymbol{V}}{\partial t} + (\boldsymbol{V}\nabla)\boldsymbol{V} = -\frac{1}{\rho}\nabla p + \nu\Delta\boldsymbol{V} \quad , \tag{2}$$

$$\frac{\partial C_k}{\partial t} + \nabla(\boldsymbol{V_k}C_k - D_k\nabla C_k) = F_k(C_1, ..., C_m) \tag{3}$$

D_k- the diffusion coefficient of the k metabolite, C_k-- their concentration, $F_k(C_1, ..., C_m)$ the term describing the kinetics of local production of the substance, V_k-- its rate of convective transfer. It is assumed that the transfer rate of each of the main metabolites is given by $V_k = b_kV$, b_k, D_k are allowed to be zero for fibrin, and b_k is one for all soluble metabolites. The flow is missing where the polymer clot have a density above a certain value ψ^c. The velocity of the flow at the interface of the polymer clot is considered to be zero. We assume that in the area of injury inputted the activator, that is local increase in the activator concentration is given in the initial time. The equations describing production and decay of the spatial transfer of activator and inhibitor, as well as the production of fibrin are as follows [14].

$$\frac{\partial \theta}{\partial t} = D_1\Delta\theta - div\,(\boldsymbol{V}\theta) + \frac{\alpha\theta^2}{\theta + \theta_0} - \gamma\theta\phi - \chi_1\theta \tag{4}$$

$$\frac{\partial \phi}{\partial t} = D_2\Delta\phi - div\,(\boldsymbol{V}\varphi) + \beta\theta\left(1 + \frac{\phi^2}{\phi_0^2}\right) - \chi_2\phi \tag{5}$$

$$\frac{\partial \psi}{\partial t} = k\theta \tag{6}$$

The model describes the formation of the main regulators of fibrin polymerization in the blood - activator of clotting (thrombin), the concentration of which is noted by θ, the inhibitor concentration is indicated by ϕ. Thrombin catalyzes a reaction to convert the precursor of fibrin - fibrinogen into fibrin monomer, concentration of which is denoted by ψ, it in turn polymerizes in case and gives thrombus.

We could rewrite the equations (5), (6) cause of $div\boldsymbol{V} = 0$.

$$\frac{\partial \theta}{\partial t} = D_1\Delta\theta - \boldsymbol{V}\nabla\theta + \frac{\alpha\theta^2}{\theta + \theta_0} - \gamma\theta\phi - \chi_1\theta \tag{7}$$

$$\frac{\partial \phi}{\partial t} = D_2 \Delta \phi - \boldsymbol{V} \nabla \phi + \beta \theta \left(1 + \frac{\phi^2}{\phi_0^2}\right) - \chi_2 \phi \tag{8}$$

Thus, the mathematical model (2), (6), (7), (8) describes the change in the velocity field in the formation of thrombus in the vessel. To simulate the obstacles of arbitrary shape (in this problem blood clot) is introduced by a discrete-time artificial power. This force is applied only on the surface and within the constraints of the body. Force application point disposed in a spaced, similar velocity components defined on a staggered grid. When the point of application of force coincides with a virtual border, an artificial force is applied so as to satisfy the boundary conditions on the obstacle. The cell containing the virtual boundary, does not satisfy the equation of conservation of mass. Therefore, we introduce the source / drain weight to the cell that contains the virtual border. Discrete in time force is used to meet the conditions of adhesion on a virtual border, while the source / drain weight, to meet the conservation of mass for the cell that contains the virtual boundary. Procedure nondimensionalization this system involves choosing the characteristic scales: the concentrations θ_0 and ϕ_0, lines size L , the characteristic scale of velocity $\boldsymbol{V}$. In view of the above equations (1) - (2) takes the form:

$$div \boldsymbol{V} - q = 0 \tag{9}$$

$$\frac{\partial \boldsymbol{V}}{\partial t} + (\boldsymbol{V} \nabla) \boldsymbol{V} = -\nabla p + \frac{1}{Re} \Delta \boldsymbol{V} \quad + f_i \tag{10}$$

where $Re = LV/\nu$- Reynolds number, f_i - components of artificial power defined on a cell boundary in a virtual boundary or within of the body ($f_i = (f_u, f_v)$), q- source / drain of weight defined in the center of the cell on the virtual border or inside the body. So

