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TWENTY-FIVE YEARS OF THE CAMES

Modelling of blood thrombosis at microscopic and mesoscopic scales

Magdalena Kopernik
AGH University of Science and Technology
al. Mickiewicza 30, 30-059 Kraków, Poland
e-mail: kopernik@agh.edu.pl

Blood coagulation at the place of the complete severing of a vessel or puncturing of a vessel sidewall is usually a beneficial reaction, as it protects the body from bleeding and maintains hemostasis, while the formation of a blood clot inside the blood vessel is a pathological phenomenon, which is highly dangerous, and sometimes leads to serious complications. In this paper, two scales of modelling blood thrombosis will be introduced using numerical methods and fluid dynamics. The meso-scale model of the flow is described by Navier-Stokes equations and the blood thrombosis model is based on equations of transport and diffusion. The equations describing levels of concentrations of factors responsible for blood coagulation can be implemented into a solver solving Navier-Stokes equations, what will enable simulation of blood flow and estimation of the risk of thrombus formation related to flow conditions. The proposed micro-scale model is using molecular dynamics to simulate interactions between blood cells and vascular walls. An effective combination of both models is possible thanks to the introduction of the multiple-time stepping algorithm, which enables a full visualization of blood flow, coupling molecular interaction with the fluid mechanics equation. The goal of the paper is to present the latest literature review on the possibilities of blood coagulation modelling in two scales and the main achievements in blood thrombosis research: the key role of transport and experimental background.

Keywords: multi-scale model, molecular dynamics, fluid dynamics, blood rheology, blood thrombosis.

1. Introduction

Blood coagulation at the place of complete severing of a vessel or puncturing of a vessel sidewall is usually a beneficial reaction, by protecting the body from bleeding and maintaining hemostasis, while the formation of a blood clot inside the vessel is a pathological phenomenon, highly dangerous, sometimes leading to serious complications [85]. The initiation of the coagulation cascade activates platelets and leads to coagulation process [90]). However, it should be added that coagulation is balanced by thrombolysis, which is induced by coagulation. Recent researches in the field of surface engineering to improve athrombogenicity have been conducted for polymers [62]. In the [62] research such a surface was created: conjugating a factor H-binding peptide and an adenosine diphosphate (ADP)-degrading enzyme using a polyethylene glycol (PEG) linker. When exposed to human blood, factor H was recruited to the surfaces and inhibited complement attack. Activation of platelets and coagulation was attenuated, by degrading ADP. Such hybrid surfaces can also be prepared by creating polymer micro-arrays [44] which enable thousands of cell-material interactions to be monitored on a single chip. It seems equally promising to test surface modification in the direction of achieving the desired athrombogenic properties (coating repellent blood), which were obtained at the Harvard University in Boston [52]. In a two-step surface-coating process, a monolayer of perfluorocarbon, which is similar to Teflon, was chemically attached. This coating prevented fibrin attachment, reduced platelet adhesion and activation, suppressed biofilm formation and was stable under blood flow *in vitro* tests.

Besides the experimental studies presented in the previous paragraph aimed to improve the athrombogenic properties of surfaces, there is also a group of model tests designed to simulate the phenomena occurring in the blood, which lead to the formation of blood clots. In the literature, modeling of blood coagulation is carried out in three scales: 1) a meso-scale (~100 microns) – hemodynamics and kinetics of chemical reactions of blood coagulation, 2) a micro-scale (~1 micron) – interaction of platelets with the vessel wall, leucocytes and other cellular blood components, and 3) a nano-scale (< 0.1 microns) – precipitation of fibrin [87].

In this paper, the first two scales of modelling blood thrombosis will be introduced using numerical methods and fluid dynamics. Modelling of blood flow in a meso-scale enables to obtain the phenomena associated with the formation of blood clots by developing phenomenological models or simplified analytical models of formation and growth of blood clot. In such approaches, the increase of thrombus is described by partial differential equations that show changes in the concentration of the factors responsible for the formation of clots and their diffusion. The creation and development of thrombus formation are determined by the chemical reactions in the complete severing of a vessel or puncturing of a vessel sidewall and the blood flow conditions [56]. The choice of an appropriate rheological model is critical in the modelling of blood flow due to very complex properties of blood. In the literature, a dozen different kinds of rheological models of blood can be found. The most popular of them are: Carreau-Yasuda, Casson, power law, Cross [14, 33, 47]. The mentioned models are not multiphase models, and a constant viscosity of plasma is assumed.

The present paper will also provide a brief comparative analysis of different blood rheological models. One of the approaches presented in the literature for modelling the blood thrombosis in the meso-scale considers blood as a two-component fibrous medium [86] in which the radius of fibrin fibers is much smaller than the size of single platelet. Such approaches are used to model the thrombus-flow interaction applying the permeability of a porous medium calculated from Darcy's law, and the media is described using the higher-order Brinkman equation in the Navier-Stokes equations [16, 42].

The model of blood flow in the meso-scale can be described by the Navier-Stokes equations (they assume a Newtonian model for rheology), and the blood thrombosis model is based on the equations of transport and diffusion. In order to identify the parameters of the empirical model, micro-flow tests are to be conducted. The meso-model of blood thrombosis can be based on the methodology described in the literature [17, 63]. The equations describing the levels of concentration of factors responsible for the blood coagulation (such as thrombin, fibrin, and others) are introduced to the solver computing the Navier-Stokes equations, which enables the simulation of blood flow and estimates the risk of clot formation depending on the flow.

The blood platelets are usually modelled using a coarse-grained molecular dynamics (CGMD) that allows determining the distribution of deformation on the surface of blood platelets under the influence of stresses induced by the flow of plasma [48, 70]. In the most complex model of CGMD within the platelets, there can be distinguished cytoskeleton, membrane and cytoplasm, and the simplified models consist of homogeneous groups of particles and form clusters [48, 70]. The elasticity of the platelet model is defined by a spring which acts between two neighbouring particles [48]. Thus, the modelled particles can attach to the surface, form aggregates and detach from the surface [48, 70]. These interactions are defined by the spring force and the adhesion force [48]. The analysis of models of platelets composed of a plurality of particles allows an exact determination of the deformation-induced shear stress [70]. There are also mechanical interactions between platelets, red blood cells (RBCs) and clot. Such impacts include some multi-scale models of coagulation, and in such models, blood cell elements are also modelled using molecular dynamics (MD) [48].

Equally important issue, as modelling the particles themselves and the interactions between them and the vessel wall, is the combination of the solutions of the meso- and micro-scale, in order to obtain a solution in a reasonable time and with good accuracy. Here, the new algorithm called multiple time-stepping (MTS) seems to be helpful [93]. The meso-scale model of plasma and the micro-CGMD model of platelets communicate via a hybrid interface of force field, while an MTS

algorithm introduces four time-step sizes, which leads to a considerable shortening of the calculation time [93]. Deformation of blood cells (blood damage index, for example, presented in [22] can be measured during their micro-flow through the capillaries [24].

Therefore, the goal of this paper is to present the latest literature review on the possibilities of blood coagulation modelling in meso- and micro-scales, as well as the main achievements in blood thrombosis research: the key role of transport and experimental background.

2. Blood coagulation

2.1. Motivation

It was proved that clot consists of 50% of red blood cells and 50% of fibrin/platelets, where 25% are platelets. It means that in the clot there are 100 times more platelets than in the plasma [1]. However, the difference in the construction of the clot can be seen in the veins and arteries. In the veins, where blood flow is slow, the clot consists of fibrin gel (and red blood cells). With fast flow in the arteries, it consists mainly of platelets. The most fundamental complication of thrombosis is arterial stenosis leading to ischemic stroke. The formation of blood clots also affects many life-threatening situations, such as coronary heart disease or biomechanical complications in the presence of a heart valve [50]. Another example is stent thrombosis (ST), most commonly associated with myocardial infarction resulting from sudden occlusion of the vessels. The mortality associated with ST is between 20% and 45%. Inadequate clot formation can also cause haemorrhage due to impaired thrombosis on damaged vessels or thrombosis following improper intravascular coagulation (a disease in which blood-forming proteins are over-active). These processes are associated with stroke (haemorrhage or thrombotic), complications associated with cancer, coronary infarction, and venous artery thrombosis. The latter one causes 250 000 hospitalizations annually in the United States, and its incidence increases as the population ages [87].

The course of thrombosis is a big problem in the construction of medical devices used to perform in contact with blood. These include implantable blood pumps, hemodialysers and ECMO (membrane oxygenation) [87]. The problems occur when the clot reaches a size that disrupts the natural flow or is torn off, therefore blocking the vessel. For medical device design, the numerical methods and computational fluid dynamics (CFD) are most often used. Despite the available advanced methods, prediction of thrombosis is still a problem. Current techniques find application mainly using low shear rates and simple vessel shapes. In order to use the model and apply it to practical biomedical solutions, it should be subjected to experimental validation for high shear rates and complex shapes of flow channels.

2.2. Coagulation mechanism

The coagulation mechanism is very complex, as it contains about 30 different substances that are subjected to many reactions [13]. Thrombus formation is the result of two mutually linked processes – platelet interaction and activation of the coagulation pathway. Immediately after damage to the vessels, the platelets adhere to the vascular lesion, forming a single cellular layer. Then, the shallows stick together and form cell aggregates. In addition, significant morphological changes occur in the platelets. By applying simplification, three main stages in the blood coagulation process can be distinguished [85]:

1) the first step is to create a substance called prothrombin activator, in response to complete severing of a vessel or puncturing of a vessel sidewall or change of blood itself;
2) in the second stage, prothrombin activator catalyses the conversion of prothrombin to thrombin;
3) in the third step, thrombin acts as an enzyme that turns fibrinogen into fibrin. The polymerized fibrin together with platelets forms a hemostatic plug or clot over a wound site.

