COMPUTATIONAL HEMORHEOLOGY: PROGRESS IN BLOOD COAGULATION MODELLING

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ABSTRACT

In this paper we present a brief description of the physical properties of blood and its formed elements followed by a short overview of some constitutive models that can mathematically characterize blood rheology and be used in computer simulations. In particular, preliminary numerical results obtained for a comprehensive model of blood coagulation and clot formation, that integrates physiologic, rheologic and biochemical factors will be presented and discussed.

Key-words: blood rheology, coagulation, shear-thinning flows, numerical simulations, finite--volumes.

INTRODUCTION

Blood is a concentrated fluid suspension of multiple deformable cells with complex rheological characteristics. Blood performs the essential functions of delivering oxygen and nutrients to all tissues, it removes waste products and defends the body against infection through the action of antibodies. The blood circulation in the cardiovascular system depends not only on the driving force of the heart and the architecture and mechanical properties of the vascular system, but also on the rheology and flow properties of blood itself. Hemodynamic factors such as flow separation, flow recirculation, or low and oscillatory wall shear stress are recognized as playing an important role in the localization and development of arterial diseases. However, the composition and

the physical properties of blood constituents are essential to analyze and model the circulation.

Hemorheology is the science that studies the flow properties of blood and its formed elements and the relationship to normal and abnormal physiology. This field involves the investigation of the macroscopic behaviour of blood determined in rheometric experiments, its microscopic properties *in vitro* and *in vivo* and studies of the interactions among blood cellular components and between these components and the endothelial cells that line blood vessels. Advances in hemorheology have contributed in particular to the fundamental understanding of the changes in the rheological properties of blood and its components due to pathological disturbances and are based on the evidence that they might be the primary cause of many cardiovascular diseases.

The interactions between hemorheological factors and hemodynamical mechanisms are highly complex and the role of blood rheology in physiopathological processes is still not well understood. Therefore the mathematical and numerical study of powerful, yet simple, constitutive models that can capture the rheological response of blood over a range of physiological flow conditions is ultimately recognized as an important tool for clinical diagnosis and therapeutic planning.

The aim of this paper is to present a brief description of the physical properties of blood, including its non-Newtonian characteristics, and review some of the continuum mathematical models of blood rheology that have been proposed in the literature and can be used in computer simulations. A discussion of some preliminary numerical results obtained for a physiological meaningful model of blood coagulation and clot formation, based on the model introduced in[3] will also be included in this paper.

PHYSICAL PROPERTIES OF BLOOD

Whole blood is a concentrated suspension of formed cellular elements that includes red blood cells (RBCs) or erythrocytes, white blood cells (WBCs) or leukocytes and platelets or thrombocytes. These cellular elements are suspended in an aqueous polymeric and ionic solution of low viscosity, the plasma, containing electrolytes and organic molecules such as metabolites, hormones, enzymes, antibodies and other proteins. The formed elements represent approximately 55% by volume of the normal human blood. The process by which all formed elements of the blood are produced (hematopoiesis), occurs mostly in the bone marrow, where cells mature from a primitive stem cell. Important factors in regulating blood cell production include the environment of the bone marrow, interactions among the cells, and secreted chemicals called growth factors[7,8].

Plasma (separable by centrifugation) consists primarily of water (approximately 90-92% by weight) in which inorganic and organic substances (approximately 1-2%) and various proteins (fibrinogen, prothrombin, tissue-factor, albumin, lipoproteins, immune proteins, etc.) are dissolved along with various ions. Plasma's physiological function is the transport of nutrients and wastes throughout the body.

RBCs are highly flexible biconcave discoid particles, without nuclei, typically 6-8 μm in diameter, with a very thin membrane (of maximum thickness 50-100 angstroms[15]) consisting of proteins (spectrin) and lipids. They are filled with a fluid, which is an almost saturated solution (approximately 32% by weight) of hemoglobin, 65% of water, the remainder being other proteins, lipids, adenosine diphosphate (ADP), adenosine triphosfate (ATP) and ions. Hemoglobin is the protein inside red blood cells that gives blood its red color and is primarily involved in oxygen and carbon dioxide transport between the lungs and the living tissues of the body. Erythrocytes are the most numerous of the formed elements (about 98%) and have the largest influence on the mechanical properties of blood. The volume concentration of RBCs in whole blood is called the hematocrit (Ht). The normal values of hematocrit in

humans range from 40-45%, for adults in normal health conditions, to 55-68% for newborns. These values depend on several factors including age, sex of the individuals or health conditions and have a strong influence on the rheology of blood, in particular on blood viscosity.