$$f_u = \left\{ \begin{array}{l} 0, \ (x,z) \in \Omega / \Omega_0 \\ f_u, (x,z) \in \Omega_0 \end{array} \right\}, \quad f_v = \left\{ \begin{array}{l} 0, (x,z) \in \Omega / \Omega_0 \\ f_v, (x,z) \in \Omega_0 \end{array} \right\}, \quad q = \left\{ \begin{array}{l} 0, (x,z) \in \Omega / \Omega_0 \\ q, (x,z) \in \Omega_0 \end{array} \right\}$$

where Ω_0 - region of thrombus, Ω- region without thrombus. Note that the model due to the rigidity of the reaction part of the system is difficult for numerical implementation. The flows of matter were basic calculated values in the numerical implementation [15], which allows to build a conservative difference schemes for stiff systems. The characteristic scales of concentrations were used to nondimensionalization of model equations. Thus, the transfer equation of reagents will take the form:

$$\frac{\partial \theta}{\partial t} = \frac{1}{Pe} \Delta \theta - \boldsymbol{V} \nabla \theta + \frac{1}{M} \left(\frac{\theta \left(\theta - \overline{\chi_1}\right)}{\theta + 1} - \overline{\gamma} \theta \phi \right) \tag{11}$$

$$\frac{\partial \phi}{\partial t} = \frac{1}{Pe} \Delta \theta - \boldsymbol{V} \nabla \phi + \frac{1}{M} \left(b\theta \left(1 - \varepsilon \phi\right) \left(1 + \phi^2\right) - \chi_2 \phi \right) \tag{12}$$

where $M = \frac{V}{a_* L}, Pe = \frac{LV}{D}$, $\chi_1 = a_* \overline{\chi_1}$, $\chi_2 = a_* \overline{\chi_2}$, $b = \frac{\beta \theta_0}{\varphi_0 a_*}$, $c = \frac{\varphi_0}{\varepsilon}$. The value of the constants listed in [16].

The boundary conditions for the Navier-Stokes equations were taken as follows: on the walls of the vessel and the surface of a blood clot non split conditions were taken. On the left and right boundaries of the field to set values of pressure. It was assumed vertical components of velocity are zero at the inlet, free conditions were given on the output of the boundary.

3 Numerical Method

For the numerical solution of the problem used the method of splitting into physical parameters. To solve the system used the approximation on the staggered grid. The presence of thrombus counted by adding a special function in the equations of motion [17] that allows you to accurately represent streamlined border area. Unknown special function determined at the numerical step of the solution problem, thus removing the requirement of elastic border. Below is given a numerical algorithm to determine the dynamics of blood flow.

1. The intermediate speeds $\tilde{u},\ \tilde{v}$ were determined when $f_u = 0,\ f_v = 0$ on the entire area (outside of the thrombus) explicitly:

$$\frac{\tilde{u} - u^n}{\Delta\tau} = -u^n \frac{\partial u^u}{\partial x} - v^n \frac{\partial u^n}{\partial y} - \frac{\partial p^n}{\partial x} + \frac{1}{Re}\left(\frac{\partial^2 u^n}{\partial x^2} + \frac{\partial^2 u^n}{\partial y^2}\right)$$

$$\frac{\tilde{v} - v^n}{\Delta\tau} = -u^n \frac{\partial v^u}{\partial x} - v^n \frac{\partial v^n}{\partial y} - \frac{\partial p^n}{\partial y} + \frac{1}{Re}\left(\frac{\partial^2 v^n}{\partial x^2} + \frac{\partial^2 v^n}{\partial y^2}\right)$$

2. Then $f_u,\ f_v$ were determined:

$$f_u = \frac{\tilde{U} - u^n}{\Delta\tau} - u^n \frac{\partial u^u}{\partial x} - v^n \frac{\partial u^n}{\partial y} + \frac{\partial p^n}{\partial x} - \frac{1}{Re}\left(\frac{\partial^2 u^n}{\partial x^2} + \frac{\partial^2 u^n}{\partial y^2}\right)$$

$$f_v = \frac{\tilde{V} - v^n}{\Delta\tau} - u^n \frac{\partial v^u}{\partial x} - v^n \frac{\partial v^n}{\partial y} + \frac{\partial p^n}{\partial y} - \frac{1}{Re}\left(\frac{\partial^2 v^n}{\partial x^2} + \frac{\partial^2 v^n}{\partial y^2}\right)$$

where $\tilde{U},\ \tilde{V}-$speeds, which are determined by interpolation.