Blood platelets also play an important role. Platelets are discoid cells in the unactivated state represented as a rigid body. They are about 2 μm of diameter and 0.5 μm of thickness, and they are smaller than red blood cells. Platelets can occur in three phases binary, either resting or fully activated depending on activator concentration. They have many receptors on their surface to make bonds with proteins (for example von Willebrand factor – vWF, collagen).

Blood platelets contain phospholipids, which are an essential component of prothrombin, as well as certain other ingredients (e.g., P-selectin, fibrinogen, $\beta 2$ integrin) that increase platelet aggregation and adhesion [26, 82]. They contribute to the development of a spigot that can stop bleeding by blocking the discontinuity of the vessel. Among others, it was observed that important factors for platelet adhesion are fibrinogen and vWF, the latter one especially with higher shear rates. However, the high level of vWF creates the risk of venous thrombosis. A platelet vWF is a linear chain, which consists of a large number of multimers secreted by activated platelets [27].

The first layer of platelets is often sufficient for thrombin produced on the surface, so platelets do not inhibit the flow when its level is not exceeded [94]. The number of platelets depends, in particular, on the shear rate and hematocrit, which is a more important factor. It is also known that platelets margination is not dependent on the initial amount of red blood cells but on the difference in platelets and RBCs deformation.

Fogelson and Neeves' review [35] organizes the latest achievements presented in the literature related to biophysics and biology of coagulation process and transport between platelets. During flow, platelets use two types of transport: diffusion and drift. It was observed that their movement during diffusion is the fastest in the middle and decreases as they approach the walls. However, drift is necessary for platelets to connect to the clot. Moreover, in the simulation there should be adapted unsteady diffusion coefficient, so the results are similar to the real flow. The work [35] also describes the mechanism of platelet margination, adhesion to the subendothelium, aggregation, cohesion, as well as vWF function and size, basis of coagulation as two subprocesses, initialization of coagulation and procoagulant role of platelets. The special focus is given to hindered solute transport in the interstitial spaces between platelets which regulates clot growth. Here, the protein transport produces smaller thrombi with a dense core of platelets compared to the unhindered example. Hindering protein transport limits the ability of fluid-phase prothrombin to penetrate the thrombus and reduces thrombin production.

In fact, the coagulation mechanism is a very complex process. It should be added that there are internal and external paths of coagulation, the complement system plays an important role in coagulation, especially during the inflammatory reaction or septic stroke. Simple platelet activation caused by endothelium broke indeed is caused by the electrostatic influence of positively charged collagen, etc.

2.3. Physics of coagulation

In the case of small blood vessels, the flow velocity due to the viscous resistance is small. The fluid velocity becomes proportional to the applied force (pressure), and its motion can be mathematically described by the linear differential equation (Stokes equation). Low flow velocity in small blood vessels leads to lack of turbulence playing a fundamental role in a macro-scale mixing. Consequently, fluid retention in the miniaturized flow systems is dominated by diffusion. Hydrodynamic interactions in a micro-scale are one of the many emerging forces. On a smaller scale, there is a great deal of an extra force. In the first place, surface forces arising from unbalanced molecular interactions (van der Waals) at the boundaries of the separation of two centres are beginning to play an important, and often decisive, role in small scales. In general, these are duct surfaces and surfaces between the phases of the flowing liquid. For liquid molecules in nano-metric scales, the vessel wall is also a collection of more or less regularly arranged molecules. At the boundary of the fluid wall, there is a hydraulic slip occurring between the particles, i.e., fluid flow does not

meet the basic macro-hypothesis of Newton, which says that the flow velocity of the viscous fluid on the channel walls is equal to zero.

The behaviour of blood cells in impaired flow is crucial for understanding atherosclerosis. However, numerical modelling of blood flow through vessels with a diameter of 20–500 μm is a challenge. This is because, under these conditions, the blood behaves as a multiphase suspension of deformable particles. The use of a homogeneous model in this case makes no sense since individual RBCs move independently and are additionally deformable [7]. This feature leads to several effects (including the Fahraeus-Lindqvist effect) and the formation of a cell-free layer established by plasma near the wall. This leads to a decrease in the apparent viscosity of the blood. The multiphase fluid nature of blood is the physical reason behind the Fahraeus-Lindqvist effect. Pries in [67] presented an empirical correlation for blood viscosity in terms of tube diameter and hematocrit.

The work conducted by Brass and Diamond [18] introduced biophysical mechanisms of transport observed during haemostasis and arterial thrombosis. The first case was shown for a complete severing of a vessel or puncturing of a vessel sidewall which led to pressure gradient to drive flow out of the pressurized vascular compartment into an interstitial compartment or to the atmosphere. The vessel lost pressure, and vasoconstriction reduced blood loss. As platelets and coagulation produce a haemostatic plug to stop bleeding, pressure gradients exist across the thrombus to drive plasma constituents across the clot to the extravascular compartment. The second situation was presented for a ruptured atherosclerotic plaque which triggered thrombosis under conditions of large values of wall shear stresses and wall shear rates as blood jetted through the stenosis. A vWF is needed for platelet capture under arterial flow conditions and large values of wall shear stresses can provide for the vWF fiber formation on a collagen surface.

Turbulences and pulse waves also appear in medical devices (in cardiac support chambers). However, the analysis of these micro-phenomena on morphotic blood elements can take place only in conditions identical to small vessels. Hence, in the present paper, the modelling area has been limited to these cases [25].

2.4. Measurement of blood micro-flow

Many mathematical models of blood thrombosis shown in the literature are not supported by physical models [5], and there is lack of their experimental verification, which is now available with modern and developing methods [59]. Although the experimental base may not give accurate results at once and remains still in the phase of a laboratory experiment, it creates new possibilities that should be taken into account in the present paper. The similar approach to the necessity of conducting experimental research has been shown, for example, in works by Hook [44] and Diamond [28].

The main factors that influence the initiation of coagulation are flow parameters (wall shear stress, wall shear rate, velocity profile and flow rate), in addition to injury size, surface chemistry and blood biology [18]. One of the physical quantities that describes fluid motion in a healthy cross-section of the blood vessel is the maximum velocity [12]. Measurement of fluid velocity is not easy, and in microscopic studies, the breakthrough has been a modification of the imaging anemometer used for years, or particle image velocimetry (PIV). In the micro-scale, detection of indicator particles and separation of information from other optical distortions practically excludes the use of standard PIV techniques and therefore, fluorescent particles are used and called a marker. As a result of the fluorescence of the particles, it is possible to filter out their light with the light of the incident wavelength and to identify the position of the particles, even if the object being recorded is only a diffused diffraction disk. The position of the particle is identified by determining the center of the diffraction pattern, and the position change for the subsequent images is the velocity field sought. This method, called micro-PIV, allows to study not only the movement of liquid in complex micro-flow systems but also *in vivo*, e.g., in the cytoplasm of cells or in the heart of the chicken embryo [28]. The PIV method allows for measuring the components of the velocity

vectors (such as colour maps of velocity distributions) by the micro-flow in channels of different shape, which allows to observe the behaviour of the individual components suspended in a liquid (strain) and components flowing in groups (clumping, repulsion, other impacts) [40, 64].

Deformation of blood cells, i.e., primarily red blood cells, is measured during their capillary flow [80]. Such systems are developed for PIV flow monitoring [4, 53]. However, MEMS micro-electro-mechanical systems (MEMS) are more suitable for measuring deformations and mechanical interactions of blood cells, mainly due to the small size of the projected measurement systems, which is especially important for platelet monitoring [65, 84]. Shapes of channels used for numerical simulation or experimental studies of micro-fluences including blood cells are different, most often straight channels with stenosis [31, 54], crosstalk channels [55, 84] and multi-chamber channels [59] with recirculation zones [83]. The latest achievements in the measurement of velocities in micro-scale couple different methods, such as micro-PIV, particle tracking velocimetry (PTV) and infrared spectroscopy (IR). The velocities equal to micrometers per second can be measured in capillaries [59].

3. Multi-scale modelling of blood thrombosis – physical phenomena

The diagram showing the combination of problems foreseen in the paper is presented in Fig. 1, which relates to the development of a two-scale blood thrombosis model based on the literature review. The two-scale approach is often applied not only for blood thrombosis problems, but it is also well known for other tasks related to blood modelling, for example, RBCs [53] and was also applied by the author of the present paper [49]. The complete conception of the multi-scale model of blood thrombosis based on [87] is shown in Table 1.