WBCs, which are much less numerous than erythrocytes (less than 1% of the volume of blood), are normally roughly spherical in shape with diameters ranging from about 7-22 μm. They have nuclei and are composed of five morphologically different cell types: basophils, eosinophils and neutrophils (collectively called granulocytes) and also monocytes and lymphocytes. Leukocytes circulate in the blood stream and when activated by inflammation or by the presence of foreign organisms, change their rheological properties such as deformability. This activation generates an inner force governing a complex cascade of rolling along the vessel wall, induces adhesion to the microvascular endothelium and, ultimately, leads to extravascular migration into the surrounding tissue. However, these processes are believed to have little influence on the rheology of blood, except in extremely small vessels like capillaries or in disease conditions, e.g.[19]. Leukocytes play a key role in the immune system, namely in the protective mechanisms of the body against diseases, in tissue inflammation and in other physiologic and pathological processes, related to early stages of development of cardiovascular diseases. The study of the mechanics of leukocytes is therefore of great interest, see e.g.[12,13,17,32].

Platelets, small discoid non-nucleated cell fragments containing various chemicals such as serotonin, thrombin, and ADP, are much smaller than erythrocytes (approximately 6 μm^3 in size as compared to 90 μm^3) and form a small fraction of the particulate matter in human blood (around 3% by volume). Due to several biochemical reactions and mechanical processes related to prolonged exposure to high shear stress or rapid increases in shear stress, platelets can be activated and become involved in the formation of clot cascades and blood coagulation. If blood is allowed to clot, the remaining fluid is called serum, which is similar to plasma but is missing the protein fibrinogen. Of all the components of blood, platelets are by far the most sensitive to chemical and physical agents and play a critical role in the coagulation process as will be briefly discussed in the next Section.

PLATELET ACTIVATION AND BLOOD COAGULATION

Hemostasis is a complex physiological process involving an interaction between blood vessels, platelets, coagulation factors, coagulation inhibitors and fibrinolytic proteins. When blood coagulates in a blood vessel during life, the process is called thrombosis. Hemostasis keeps blood flowing while allowing solid clot formation, or thrombosis, to prevent blood loss from sites of vascular damage. The hemostatic system preserves intravascular integrity by achieving a balance between hemorhage and thrombosis.

Blood platelets participate in both hemostasis and thrombosis. The first stage of thrombogenesis is platelets activation, followed by platelets aggregation, adhesion and blood coagulation, with the formation of clots. Blood platelets can be activated by prolonged exposure to high or rapid increase in shear stress that lead to erythrocytes and platelets damage. This is due to mechanical vascular injuries or endothelial dysfunction, alterations in the blood composition, fissuring of atherosclerotic plaques as well as to the contact of blood with the surfaces of medical devices. Numerous experimental studies recognize that clot formation rarely occurs in regions of parallel flow, but primarily in regions of stagnation point flows, within blood vessel bifurcations, branching and curvatures.

Following endothelial disruption, there is an immediate reflex that promotes vasoconstriction, minimizing vessel diameter and diminishing blood

loss. Vasoconstriction slows blood flow, enhancing platelet adhesion and activation. During activation platelets undergo intrinsic and extrinsic mechanisms leading to a series of chemical and morphological changes. Organelles contained in the platelet cytoplasm bind to collagen (exposed by arterial damage), release their contents of cytoplasmic granules containing serotonin, adenosine diphosphate (ADP) and platelet-activating factors and platelets become spheroids in shape. Additional platelets attracted by ADP are activated, interact with plasma proteins like fibrinogen and fibrin and promote platelet aggregation and adhesion to sub-endothelial tissue. This results in the formation of hemostatic plugs and concludes the primary hemostasis. However, when the concentration of activators exceeds a certain value, platelet aggregates that are formed by this process can break up, damaging the platelets and causing aggregation at locations other than at the site of damage.

The final hemostatic mechanism or secondary hemostasis is coagulation. The biochemical process leading to clot formation involves a very complex cascade of enzymatic reactions. Thrombin is the bottom enzyme of the coagulation cascade. Prothrombin activator converts prothrombin to thrombin. Thrombin activates platelets that release ADP which lead in turn to the activation of other platelets. It converts fibrinogen, a blood protein, into polymerized fibrin, stabilizing the adhered platelets and forming a viscoelastic blood clot (or thrombus) (e.g. [27,31]).