3. Then $\hat{u},\ \hat{v}$ were determined with $f_u\ ,\ f_v$

$$\frac{\hat{u} - u^n}{\Delta\tau} = -u^n \frac{\partial u^u}{\partial x} - v^n \frac{\partial u^n}{\partial y} - \frac{\partial p^n}{\partial x} + \frac{1}{Re}\left(\frac{\partial^2 \hat{u}}{\partial x^2} + \frac{\partial^2 \hat{u}}{\partial y^2}\right) + f_u$$

$$\frac{\hat{v} - v^n}{\Delta\tau} = -u^n \frac{\partial v^u}{\partial x} - v^n \frac{\partial v^n}{\partial y} - \frac{\partial p^n}{\partial y} + \frac{1}{Re}\left(\frac{\partial^2 \hat{v}}{\partial x^2} + \frac{\partial^2 v^n}{\partial y^2}\right) + f_v$$

4. After definition $\hat{u},\ \hat{v},\ q = \frac{1}{\Delta x \Delta y}\left(-\hat{u}\Delta y - \hat{v}\Delta x\right)$ is determined for cell containing virtual boundaries, that means $f_u \neq 0,\ f_v \neq 0,\ q = 0$ in the fluid, outside of body.

5. Then the equation for quazipressure is solving:

$$\frac{\partial^2 \varphi^{n+1}}{\partial x^2} + \frac{\partial^2 \varphi^{n+1}}{\partial y^2} = \frac{1}{\Delta t}\left(\frac{\partial \hat{u}}{\partial x} + \frac{\partial \hat{v}}{\partial y} - q\right)$$

6. Final values of velocity have form:

$$u^{n+1} = \hat{u} - \Delta t(\frac{\partial \varphi^{n+1}}{\partial x})$$

$$v^{n+1} = \hat{v} - \Delta t(\frac{\partial \varphi^{n+1}}{\partial y})$$

7. Final field of pressure is defined:

$$p^{n+1} = p^n + \varphi^{n+1} - \frac{\Delta t}{Re}(\frac{\partial^2 \varphi^{n+1}}{\partial x^2} + \frac{\partial^2 \varphi^{n+1}}{\partial y^2}).$$

Linear and bilinear interpolation were used to improving the order of approximation of the dynamic characteristics on thrombus [18].

4 The Numerical Results

Development of the thrombus is presented in Fig. 1. Initiation of blood clotting due to a local increase in the activator concentration is accompanied by the formation of a blood clot, which displaces the blood flow from the area adjacent to the site of injury. Formation of localized thrombus is determined by the interaction between the activator and an inhibitor and also hydrodynamic flow [14]. In the case of low flow velocities, the wave of coagulation activation is damped by wave of inhibitor and thrombus growth is stopped. Thrombus covers up more one-third of the transverse dimension of the vessel as in [16]. The calculations were performed for $Re = 0.01$, $Pe = 1$ on the grid with size 81x81 and $\delta t = 0.0015, \delta x = 0.0125, \delta y = 0.00125$ at time $t = 0.45 - (a)$, $t = 1.2 - (b)$, $t = 1.8 - (c)$.

Fig. 2 shows the demolition of clot downstream. The physical cause of that development of thrombosis is the failure of inhibitor to reduce coagulation until threshold value in the case of high speed. The results were obtained with the same parameter values, only $Re = 1$. The increase in speed leads to a qualitative change in the nature of a blood clot. Secondary blood clot appears for away from the injury site in vascular channel. This can be seen from Fig. 3, which shows the results of numerical calculations for $Re = 1$, $Pe = 24$. The complex topological structure of blood clots is the result of nonlinear interaction between activators, inhibitors and a flow in a changing geometry of the area under consideration. Reaction of polymerization provides thrombus growth. The process of thrombus growth affects to the characteristics of the surrounding blood. Thrombus formation in the bloodstream can be activated by a change of parametric of the problem.