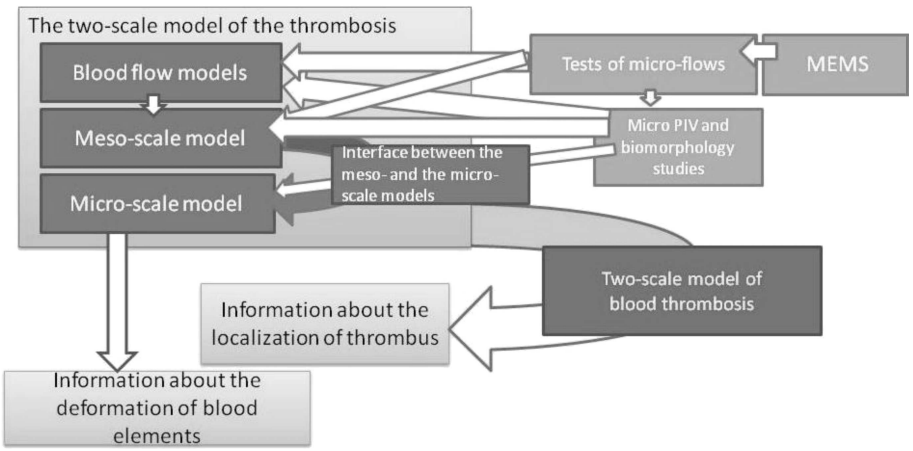

Fig. 1. Scheme of data flow in the conception of the two-scale model of blood thrombosis.

Table 1. Table shows the scale from subcell level to blood vessel level and corresponding modelling methods (table based on [87]).

Scale	Mechanism	Modelling method
Meso (~100 μm)	Integrated multi-physics models	Navier-Stokes
Micro (~1 μm)	Cell movement Cell-cell adhesion Cell aggregation	Cellular Potts model Flow energy Adhesion energy
Nano < (~ 0.1 μm)	Fibril generation Coagulation pathway Thrombin generation Cell-state transition	Kinetic equations Cell map

The haemostatic system involves complex interactions between multiple molecular and cellular components in the blood and vessel wall, and the impact of flowing blood. Improper regulation of these processes can result in bleeding after thrombus creation of damaged blood vessel or the wrong intravascular coagulation. Due to the extremely complex nature of the coagulation of blood, almost all attempts to model the coagulation process and the calculation of the mathematical model are presented in the form of nonlinear ordinary differential equations (ODEs), or partial differential equations (PDEs), which tend to focus on small subsets of the whole process [29].

For example, in [56] the two mathematical models were developed to study the increase in congestion in the flow adjacent to the wall. They showed that the growth of thrombus depends on the blood flow and chemical reactions. In the papers by Beltrami and Jesty [10, 11], several models were focused on specific aspects of coagulation, and it was shown that the rate of activation of the enzyme cascade was influenced by flow rate, damage size and initial concentrations of active enzymes.

In Fogelson [36, 37] and Sorensen *et al.* [71] Newtonian fluid models have been developed in the form of conjugated convective-reaction-diffusion equations without platelets. These models did not take into account the effect of growing thrombus on the flow field. In Fogelson and Robert [38], a PDE model with flexible cells describing platelet adhesion to the damaged wall and cohesion between activated platelets was introduced. The recent model of fluid viscoelastic thrombosis [3] includes both rheological properties of thrombus and numerous biochemical reactions. The formation and dissolution of the thrombus are modelled as the increase/decrease of the thin, thin-walled viscoelastic area. Convective diffusion equations are used for modelling platelet activation, external coagulation and fibrinolysis.

In addition, many researchers used experimental approaches or simplified models to test blood flow under different physiological conditions, leading to hemostasis [9, 51]. For example, in [6], platelet aggregation was strongly influenced by platelet deposition [87].

The effect described by Fåhræus and Lindqvist occurs in the blood flow from a large diameter vessel to a smaller one, where the hematocrit level decreases, and the apparent viscosity also changes as the vessel diameter decreases. In particular, the Fåhræus-Lindqvist effect was bound by Fåhræus and Lindqvist with the accumulation of red blood cells, leading to a decrease in apparent viscosity. Blood flow resistance occurs in the microvascular part, where the Fåhræus-Lindqvist effect reduces microangiopathy resistance. With very small pipe diameters excluded in this analysis (less than 4–6 μm), the apparent viscosity increases drastically when the pipe diameter decreases because the erythrocytes must deform in order to have a flow [20].

The latest works which present the most advanced reviews of biophysical bases and multi-scale modelling approach [45, 88] of thrombogenesis mainly repeat the results obtained by Brass, Diamond and Fogelson [18, 28, 35, 78]. For example, the latest work of Diamond's group [78] deals with multi-scale systems biology of trauma-induced coagulopathy. Their paper distinguishes three levels of the problem:

1) the blood circulation sets the global pressure in response to blood loss and resuscitation therapy;

2) local tissue perfusion is altered by vasoregulatory mechanisms and bleeding;

3) altered blood and vessel biology resulting from the trauma as well as hemodynamics control the assembly of clotting components at the site of injury.

In the first phase of the thrombogenesis, flow disturbances do not influence its course [35]. However, in the following part of the simulation, in which not only the initial stage is taken into consideration, fluid dynamics should be taken into account, as well as transport of cells and chemicals, platelet activation, adhesion and cohesion mechanics, and growth of a fluid-perturbing platelet mass. Such an approach implies multi-scale modelling of a trauma patient to over six orders of magnitude. Furthermore, in [45] an overview of rheological models was presented indicating which model should be selected in numerical simulations of blood flow occurring under different blood flow conditions in macro-scale.

The idea of the two-scale model proposed in the present paper and at the beginning of the chapter does not take into account all the chemical parameters of thrombus formation in the blood vessel. The literature review presented in [87] shows that for the purpose of investigating the formation of blood clots, a two-part multiphase model is sufficient. It includes ingredients for modelling viscous, incompressible blood plasma, inactivated and activated platelets, blood cells, activating chemicals, fibrinogen and vascular walls, and their interactions. Blood flow dynamics is described by the Navier–Stokes equations. Micro-scale interactions between activated platelets, platelets and fibrinogen, and platelets and vascular walls are described using the Potts extended stochastic discrete cell model. The model is tested for resistance to fluctuations using basic parameters.

3.1. Blood rheology models

Some liquids behave differently with stress (application of force) over time. Rheopectic liquids increase in viscosity as stress over time increases. Thixotropic liquids decrease in viscosity as stress over time increases. Non-Newtonian fluids change their viscosity or flow behaviour under stress. If a force is applied to such fluids, the sudden influence of stress can cause them to get thicker and act like a solid, or in some cases, it results in the opposite behaviour. Removing the stress (or only moving them slowly) results in return to their earlier state.

Blood is a suspension – a mixture of liquid and cellular components, behaving as a non-Newtonian fluid [72, 81]. For a better understanding of the blood coagulation process, here will be presented some of the most important aspects, based on work by Bodnár *el at.* [13]. These are the complexity of blood, sensitivity, variability, multi-scale and multidisciplinary nature. Blood is an incredibly complex liquid. Its unique properties, variable nature (even among the same species), lack of a full description of behaviour, and strong influence of external and internal stimuli, prevent the repetition of the same simulations. Ultimately, multi-scale character that occurs both in time and space, makes it impossible to accurately reflect the problem in one mathematical model. It leads to the conclusion that the research on blood combines areas such as physics, chemistry, biology and ultimately computer science. Combining such extensive fields is a difficult task, although feasible to some extent. In this work, the particular focus is given to physical and mathematical solutions of the problem. The biological and chemical aspects will therefore be simplified to a perfect fluid model.

Viscosity increases with high hematocrit and low flow velocity. It also depends on the degree of aggregation of red blood cells. The greater the aggregation of blood cells, the higher the blood viscosity. Erythrocytes have the ability to change their shape, so at higher velocities the blood resembles emulsions.

Based on the analysis of rheological characteristics of blood, it is possible to describe its behaviour in blood vessels [60]. The methodology proposed in the literature is to directly measure the viscosity of whole blood, plasma viscosity and other factors that affect rheology. The main factors influencing blood rheology are: hematocrit, fibrinogen concentration, deformation and red cell aggregation, temperature, and blood vessel shape.

There are three shear rate ranges for blood viscosity: low shear region where blood can be considered Newtonian, viscosity is constant and can be as high as 16–56 mPa$\cdot$s, middle (shear-thinning) region where the apparent viscosity decreases with increasing shear, and high shear region where blood behaves Newtonian and viscosity values can be as low as 1–4.76 mPa$\cdot$s. During a cardiac cycle, the local fluid shear rate varies from 0 to 1 400 s^{-1}. Therefore, when simulating flow under realistic conditions, there are periods that the blood should be modelled as a non-Newtonian fluid. Thus, several models are developed to model the non-linear behaviour of blood viscosity under different conditions.

The relation between the viscosity and the shear rate, values of coefficients and literature sources for the most important rheological models of blood [30] are presented in Table 2. Value of hematocrit 45% was used in all models shown below.

Table 2. Viscosity vs. shear rate relation of blood models and values of their coefficients taken from the literature.