The clot attracts and stimulates the growth of fibroplasts and smooth muscle cells within the vessel wall, and begins the repair process which ultimately results in fibrinolysis and in the dissolution of the clot (clot lysis). Clot dissolution can also occur due to mechanical factors such as high shear stress[27]. In practice a blood clot can be continuously formed and dissolved. Generally, many factors affect its structure, including the concentration of fibrinogen, thrombin, albumin, platelets and red blood cells and other not specified factors which determine cross-linked structure of the fibrin network. At the end of the hemostatic process, normal blood flow conditions are restored. However, some abnormal hemodynamic and biochemical conditions of flowing blood, related to inadequate levels or dysfunction of the hemostatic system, may lead to pathologies like thromboembolic or bleeding disorders of great clinical importance.

The mechanism of platelet activation and blood coagulation is quite complicated and not yet completely well understood. Recent reviews detailing the structure of the blood coagulation system are available for example in [3,31].

BLOOD CONSTITUTIVE MODELLING

The study of blood flow in the vascular system is complicated in many respects and thus simplifying assumptions are often made.

Plasma behaves as a Newtonian fluid but whole blood has non-Newtonian properties. In the large vessels where shear rates are high enough, it is also reasonable to assume that blood has a constant viscosity and a Newtonian behaviour. However in smaller vessels, or in some diseased conditions, the presence of the cells induces low shear rate and whole blood exhibits remarkable non-Newtonian characteristics, like shear-thinning viscosity, thixotropy, viscoelasticity and possibly a yield stress. In particular, at rest or at low shear rates, blood seems to have a high apparent viscosity (due to RBCs aggregation into clusters called *rouleaux*) while at high shear rates the cells become disaggregated and deform into an infinite variety of shapes without changing volume (deformability of RBCs), resulting in a reduction in the blood's viscosity. The deformed RBCs align with the flow field and tend to slide upon plasma layers formed in between. Attempts to recognize the shear-thinning nature of blood were initiated by Chien et al.[10,11] in the 1960s. Empirical models like the power-law, Cross, Carreau or W-S generalized Newtonian fluid models (see, [5,37]) have been obtained by fitting experimental data in one

dimensional flows. Recently, Vlastos et al.[36] proposed a modified Carreau equation to capture the shear dependence of blood viscosity.

Experiments on blood at low shear rates are extremely difficult to perform and consequently a controversy remains on the behavior of blood at the limit of zero shear rate, leading researchers to believe in the existence of a critical value of stress (yield stress) below which blood will not flow. The treatment of yield stress as a material parameter should be independent of experimental factors and of yielding criteria and this is not the case for blood. In fact there exists a large variation in yield stress values for blood reported in the literature (e.g [22]). The finite time required for the changes in blood microstructure is related to blood yield stress and thixotropy. Charm et al.[9] found that Casson's model gives the best fit to blood data. Casson's and Herschel-Bulkley models[30] are generalizations of the Bingham model that can capture both the yield stress and the shear thinning behavior of blood.

None of these homogeneized models are capable of describing the viscoelastic response of blood. Blood cells are essentially elastic membranes filled with a fluid and it seems reasonable, at least under certain flow conditions, to expect blood to behave like a viscoelastic fluid. At low shear rates RBCs aggregate and are 'solid-like', being able to store elastic energy that accounts for the memory effects in blood. Dissipation is primarily due to the evolution of the RBC networks and, given the paucity of data on temperature effects, the internal energy is assumed to depend only on the deformation gradient. At high shear rates, the RBCs disaggregate forming smaller rouleaux, and later individual cells, that are characterized by distinct relaxation times. RBCs become 'fluid-like', losing their ability to store elastic energy and the dissipation is primarily due to the internal friction. Upon cessation of shear, the entire *rouleaux* network is randomly arranged and may be assumed to be isotropic with respect to the current natural configuration. Thurston (see [34]) was among the earliest to recognize the viscoelastic nature of blood and that the viscoelastic behaviour is less prominent with increasing shear rate. He proposed a generalized Maxwell model that was applicable to one dimensional flow simulations and observed later that, beyond a critical shear rate, the non-linear behaviour is related to the microstructural changes that occur in blood (see [35]). Recently an approximate model inspired on the behaviour of transient networks in polymers and exhibiting shear-thinning, viscoelasticity and thixotropy, related to the microstructure of blood, has been derived by Owens[21].