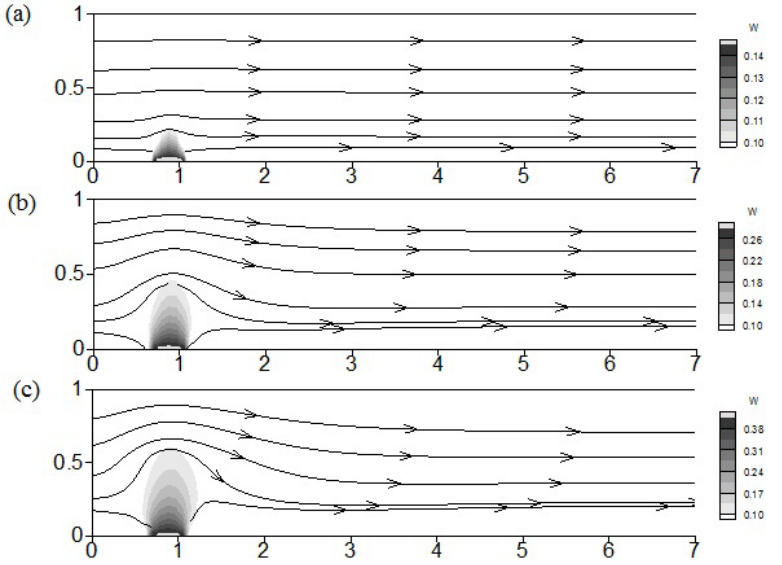

Fig. 1. Thrombus formation at low flow rates: $t = 0.45 - (a)$, $t = 1.2 - (b)$, $t = 1.8 - (c)$, $Re = 0.01$, $Pe = 10$.

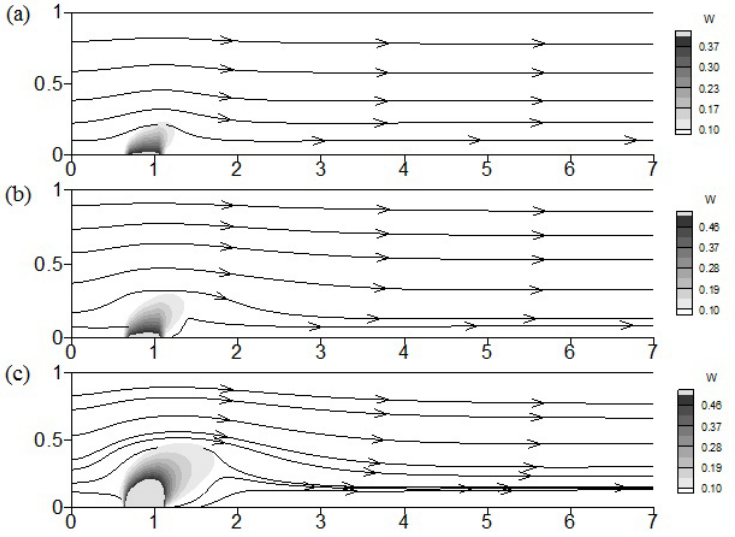

Fig. 2. Thrombus development. $Re = 1$, $Pe = 10$, $t = 0.45 - (a)$, $t = 1.2 - (b)$, $t = 1.8 - (c)$.

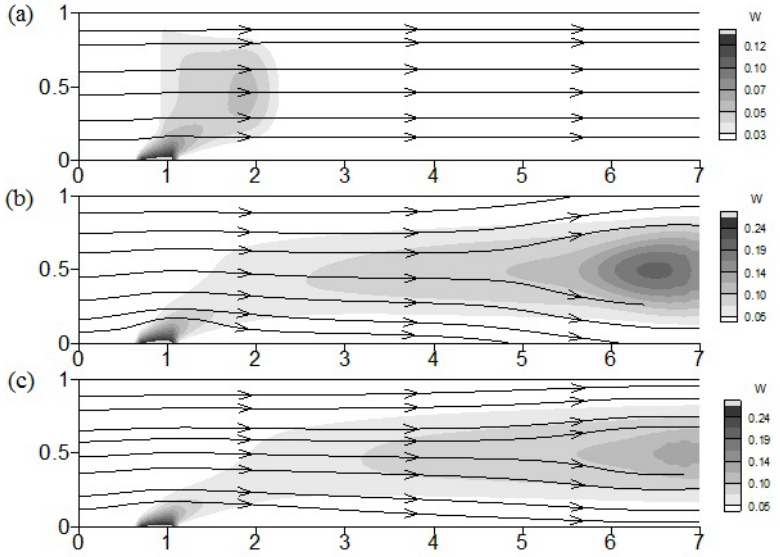

Fig. 3. Thrombus development. $Re = 1$, $Pe = 24$, $t = 0.45 - (a)$, $t = 1.2 - (b)$, $t = 1.8 - (c)$.

5 Conclusion

The aim of this paper was to construct an efficient numerical algorithm for calculating flows in geometrically complex areas. Numerical results obtained by the example of the process of thrombosis, which are qualitatively consistent with the results of other authors [16]. Since the model used is based on a number of assumptions, the most complex development of thrombosis remain outside consideration. The proposed numerical algorithm based on the immersed boundary method increases the accuracy of boundary conditions on the obstacles. Further modification of the proposed algorithm will allow more detailed study of the process of thrombus formation in vessels of complex geometry, including a region with moving boundaries.

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Chapter 11

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