Model	Equation	Coefficients	References
Power Law	$\eta = k\dot{\overline{\gamma}}^{n-1}$	$k = 9.27$ mPas^n, $n = 0.828$	[68]
Carreau	$\eta = \eta_\infty + (\eta_0 - \eta_\infty)\left(1 + \lambda\dot{\overline{\gamma}}^n\right)^{\frac{q-1}{n}}$	$\eta_\infty = 2.2$ mPas, $\eta_0 = 22$ mPas, $\lambda = 0.11$ s$^{1/n}$, $n = 0.644$, $q = 0.392$	[21]
Bi-exponent equation	$\eta = \eta_\infty + \eta_D \exp\left(-\sqrt{t_D\dot{\overline{\gamma}}}\right) + \eta_A \exp\left(-\sqrt{t_A\dot{\overline{\gamma}}}\right)$	$\eta_\infty = 4.24$ mPa, $\eta_D = 2.756$ mPa, $\eta_A = 41.425$ mPa, $t_D = 0.14$ s, $t_A = 4.04$ s	[92]
Casson	$\eta = \left(\sqrt{\eta_\infty} + \sqrt{\frac{\tau_y}{\dot{\overline{\gamma}}}}\right)^2$	$\eta_\infty = 3.1$ mPas, $\tau_y = 10.86$ mPa	[68]
Herschel-Bulkley	$\eta = \eta_H\dot{\overline{\gamma}}^n + \frac{\tau_y}{\dot{\overline{\gamma}}}$	$\eta_H = 8.9721$ mPas^{1-n}, $\tau_y = 17.5$ mPa, $n = -0.1399$	[79]
Quemada	$\eta = \eta_F\left(1 - \frac{1}{2}\frac{k_0 + k_\infty\sqrt{\hat{\dot{\gamma}}}}{1 + \sqrt{\hat{\dot{\gamma}}}}\varphi\right)^{-2}$ where $\hat{\dot{\gamma}} = \frac{\dot{\overline{\gamma}}}{\dot{\gamma}_c}$	$\eta_F = 1.2$ mPas, $k_\infty = 2.07$, $k_0 = 4.33$, $\dot{\gamma}_c = 1.88$ s^{-1}	[61]
Papanastasiou	$\eta = \left\{\sqrt{\eta_\infty} + \sqrt{\frac{\tau_y}{\dot{\overline{\gamma}}}}\left[1 - \exp\left(-\sqrt{q\dot{\overline{\gamma}}}\right)\right]\right\}^2$	$\eta_\infty = 3.1$ mPas, $\tau_y = 10.82$ mPa, $q = 120$ s	[19]

The clot formed in the wall of the vessel leads to stenosis [58], which changes the characteristics of blood flow. The different degrees of stenosis and shapes of blood vessels are often based on the literature research [31, 54]. The following tasks were performed for the blood thrombosis preliminary research done by the author of the present paper in [73]:

1) simulations were carried out using the blood vessel model with different degrees of stenosis in 2D and 3D to determine: the optimal densities of the finite element method (FEM) grid and the effect of stenosis on blood flow velocity and shear stress in blood vessel model using Ansys software;

2) numerical tests were carried out for two types of flow: laminar and turbulent to show the differences in flow in blood vessel models with stenosis. The example of results presented in [73] of velocity profiles obtained for all blood vessel models under laminar and turbulent flow is shown in Fig. 2. The bigger the degree of stenosis, the bigger the flow velocity is observed. Velocity measurement profile was placed in the center of stenosis through the thickness.

There is also a group of works related to multi-phase modelling of blood [69]. The blood flow results obtained for multi-phase blood medium are different than for blood treated as a single-phase medium. These results are especially different for arteries with stenosis. The following parameters are calculated based on flow results [43]: relative residence time, oscillatory shear index and time-averaged wall shear stress.

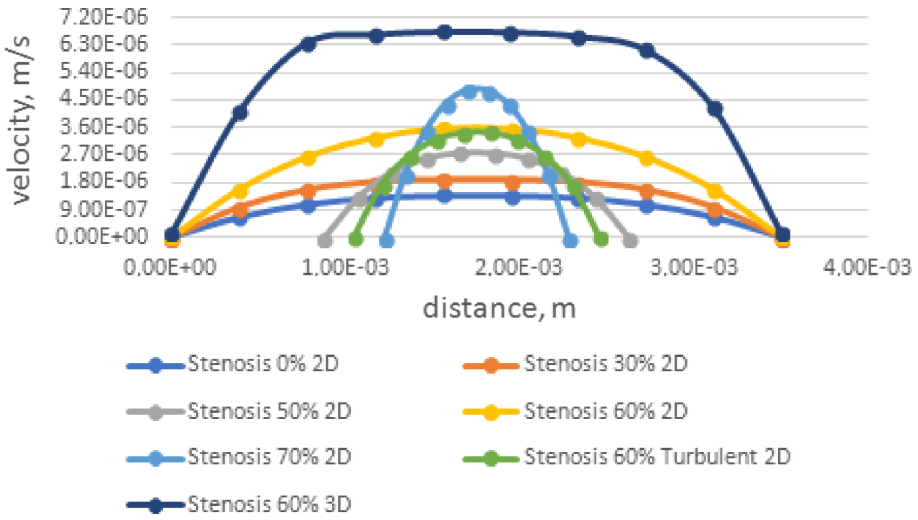

Fig. 2. Velocity obtained for all blood vessel models under laminar and turbulent blood flow.

The example of the application of blood rheology models is a work by Flamm and Diamond [34] in which large scale finite element calculations provide quantification of complex 3D flows. These simulations deploy deformable wall boundary conditions, anatomies derived from medical imaging, and complex oscillatory input flows. Another example of the application of finite element program using fluid dynamics is a carotid bifurcation in humans based on anatomy and volumetric blood flow measurement with magnetic resonance imaging [41]. This example shows the flow through two neck arteries. Such modelling using blood rheology model is essential for improving medical devices or determining vascular evolution.

3.2. Meso-scale modelling of blood thrombosis

The movement of the modelled fluid depends on the Navier-Stokes equations used in macroscopic modelling of blood flow. This approach to modelling blood flow was also presented in the paper by Flamm and Diamond [34] and in many other papers, as well as in work of Xu *et al.* [89], where the bulk blood flow was also solved with the Navier-Stokes equations. In work by Flamm and Diamond [34], an overview of multi-scale blood thrombosis models was shown, and the following examples were presented. Leiderman and Fogelson's model considers thrombin (coagulation cascade) production, ADP release and platelet deposition using spatially resolved convection-diffusion-reaction equations for species' (including platelets) transport/generation and Navier-Stokes equations for fluid flow. Xu *et al.* [89] model presents thrombin (coagulation cascade) production, ADP and TXA_2 release, and platelet deposition using a cellular Potts model for platelet deposition, convection-diffusion-reaction equation for species' transport/generation, and Navier-Stokes equations for fluid flow. During movement, the blood cells deform, the cell membrane is stretched, and the force is produced on the membrane. Deformation of individual cells affects flow. Both of these methods combine the Casson model. This model describes the relationship between viscosity and hematocrit.

Blood flow can be modelled as a liquid with a suspension of RBCs [60, 75]. In the selected model, the blood cells are moving through a 2D rectangular channel, from left to right. In addition, a slipping condition is assumed on the walls of the channel. This approach was proposed by Peskin (applying immersed boundary methods) and then extended by the Tryggvason's team. It was used in the shear flow. Red blood cells were modelled as liquid elements so they can deform. For a meso-scale model, this is sufficient because it omits the detailed molecular structure of the double lipid layer and the cytoskeletal network is based on it. By deforming the blood cells, all fluids have assumed a non-Newtonian behaviour [74].

The model of coagulation and thrombus formation can be applied in the meso-scale. The initial values of the parameters in the equation for the initiation of the thrombogenesis phase can be obtained from the literature, while the initial values for the propagation of the thrombus phase must be adjusted on the basis of experimental data. Blood flow determines changes in thrombin levels, such as thrombin, prothrombin or platelets. This relationship between the condition of blood flow and the concentration of thrombotic factors can be described by means of mass transfer and diffusion theory. The results of the meso-blood flow simulation and thrombosis are treated in the literature as starting points for the microscopic scale simulations of thrombosis. Calculated velocities and force fields in the meso-scale, as well as the concentration of thrombotic factors, are transferred to the microscopic model as boundary conditions. From a model point of view, the growth of the clot is not critical because it is crucial whether coagulation is present or not. So the model will predict clots only if the clot formation conditions are met or not, depending on the flow.

Thus, the model of thrombosis and coagulation in meso-scale can be based on the model described in the literature, for example, in [63]. The production of thrombin and generally the coagulation process is mainly attributed to activated platelets, while the initiation phase is located at the site of the vessel surface reaction. Thrombin generation is thought to occur when small amounts of thrombin generated during the initiation phase cause the thrombin concentration to exceed the threshold. The conversion of prothrombin to thrombin is then attributed to the platelets after activation. Platelets can be activated by other activated platelets or by thrombin when their concentration reaches the threshold value, and also by tissue liquid in the skin, as well as tissues inside wounded organs.