Other rate type constitutive models for describing blood rheology have been proposed in the recent literature. Yeleswarapu[39] has obtained a three constant generalized Oldroyd-B model by fitting experimental data in one dimensional flows and generalizing such curve fits to three dimensions. It captures the shear-thinning behavior of blood over a large range of shear rates but it has its limitations, given that the relaxation times do not depend on the shear rate, which does not agree with experimental observations. The model developed by Anand and Rajagopal[1] in the general thermodynamic framework of Rajagopal and Srinivasa[25] includes relaxation times depending on the shear rate and gives good agreement with experimental data in steady Poiseuille flow and oscillatory flow.

Continuum models for blood flow are very important (see the recent reviews [28,29,33]) but they are not appropriate in the capillary network (see, e.g. Popel and Johnson[23] and Pries and Secomb[24] for an overview of hemorheology in the microcirculation).

It is now recognized the increasing importance of considering phenomena at the molecular scale where interactions between individual proteins are relevant and an enormous variety of biochemical and biological phenomena at the cells level are influenced and even controlled by fluid dynamic forces[16]. As a consequence, new insights emerged into the pathogenesis of diseases as in the case of atherosclerosis, or into the prevention of important physiological processes like thrombus formation in surgical patients.

NUMERICAL SIMULATIONS OF A BLOOD COGULATION MODEL

While there has been a considerable research effort in blood rheology, the constitutive models have thus far focused on the aggregation and deformability of the RBCs, ignoring the role of platelets in the flow characteristics. In the last two decades mathematical modelling and computer simulation research has emerged as a useful tool, supplementing experimental data and analysis and giving new insights in the studies of the regulation of the coagulation cascade, in clinical applications and device design. Reliable phenomenological models that can predict regions of platelet activation and deposition (either in artificial devices or in arteries) have the potential to help optimize design of such devices and also identify regions of the arterial tree susceptible to the formation of thrombotic plaques and possible rupture in stenosed arteries. Most of the models that are currently in use neglect some of the biochemical or mechanical aspects involved in the complex phenomena of blood coagulation and must be considered as first approaches to address this oversight, see for example [14,18,38]. M. Anand, K. Rajagopal and K. R. Rajagopal[2,3] recently developed a phenomenological comprehensive model for clot formation and lysis in flowing blood that extends existing models to integrate biochemical, physiologic and rheological factors. In what follows we present some preliminary numerical results for a simplified version of this model. A detailed description of these results can be found in [6].

Governing Equations

A generalized Newtonian model with shear--thinning viscosity has been adopted for describing the flow of blood. We denote by ***u****(x,t)* and *p(x,t*) the blood velocity and pressure in the domain *Ω*, the vascular lumen, with $t \geq 0$. The application of the physical principles of momentum and mass conservation for an incompressible viscous fluid leads to the equations defined in *Ω*

$$\rho\frac{\partial \mathbf{u}}{\partial t} + \rho(\mathbf{u}\cdot\nabla)\mathbf{u} + \nabla p - \operatorname{div}\boldsymbol{\tau}(\boldsymbol{u}) = 0 \quad \textbf{(1)}$$

$$\operatorname{div}\mathbf{u} = 0$$

completed with appropriate initial and boundary conditions. Here ρ is the fluid density and $\tau(u)$ is the deviatoric stress tensor, proportional to the symmetric part of the velocity gradient, given by

$$\boldsymbol{\tau}(\boldsymbol{u}) = \mu(\dot{\gamma})(\nabla\boldsymbol{u} + (\nabla\boldsymbol{u})^T)$$

where $\dot{\gamma} = \sqrt{\frac{1}{2}(\nabla\boldsymbol{u} + (\nabla\boldsymbol{u})^T) : (\nabla\boldsymbol{u} + (\nabla\boldsymbol{u})^T)}$ is the shear rate (a measure of the rate of shear deformation) and $\mu(\dot{\gamma})$ is the shear dependent viscosity function which decreases with increasing shear rate. The generalized Cross model has frequently been used for blood. The corresponding viscosity function is written as

$$\mu(\dot{\gamma}) = \mu_\infty + \frac{\mu_0 - \mu_\infty}{(1 + (\lambda\dot{\gamma})^m)^a} \quad \textbf{(2)}$$