The aim of the meso-scale model is to propose a set of equations that describe the thrombin generation in blood using the minimum possible number of parameters but which can describe with acceptable accuracy the process [29]. Assuming that all platelets are instantly activated when thrombin reaches its threshold value, the concentration of platelets is zero when thrombin concentration is below the threshold value and equal to the resting platelet concentration when thrombin exceeds the threshold values. The equations describing thrombin and prothrombin concentration become:

$$\frac{\partial [T_g]}{\partial t} = -k_{\text{in}}[T_g] + k_{\text{tot}} \cdot [PT], \tag{1}$$

$$\frac{\partial [PT]}{\partial t} = -k_{\text{tot}} \cdot [PT], \tag{2}$$

where $[T_g]$ – thrombin concentration, $[PT]$ – prothrombin concentration, k_{in} – thrombin inhibition and k_{tot} represents the total rate of prothrombin conversion to thrombin and includes both the production on the reacting site and the platelet surfaces:

$$k_{\text{tot}} = k_{\text{surf}} + k_{PT}^{AP} \cdot [PL], \qquad \text{if} \qquad [T_g] > [T_g]_{\text{thr}}, \tag{3}$$

$$k_{\text{tot}} = k_{\text{surf}}, \qquad \text{if} \qquad [T_g] \leq [T_g]_{\text{thr}}, \tag{4}$$

where k_{surf} – thrombin generation on reacting surface, k_{PT}^{AP} – thrombin generation by activated platelets, $[T_g]_{\text{thr}}$ – thrombin concentration threshold for platelet activation. This leads to the direct solution for prothrombin concentration:

$$[PT](t) = [PT] \cdot e^{-k_{\text{tot}} \cdot t}. \tag{5}$$

The differential equations describing thrombin concentration become

$$\frac{\partial [T_g]}{\partial t} = -k_{\text{in}}[T_g] + k_{\text{tot}} \cdot [PT]_0 \cdot e^{-k_{\text{tot}} \cdot t} \tag{6}$$

or

$$\frac{dx}{dt} = Ax - CBe^{Ct}, \tag{7}$$

where $A = -k_{\text{in}}$, $B = [PT]_0$ and $C = -k_{\text{tot}}$. The last equation can be rewritten as follows:

$$\frac{dy}{dt} = (A - C) \cdot y - CB, \tag{8}$$

where

$$y = x \cdot e^{Ct}. \tag{9}$$

The last expression leads to an analytic solution for temporal evolution of thrombin concentration (X):

$$X(t) = \frac{e^{Ct}}{A - C} = \left[\left((A - C)X_0 e^{-Ct_0} - CB\right) e^{(A-C)t} + CB\right], \tag{10}$$

or

$$[T_g](t) = \frac{e^{-k_{\text{tot}} \cdot t}}{k_{\text{tot}} - k_{in}} \left[\left((k_{\text{tot}} - k_{\text{in}})\,[T_g]_0\, e^{k_{\text{tot}} \cdot t_0} + k_{\text{tot}} \cdot [PT]_0\right) e^{(k_{\text{tot}} - k_{\text{in}})t} - k_{\text{tot}} \cdot [PT]_0\right]. \tag{11}$$

For $[T_g](t = 0) = 0$ the equation gets the simplified form:

$$[T_g](t) = \frac{k_{\text{tot}} \cdot t[PT]_0}{k_{\text{in}} - k_{\text{tot}}} \left(e^{-k_{\text{tot}} \cdot t} - e^{-k_{\text{in}} t}\right). \tag{12}$$

In the case the data from the curve is available, there is also another method for obtaining model constants. The reaction rate is obtained by solving the last equation:

$$[T_g]_{\text{thr}} - \frac{k_{\text{surf}} \cdot t[PT]_0}{k_{\text{in}} - k_{\text{tot}}} \left(e^{-k_{\text{surf}} T_{\text{lag}}} - e^{-k_{\text{in}} T_{\text{lag}}}\right) = 0, \tag{13}$$

where T_{lag} – lag time determines the initial thrombin production rate, and $[T_g]_{\text{thr}}$ – thrombin concentration threshold for platelet activation.

As the activated platelet concentration is approximately

$$[AP] = [RP](0)\left(1 - e^{-(t - T_{\text{lag}})k_{AP}^{T_g}}\right), \qquad t > T_{\text{lag}}, \tag{14}$$

where $[AP]$ – concentration of activated platelets and $[RP]$ – concentration of resting platelets, and $k_{AP}^{T_g}$ – platelet activation by thrombin.

The analytical expression can be obtained for prothrombin concentration versus time:

$$[PT](t) = [PT](t = 0) \cdot e^{-k_{\text{tot}}(t) \cdot t} \tag{15}$$

and therefore for the differential equation describing thrombin evolution for $t > T_{\text{lag}}$:

$$\frac{d[T_g]}{dt} = -k'_{\text{in}} \cdot [T_g] + k_{\text{tot}}(t) \cdot [PT](t) \tag{16}$$

and the constants can be obtained numerically using the iterative process.

The initial values of constants and parameters used in equations in the meso-model such as k_{in}, k_{surf}, k_{PT}^{AP}, k_{AP}^{AP}, $k_{AP}^{T_g}$ and $[T_g]_{\text{thr}}$ are available, and can be taken from the cited literature. In the present paper, computations have not been carried out, and consequently, in the formulas, no constant values were given, as well as their units were not given in the description of equations.

In the paper by Diamond [28] there is presented the latest review of models which predict blood coagulation in meso-scale and they are focused on:

1) quantitative protease cascades, here are mainly mentioned the Hockin-Mann model and its updated version, which forms the model of thrombin production in the presence of thrombin-dependent activation of platelets extended by contact activation, platelet activation that reduces protein dissociation rates from complexes, thrombin-mediated cleavage of fibrinogen and fluorogenic detector, and other reactions;

2) quantitative protease cascades with emphasis on quantitating platelet signalling with particular emphasis on the multi-scale model of the Flamm-Diamond which enables lattice kinetic Monte Carlo simulations conducted for platelet motion in convective and dispersive flow fields helped each platelet to activate in response to agonists including collagen, ADP, and thromboxane;

3) thrombosis under flow which underlines Leiderman and Fogelson's model in which thrombin-mediated activation became prominent on the outer surface of the clot under high shear rates.

Such kinetic models of meso-scale models require up to about 100 parameters and up to about 1000 reactions, which are solved by using neural networks as it was presented for the Flamm-Diamond model. Otherwise, it is necessary to use microfluidic chips, which was also emphasized in the present paper (Subsec. 2.4).

Fluid mechanics' issues are a difficult engineering problem. Problems appearing in numerical simulations are the formation of air bubbles or non-Newtonian fluid properties. While there are several programs for numerical simulations, their usage is different. For example, Femap is used for mechanical and thermal calculations, and Abaqus solves mechanical problems with a number of materials. The flow phenomenon is solved by Ansys, OpenFoam, Adina, etc. Therefore, to design the meso-scale model of blood thrombosis, it is highly recommended to use Ansys based on the latest results presented in the available literature dedicated to blood flow modelling.

3.3. Models of thrombus-flow interaction

There is a group of works that are used to model the thrombus-flow interaction. Interstitial fluid flow within blood clots is a biophysical mechanism that regulates clot growth and dissolution. However, there are few measurements of the constitutive properties in clots that regulate interstitial transport. One of those properties is the permeability. The permeability of a porous medium can be calculated from Darcy's law:

$$\boldsymbol{v} = -\frac{k}{\mu}\nabla P, \tag{17}$$

where $\boldsymbol{v}$ is the interstitial fluid velocity, k is the permeability, μ is the viscosity of the percolating fluid, and P is the pressure.

The permeability is a function of the volume fraction of solids, pore size, and fiber or cell/cell aggregate size. Fibrin fibers that form between and around platelets give the clot a fibrous structure. The relative density of these two components – fibrin and platelets – dictates the interstitial fluid transport.

The model which considers a two-component fibrous medium with highly dissimilar fiber radii was presented in [86]. In the model, the radius of fibrin fibers is much smaller than the size of single platelet, and the media is described using the higher-order Brinkman equation:

$$\mu\nabla^2\boldsymbol{v} - \frac{\mu}{k_f}\boldsymbol{v} - \nabla P = 0, \tag{18}$$

where μ is the fluid viscosity, $\boldsymbol{v}$ is the fluid velocity, k_f is the fibrin permeability and P is the pressure.

In the paper by Wusfus *et al.* [86] there was examined a range of fibrin and platelet densities to bound the compositions of clots. Combination of fibrous media models and mixed porous media

models can be used to predict the permeability of clots over a wide range of fibrin and platelet volume fractions. Fibrin gels or platelet-poor clots are well described as a medium of disordered fibers with a uniform diameter. Clots with significant volume fractions of platelets are best described as a Brinkman medium. These models can be used to make predictions on the rate at which fluid can move through the interstitial spaces of a clot.

There is also a group of works that model thrombus formation in flow using the described method – a Brinkman term in the Navier-Stokes equations such as [16, 42]. In the model shown in [42], the spatiotemporal kinetics of the biochemical species was also added and it was governed by the convection-diffusion-reaction equation and enhanced diffusivity model. The developed model predicted that restoring clotting factors while simultaneously restoring fibrinogen in diluted blood can restore fibrin generation and hence improve clot formation under dilution.

The mentioned paper by Bouchnita *et al.* [16] studies the conditions of complete or partial occlusion in small vessels. The developed model is composed of the reaction-diffusion system of equations for blood factor concentrations coupled with the Navier-Stokes equations and, as well as in work by Wusfus *et al.* [86], the clot was treated as a porous medium. Contrary to the paper by Govindarajan *et al.* [42] the platelets were not included in the model. The main achievements of this work were: the critical flow velocity was determined which separates the regimes of partial and complete occlusion, as well as the existence of different regimes of clot growth were determined which depend on the velocity of blood flow.

The last group of works introduced briefly in the present section is dedicated to the other techniques used to capture clot growth in blood flow such as fluid-structure interaction [8] and free boundary problems described in a review [23]. The free boundary problem is a partial differential equation (PDE) to be solved for both an unknown function and an unknown domain. The three most widely used numerical methods to solve PDEs are FEM, finite volume method (FVM) and finite difference method (FDM), as well as other kinds of methods called mesh-free methods. The adoption of the FEM for solving the Navier-Stokes equations only started in the early 1980s, and was applied in the context of blood clotting modelling much later. For example, FEM was used to model in 2D platelet adhesion, thrombus growth and fibrinolysis. FDMs are historically the oldest and probably the simplest numerical methods for solving PDEs, especially in simple geometrical domains. These made them very attractive for solving blood clotting models in simple 2D geometries with structured grids. These methods were applied to model in 2D platelet aggregation and coagulation. The most often used are the FVMs, which are a popular alternative to the FDMs. These methods are often implemented in commercial CFD codes. The FVMs are usually used to model in 3D platelet deposition, aggregation, adhesion, and blood flow-biochemistry.

The fluid-structure interaction (FSI) is the interaction of some movable or deformable structure with an internal or surrounding fluid flow. In the paper by Bajd and Sersa [8] the net drag force on the spherical blood cell $\boldsymbol{F}_i^d$ included the fluid-structure interaction between plasma flow and the blood clot, and was defined by the equation:

$$\boldsymbol{F}_i^d(t) = -6\pi\eta_p R\left(\boldsymbol{v}_i(t) - \boldsymbol{v}_i^p(t)\right), \tag{19}$$

where η_p is the blood plasma viscosity, $\boldsymbol{v}_i(t)$ is the current velocity of the blood cell, and $\boldsymbol{v}_i^p(t)$ is the background plasma velocity at the site of the blood cell.

The same approach can also be improved to model the clot fragmentation by combining with biochemical reactions governing dissolution kinetics.

In computational fluid dynamics, the immersed boundary method is originally referred to an approach developed by Charles Peskin in 1972 to simulate fluid-structure (fiber) interactions. Treating the coupling of the structure deformations and the fluid flow poses a number of challenging problems for numerical simulations (the elastic boundary changes the flow of the fluid and the fluid moves the elastic boundary simultaneously). The immersed structures are typically represented as a collection of one-dimensional fibers. Each fiber can be viewed as a parametric curve. Physics of the fiber is represented via the fiber force distribution. Spring forces, bending resistance or any other type of behaviour can be built into this term. From the point of view of implementation, the

immersed boundary methods are categorized into continuous forcing and discrete forcing methods. In the former, a force term is added to the continuous Navier-Stokes equations before discretization, whereas in the latter, the forcing is applied (explicitly or implicitly) to the discretized equations.

The example of application the immersed boundary method in the modelling of thrombosis in the blood flow is shown in [58]. There was stated that the use of the immersed boundary method qualitatively describes the dynamics of the stenosis as a result of thrombosis. The immersed boundary is taken into account by adding a special function in the equation of motion, what accurately represents a streamlined border area. An unknown special function was determined at the numerical solution stage of the problem, thus removing the requirement of elastic boundaries. The proposed model also consists of the equations describing the dynamics of the distribution of the main metabolites of blood clotting.

3.4. Micro-scale modelling of blood thrombosis

One of many programs used to develop the micro-scale model of blood thrombosis is the (large-scale atomic/molecular massively parallel simulator (LAMMPS). It was created in Sandia National Laboratories, US Department of Energy. The scheme of action is to model the behaviour of particles in a liquid, gas or solid body using MD. Numbers of molecules can range from a few to a million or a billion. It is possible to introduce different force fields and boundary conditions for atomic, polymeric, biological, metallic, granular and coarse-grained systems. LAMMPS can be run on single-processor desktops or laptops, but the best performance is achieved for parallel computers with C++ compilers and the MPI message library. LAMMPS is an open source code, freely available and distributed under the GNU General Public License. It can be modified and expanded with new capabilities such as new force fields, atomic types, boundary conditions, or diagnostics. LAMMPS is one of the many packages that can run MD simulations and has been selected in this paper based on the latest results presented in the literature on micro-scale models of blood thrombosis.

Multi-scale methods combine models with different scales or time steps. A simulation with the behaviour of blood in the meso-scale, and in the micro-scale, is achieved by introducing biochemical reactions occurring between molecules, their behaviour in time and space, and blood flow described by the Navier-Stokes equations. These studies are extremely important to understand the mechanism of thrombosis. This knowledge is needed to develop new treatments for some diseases associated with the flow, for example, deep vein thrombosis, diabetes-related strokes, and pulmonary embolism. Despite many models described in the literature, the behaviour of thrombus development still cannot be clearly predicted. As previously mentioned, phenomena in the micro level can be modelled in the LAMMPS program [66]. The program works on the basis of a script containing information about the most important parameters. The script is composed of:

1) system initialization – surface preparation, type of units, selection of simulation corresponding to atoms used later;

2) definition of atoms – there are three possibilities: the behaviour of atoms can be read from a file, created on a grid or be duplicated with subsequent steps;

3) settings – here are boundary conditions, equations, calculations and saving the output data;

4) start a simulation – determination of the time step and the length of the simulation, and make it run.

In contrast to a macro-scale, in which platelets are considered as point particles without considering their size and shape, the micro-model assumes platelets which are round shaped particles to behave relatively stiffly. They are transported thanks to forces and torques of flow as well as through interactions between platelets and blood cells. Therefore, the translational and rotational movement of such particle is calculated by the shear and pressure forces, as well as the collision

strength between the particles. The plasma is considered as a homogeneous Newtonian fluid and its flow is constant. However, neglected are the forces associated with inertia, gravity and stickiness.

The MD code introduces the appropriate initial and/or boundary conditions, and then combines with the Newtonian equation for the accumulation of atoms, molecules or macroscopic particles that interact by short or long-range forces. The LAMMPS code may include plasma and platelets to develop a coarse-grained molecular dynamics (CGMD) blood thrombosis model, and the assumptions can be similar to that in the literature [48, 70, 91, 93]. CGMD model can be used to model 3D deformable platelets, and their initial shape will be assumed as an oblate spheroid. A reduced molecular-scale force field is proposed, and it includes the bonded interactions (springs and angles) and the nonbonded interactions (Lenard-Jones potential) and is given by:

$$V(r) = \sum_{\text{bonds}} k_b (r - r_0)^2 + \sum_{\text{angles}} k_\theta (\theta - \theta_0)^2 \sum_{\text{nonbonded pairs}} 4\varepsilon \left[\left(\frac{\sigma}{r} \right)^6 - 2 \left(\frac{\sigma}{r} \right)^{12} \right] = E_B + E_A + E_N, \quad (20)$$

where V is the total energy.

The first two terms in Eq. (20) on the right-hand side are the bond and angle components where k_b and k_θ are the force constants while r_0 and θ_0 are the equilibrium distance and angle. The last term in Eq. (20) is the nonbonded L–J potential, where ε is the depth of potential and σ is the characteristic distance at which the inter-particle potential vanishes. The bonded terms exist in a membrane and a cytoskeleton (granulomere and hyalomere) of platelet, and the nonbonded terms are set between any particle pairs within a radius of interaction. The L–J potential is used for imposing repulsive interactions between cytoplasm and membrane (compare L–J potential defined for RBCs in [39], preserving the platelet volume. Advancing from rigid spheroid models, this model characterizes the proper deforming capability of the membrane and allows to observe the responsive deformation of platelets and to investigate dynamic stress mapping on the surface membrane resulting from the fluid-platelet interaction.

Platelets are considered primarily as relatively rigid, round bodies suspended in Newton's fluid. RBCs are pseudo-rigid particles with an elliptical shape, which are subject to deformations under the influence of the shear forces. The motion of cells is based on forces acting on every particle (shear, pressure) and forces from collisions. Additionally, coordinate systems are used to observe the motion of particles. The first (local) is fitted to each particle relative to its center of gravity, the second (global) predicts the movement of particles relative to a fixed point. All results are obtained in the computation zone – collisions and movements. Particles in this area are looped, and every particle leaving the computation zone is re-introduced in the inlet zone as a new. The grid assumptions are not very important because the obtained results are similar for larger size and smaller size elements (denser grid).

The micro-scale model described in the present section provides information about the relationship between fluid forces and platelet activation, and the aggregation occurring during blood flow. One of the factors affecting platelets is the shear stress which at high values initiates the thrombosis process. The presence of erythrocytes is also of great importance. They have a mechanical and biochemical effect on platelets. Thanks to them, platelets have easier contact with the wall, which may lead to the interaction necessary to start the formation of a blood clot. The micro-scale model shows that in the presence of erythrocytes, platelets migrate towards the side surfaces, while without RBCs, they are closer to the centerline of the flow. This phenomenon is more noticeable for higher hematocrit values, more than 10%, and as the flow rate increases until the optimal value is obtained. To achieve such an effect in the Yeh and Eckstein model a random walk algorithm for platelets was used and behaviour of RBCs was added. More detailed data is included in the work of Almomani *et al.* [2]. To examine the effect of the shape and size of cells, the radius of platelet has the size of RBC and half of RBC. It is noted that the difference in the size of these cells has a greater impact on the platelet settling on the walls than the elliptical shape of RBC (Fig. 3). Research has shown that if the hematocrit is about 5%, all platelets are in the middle of the flow. However, by increasing it, the platelets begin to move towards the wall – for 10% hematocrit, about half of the