where $\mu_0 = \lim_{\dot{\gamma}\to 0}\mu(\dot{\gamma})$ and $\mu_\infty = \lim_{\dot{\gamma}\to\infty}\mu(\dot{\gamma})$ are the asymptotic viscosities at low and high shear rates. Using nonlinear regression analysis, it is possible to fit viscosity functions against blood viscosity experimental data and obtain the corresponding parameters. However, blood viscosity is quite sensitive to a number of factors including hematocrit, temperature, plasma viscosity, age of RBCs, exercise level, gender or disease state, and care must be taken in selecting blood parameters for blood flow simulations. Here we have adopted the following material constants (taken from [20]):

$$\begin{array}{ll} \mu_0 = 1.6\times 10^{-1} Pas & \mu_\infty = 3.610^{-3} Pas \\ a = 1.23, m = 0.64 & \lambda = 8.2s \end{array} \quad \textbf{(3)}$$

The viscosity function (2) with values (3) is represented in Fig. 1.

Our model (see [3]) includes not only rheological factors but also biochemical indicators that are essential to describe coagulation and fibrino-

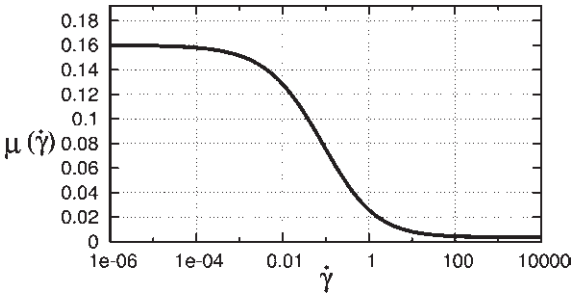


Fig. 1 – Variation of the apparent viscosity as a function of the shear rate for the generalized Cross model with physiological parameters for blood given by (3) (from [20])

lysis dynamics and consequently the formation, growth and dissolution of clots. A set of coupled advection-diffusion-reaction equations modelling the evolution in time and space of various enzymes, proteins and platelets involved in the extrinsic pathway of coagulation process, takes the following form

$$\frac{\partial C_i}{\partial t} + \mathrm{div}(C_i \boldsymbol{u}) = \mathrm{div}(D_i \nabla C_i) + R_i, \quad i = 1, \ldots, 23 \qquad \textbf{(4)}$$

In these equations C_i stands for the concentration of the i-th reactant, D_i denotes the corresponding diffusion coefficient (which could be a function of the shear rate) and $\boldsymbol{u}$ is the velocity field. R_i are the non-linear reaction terms that represent the production or depletion of C_i due to the enzymatic cascade of reactions. The specific form of the reaction terms and diffusion coefficients for the 23-model equations (4) can be found in [3] (see also [6]).

Equations (4) are complemented with appropriate initial and flux boundary conditions involving the concentration of the various species at the inner wall that reflect the injury to the blood vessel.

Under normal conditions no clot exists and we assume that the presence of all these constituents does not affect the velocity of the bulk flow. Clot formation occurs in the vicinity of the injured wall, when an activation threshold in the flux boundary conditions (related to the appearance of tissue factor TF-VIIa complex) is exceeded and the clotting cascade is initiated, which results in the increase of fibrin concentration in the clotting area. Clot growth is determined by tracking in time the extent of the flow region where fibrin concentration C_F equals or exceeds a specific critical value C_{Clot}. Clot dissolution occurs in regions where fibrin concentration drops below C_{Clot}, after initially exceeding it, or when the shear stress exceeds a certain critical value forcing clot's rupture. An important assumption of the model is to assume that the constitutive model for blood and clot are similar, but the material modulus has different values, in particular, the viscosity of the clot is 100 times higher than the viscosity of blood. The main features of the modelling approach are schematically shown in Fig. 2.