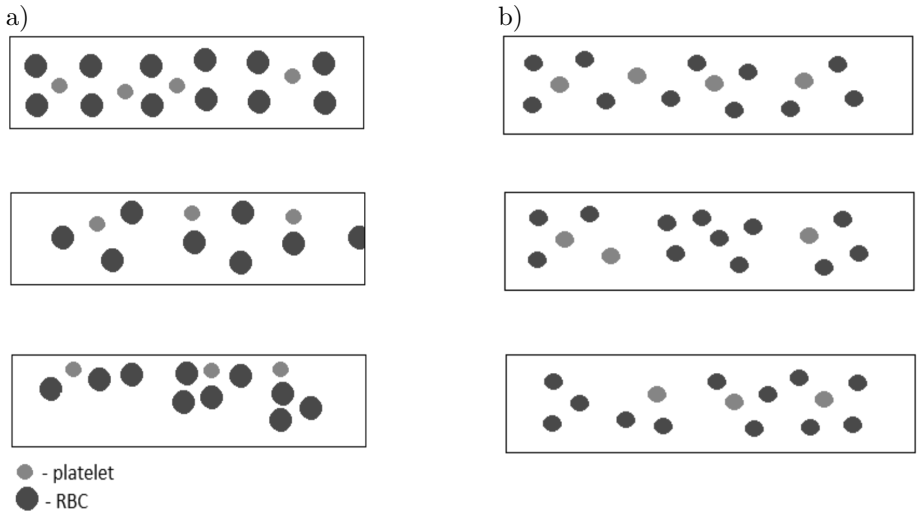

Fig. 3. Particle distribution at different time steps: a) RBCs depicted as black circular particles with a diameter equivalent to the major dimension, b) RBCs depicted as black circular particles with a diameter equivalent to one half of the major dimension. Platelet locations are circled in grey (figure based on [2]).

platelets' amount move closer to the wall, and for 15% of hematocrit most of the platelets are close to the wall (~80%), on both sides [2]. In addition, it is also known that platelets are activated after exceeding a certain shear rate.

The LAMMPS program has also been used to simulate blood flow in the arteries of the blood vessels [57]. The experiment was performed in capillaries with a diameter of 20 to 32 μm, to explain the biophysical mechanisms of blood and plasma distribution during flow through bifurcation, and to quantify the effect of branch size, and bifurcation on cell division efficiency. The results showed that blood flow in the arterial bifurcation depends on the location of the branch and the angle of the fork. For small angles, more red blood cells enter the lateral branches while for large angles they remain in the main branch.

Dissipative particle dynamics (DPD) is a relatively new stochastic simulation technique for simulating the dynamic and rheological properties of simple and complex fluids. It is often considered as a mesoscopic version of MD simulations capable of simulating larger time and length scales. Due to its simplicity, yet powerful capabilities, DPD technique is being used in simulation of many complex fluid systems, such as fibers in a viscous medium, dispersion of nanofluids, nanocomposites, surfactants, etc. The DPD method treats the fluid system as a collection of particles called beads, which interact with each other using soft repulsive potentials. The DPD system is governed by Newton's second law and force acting on each bead is the sum of internal and external forces. This approach will simulate many properties of the fluid, including its density, diffusivity, surface tension, etc. One of the advantages of DPD simulations is that they can handle the non-Newtonian flow properties of a fluid which makes it attractive for blood flow modelling.

DPD is often applied to simulate viscous shear flows, in which each particle interacts with surrounding particles. The motion of each particle is determined by:

$$d\boldsymbol{v}_i = \frac{1}{m_i} \sum_{j=1, j\neq i}^{N} \left(\boldsymbol{F}_{ij}^C dt + \boldsymbol{F}_{ij}^D dt + \boldsymbol{F}_{ij}^R \sqrt{dt} + \boldsymbol{F}_{ij}^E dt \right), \tag{21}$$

where N – point particles of mass m_i, position $\boldsymbol{r}_i$ and velocity $\boldsymbol{v}_i$.

DPD particles interact through three forces:

$$\boldsymbol{F}_{ij}^C = \alpha \omega^C (r_{ij})\, \boldsymbol{e}_{ij}, \qquad \boldsymbol{F}_{ij}^D = -\gamma \omega^D (r_{ij}) (\boldsymbol{e}_{ij} \cdot \boldsymbol{v}_{ij})\, \boldsymbol{e}_{ij}, \qquad \boldsymbol{F}_{ij}^R = \sigma \omega^R (\boldsymbol{r}_{ij})\, \zeta_{ij} dt^{-1/2} \boldsymbol{e}_{ij},$$

$\boldsymbol{F}_{ij}^C$, $\boldsymbol{F}_{ij}^D$ and $\boldsymbol{F}_{ij}^R$ are conservative, dissipative and random forces acting on the particle and $\boldsymbol{F}_{ij}^E$ is the external force exerted to each particle to lead the fluid flow, $\boldsymbol{r}_{ij}$ is the inter-particle distance,

$\boldsymbol{v}_{ij} = \boldsymbol{v}_i - \boldsymbol{v}_j$ is the relative velocity of particle i with respect to particle j, and $\boldsymbol{e}_{ij}$ is a unit vector in the direction of particles i and j; $\boldsymbol{e}_{ij} = \dfrac{\boldsymbol{r}_{ij}}{\boldsymbol{r}_{ij}}$, with $\boldsymbol{r}_{ij} = \boldsymbol{r}_i - \boldsymbol{r}_j$ and $\boldsymbol{r}_{ij} = (\boldsymbol{r}_{ij} \cdot \boldsymbol{r}_{ij})^{1/2}$.

The coefficients γ and σ define the strength of dissipative and random forces, respectively. In addition, ω^D and ω^R are weight functions, and ζ_{ij} is a distributed random variable with zero mean, unit variance $\zeta_{ij} = \zeta_{ji}$; α is the maximum inter-particle repulsion given by $\alpha = 75k_BT/\left(\varrho_f r_C\right)$, where ϱ_f is the density of flow particles, r_C is cutoff radius, which defines the length scale in the DPD system and k_B is the Boltzmann constant, and T is temperature.

The weigh function ω^C is set to zero beyond the cutoff length r_C and is given by:

$$\omega^C(r_{ij}) = \begin{cases} (1 - r_{ij}/r_C), & r_{ij<}r_C, \\ 0, & r_{ij\geq}r_C. \end{cases} \tag{22}$$

The random and dissipative forces form a thermostat and must satisfy the fluctuation-dissipation theorem in order for the DPD system to maintain equilibrium temperature T. This leads to:

$$\omega^D(r_{ij}) = \left[\omega^R(r_{ij})\right]^2, \tag{23}$$

$$\sigma = 2\gamma k_B T. \tag{24}$$

The choice for the weight function is:

$$\omega^R(r_{ij}) = \begin{cases} (1 - r_{ij}/r_C)^k, & r_{ij<}r_C, \\ 0, & r_{ij>}r_C, \end{cases} \tag{25}$$

where $k = 1$ for the original DPD method. However other choices (e.g., $k = 0.25$) can be used to increase the viscosity of the DPD fluid.

The simple model of micro-flow can be constructed based on the micro-fluidics experiment conditions (boundary conditions, size of the channel, the density of the fluid system, etc.). The example of the DPD application is shown in [32], in which the focus of the study was concentrated on mechanical aspects of platelet-mediated thrombosis which includes motion, collision, adhesion and aggregation of activated platelets in the blood. The developed mechanical model of platelet accumulation onto the vessel wall was completed using the DPD method in which the blood (i.e., colloidal-composed medium) is treated as a group of mesoscale particles interacting through conservative, dissipative, attractive and random forces. The presented model includes interaction forces between platelets both when they are in the resting state (nonactivated) and when they are activated, and therefore it can be extended to the analysis of the kinetics of binding and other phenomena relevant to thrombosis.

3.5. Interface between meso- and micro-scale models

Coupling the advantages of the highly resolved bottom scales in the platelet system with the less resolved top scales in the fluid system into a multiscale approach requires developing a force field on the boundary hybridizing the two systems into the DPD-CGMD model. To reach this a hybrid potential was developed for describing the fluid-platelet interaction and then designing an efficient method to parameterize this potential. The nonbonded pairwise interparticle interaction between the top-scale flow and bottom-scale membrane particles is defined as

$$d\boldsymbol{v}_i = \frac{1}{m_i} \sum_{j=1, j\neq i}^{N} \left(\nabla U(r_{ij}) dt + \boldsymbol{F}_{ij}^D dt + \boldsymbol{F}_{ij}^R \sqrt{dt} \right), \tag{26}$$

where

$$U(r_{ij}) = 4\varepsilon_p\left[\left(\frac{\sigma_p}{r_{ij}}\right)^6 - 2\left(\frac{\sigma_p}{r_{ij}}\right)^{12}\right],$$

$$\boldsymbol{F}_{ij}^D = -\gamma_p\omega^D(r_{ij})(\boldsymbol{e}_{ij}\cdot\boldsymbol{v}_{ij})\boldsymbol{e}_{ij},$$

$$\boldsymbol{F}_{ij}^R = \sigma_p\omega^R(r_{ij})\zeta_{ij}\sqrt{dt}\boldsymbol{e}_{ij},$$

ε_p and σ_p are the characteristic energy and distance parameters in CGMD.

Other parameters including γ_p and $\sigma_p$retain the same definitions as in the DPD model (Subsec. 3.4). All forces are truncated beyond a cutoff radius which defines the length scale in the fluid-platelet contact region.

The L–J force term $\nabla U(r_{ij})$ helps the cytoskeleton-confined shapes and the incompressibility of platelets against the applied stress of circumfluent plasma flow. The dissipative and random force terms maintain the flow of local thermodynamic and mechanical properties and exchange momentum to express interactions between the platelet and the surrounding flows. A no-slip boundary condition was applied at the fluid-membrane surface interface.

The DPD model of plasma and the CGMD model of platelets communicate via a hybrid interface of force field, while MTS algorithm introduces four time-step sizes, which leads to a considerable shortening of the calculation time [93]. MTS is a method that allows to extend the time step in the simulation. This method is based on combining iterative schemes that allow the introduction of time steps of different lengths, depending on how quickly a given chemical reaction takes place over time. In numerical analysis, the multi-step summation is a numerical time integration method that uses different time steps or time integrators for different parts of the problem. The MTS algorithm introduces a multi-level integration scheme, saving computational time by avoiding the most time-consuming step. MTS is introduced in a computational sense for solving large-scale systems in order to simulate them effectively. Integrated MTS algorithms are needed to achieve a full multi-scale particle model for physiological flows, such as platelets thrombosis. Using of MTS can achieve a significant reduction in simulation time, as shown in Fig. 4.

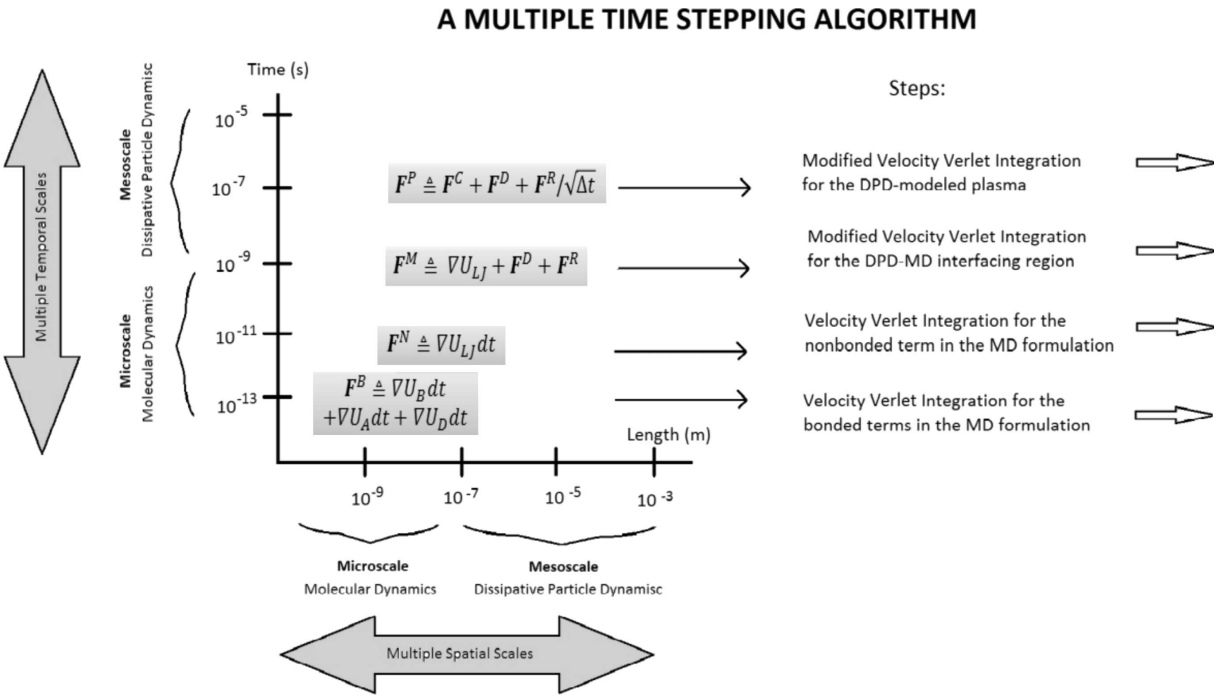

Fig. 4. Integrated multi-scale simulation algorithm for platelets in plasma (figure based on [93]).

One of the most advanced studies using the LAMMPS program was to investigate microscopic changes in platelet shape in response to macroscopic strains caused by flow [46]. Numerical measurements were focused on the details of the dynamic platelet flow system, as well as on the accuracy of calculation of stresses caused by the flow through the surface. Additionally, during this simulation, the effectiveness of the MTS algorithm was checked. There were used different time values for the algorithm – large (MTS – L), medium (two times – MTS – M1, MTS – M2) and small (MTS – S). On the other hand, the coefficients K_1, K_2, and K_3, are constants fixed to the equation (Fig. 4). The coefficients K_{1-3} are used to decrease the computation time step according to the form: $\delta t_1 = \Delta t/K_1$. The results have shown that the MTS method is much more effective than the Standard Time Step method (STS).

The model of platelet thrombosis which connects macro- and micro-scales consists of the clot growth and blood vessel for meso-scale, and model of platelets for micro-scale. The model created by Fogelson was based on the immersed boundary method. For fluid dynamics the Euler approach is used, while elastic objects are represented by the Lagrange description. In the model a simplification is also introduced, which assumes that the platelet is activated during contact with the damaged surface or at a specific distance from it. However, there are different approaches to the modelling a clot. In cooperation with Kuharsky, Fogelson eliminated simplification by separating coagulation reactions from those on platelets surface. Platelet activation is performed using the convection-diffusion-reaction equation, and all interactions between them are computed by a partial differential equation. Another model, created by Pivkin, introduces a 3D space in which platelets are spherical objects. In this case, activation takes place in a different way. This happens with a delay, and the platelet after contact with the wall returns to the passive state after a recovery time period. It is still a simplified model because more complicated calculations require high computing power and long calculation time [88].

The other papers combine the DPD method with the PDE method, and the hybrid model is constructed for example in [76, 77]. The most advanced hybrid model was developed in [77], where the DPD-PDE approach describes cloth growth in blood flow. DPD is applied to model blood plasma and platelets, which interact with fluid particles and with each other. They can aggregate in the flow or in the clot and can also detach if the force pulling them away is greater than a certain limit. PDEs are used to consider concentrations of biochemical substances in plasma, such as fibrin. Interaction of fibrin with platelets plays an important role in the biology of clot growth and in the proposed model. Simulation results confirm that at the first stage of clot formation platelets form an aggregate due to weak inter-platelet connections and then due to their activation. This enables the formation of the fibrin net in the centre of the platelet aggregate where the flow velocity is reduced. The fibrin net reinforces the clot and allows its growth. When the clot becomes sufficiently large, it stops growing due to the narrowed vessel and the increase of flow shear rate at the surface of the clot. Its outer part is detached by the flow revealing the inner part covered by fibrin. This fibrin net does not allow new platelets to attach at the high shear rate, and the clot stops growing.

4. Conclusions

The main achievements in blood thrombosis research commented in the present paper can be concluded as follows.

The key role of transport:

1) The clot growth is regulated by the hindered solute transport in the interstitial spaces between platelets. The protein transport produces smaller thrombi with a dense core of platelets compared to the unhindered example. Hindering protein transport limits the ability of fluid-phase prothrombin to penetrate the thrombus and reduces thrombin production.

2) Biophysical mechanism of transport during haemostasis: when complete severing of a vessel or puncturing of a vessel sidewall provides for the loss of pressure by vessel, and vasoconstriction

reduces blood loss. As platelets and coagulation produce a haemostatic plug to stop bleeding, pressure gradients exist across the thrombus to drive plasma constituents across the clot to the extravascular compartment.

3) Biophysical mechanism of transport during arterial thrombosis: a ruptured atherosclerotic plaque triggers thrombosis under conditions of high wall shear stress and wall shear rate as blood jets through the stenosis. VWF is required for platelet capture under arterial flow conditions and high wall shear stresses can lead to vWF fiber formation on a collagen surface.

The key role of experimental methods:

1) MEMS and micro-PIV are successfully adapted to measure deformations and mechanical interactions of blood cells, as well as the components of the velocity vectors.

2) Blood rheology. The Casson blood rheology model is the most popular in the simulation of blood flow because it predicts wall shear stress magnitudes better in oscillatory flows compared to Newtonian and power law models. This model is considered a fundamental approach to modelling a blood flow. Various upgrades of this model, which consider additional phenomena affecting the flow (stenosis), are proposed in the literature.

The key role of numerical methods:

1) The most advanced description of biophysical bases and multi-scale modelling approach of thrombogenesis mainly repeats the results obtained by Brass, Diamond and Fogelson. Their solutions of the posed problem imply multi-scale modelling to over six orders of magnitude.

The latest achievements of blood thrombosis modelling in the meso- and micro-scales are as follows:

1) Meso-scale. The most advanced models which predict blood coagulation and are adapted to meso-scale consider quantitative protease cascades (the Hockin-Mann model and the Flamm-Diamond model) and thrombosis under flow (the Leiderman and Fogelson model). These kinetic models require up to about 100 parameters and up to about 1000 reactions, which require applying neural networks and microfluidic chips.

2) Micro-scale. The most advanced models in a micro-scale developed using MD allows investigation of microscopic changes in platelet shape in response to macroscopic strains caused by flow. One of the noticeable effects is that the platelets migrate towards the walls of the vessel. This is mainly due to the difference in the size of the blood cells. As a result, platelets persist in the lateral part of the flow where the velocities are slower, while RBCs are directed towards the central part where the flow is faster. Thus, in the micro-model, the important factors to consider are erythrocytes and their interactions. In addition to the RBCs, hematocrit and shear rate affect platelets. However, no relationship with the RBCs shape was noticed.

3) Meso-scale and micro-scale interface. The DPD model of plasma and the CGMD model of platelets can effectively communicate via a hybrid interface of force field, while developed multiple time-stepping algorithm introduces four time-step sizes, which leads to a considerable shortening of the calculation time.

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