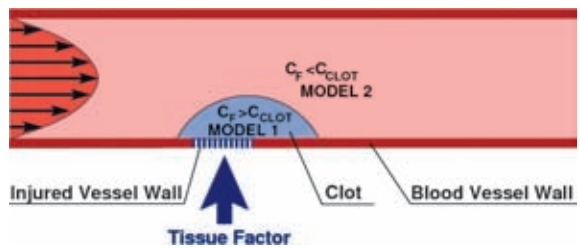


Fig. 2 – Clot modelling

Numerical Results

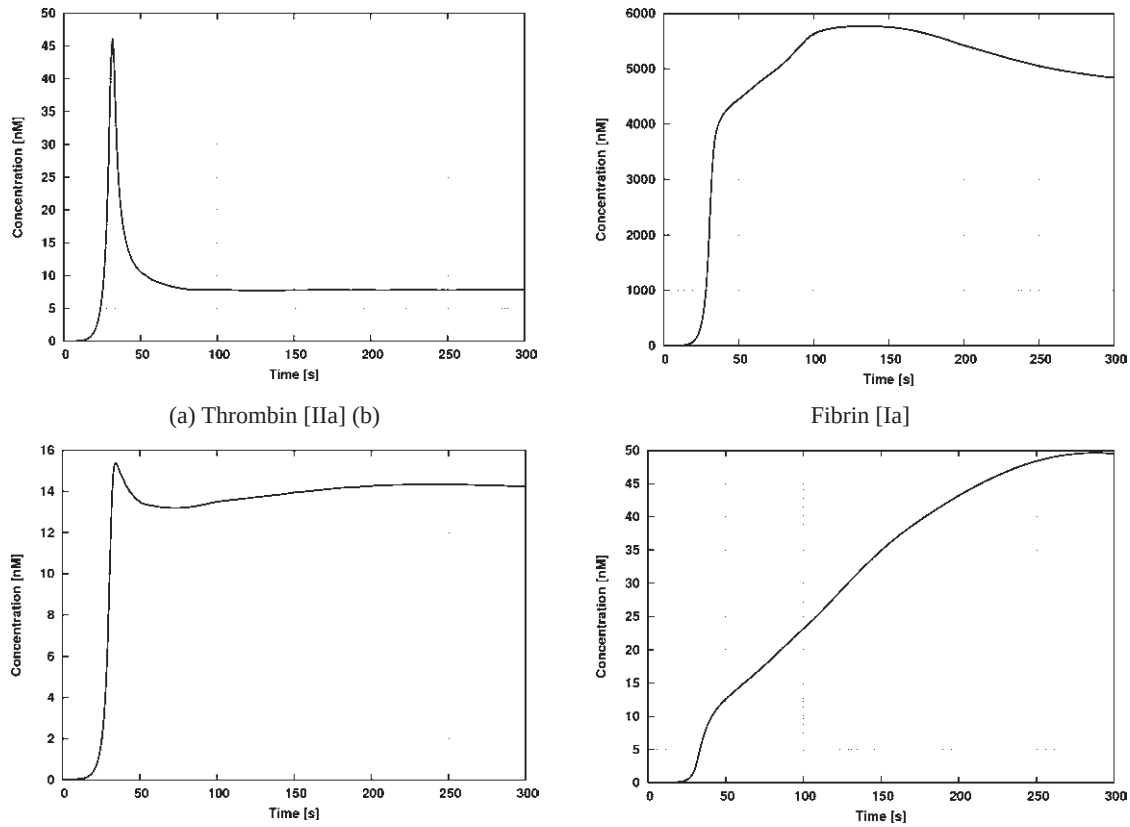
The numerical solution of the coupled fluid--biochemistry model was obtained using an original code based on a finite volume semi-discretization in space, on structured grids, and a simplified multistage time integration scheme. First, the velocity field is computed using equations (1) with a given viscosity, and the concentrations (including that of fibrin) are computed trough equations (4). The local viscosity is updated by a factor which depends on the local fibrin concentration in the clotting area and the velocity field is recomputed using the updated viscosity.

In this section we present preliminary results in a computational domain consisting of a segment of

a rigid-walled cylindrical vessel with diameter *6.2mm* and length *31mm*. A fully developed velocity profile (with mean velocity *3.1cm/s*) is prescribed at the inlet and homogeneous Neumann conditions with fixed pressure are imposed at the outlet. On the vessel wall no-slip Dirichlet conditions for the velocity field are enforced. In addition, we require normal physiological values prescribed as initial conditions for the concentrations of all chemical species (see [2,3,6]). The concentration boundary conditions, for all species, are set as homogeneous Neumann conditions (i.e. no flux) on the healthy vessel wall. In the injured wall region no flux boundary conditions are prescribed for all constituents except for seven species which are directly involved in the initiation of the coagulation cascade[2,3,6].

All the 23 chemical species play an important role in the clotting process. Their concentrations are computed pointwise in the whole computational domain. Figure 3 illustrates the evolution in time *(300s)* of four different concentrations, in the centre of the clotting surface. In particular, we observe that fibrin concentration increases rapidly and reaches its maximum value approximately *120s* after the initiation of the clotting cascade, remaining relatively stable after that time.

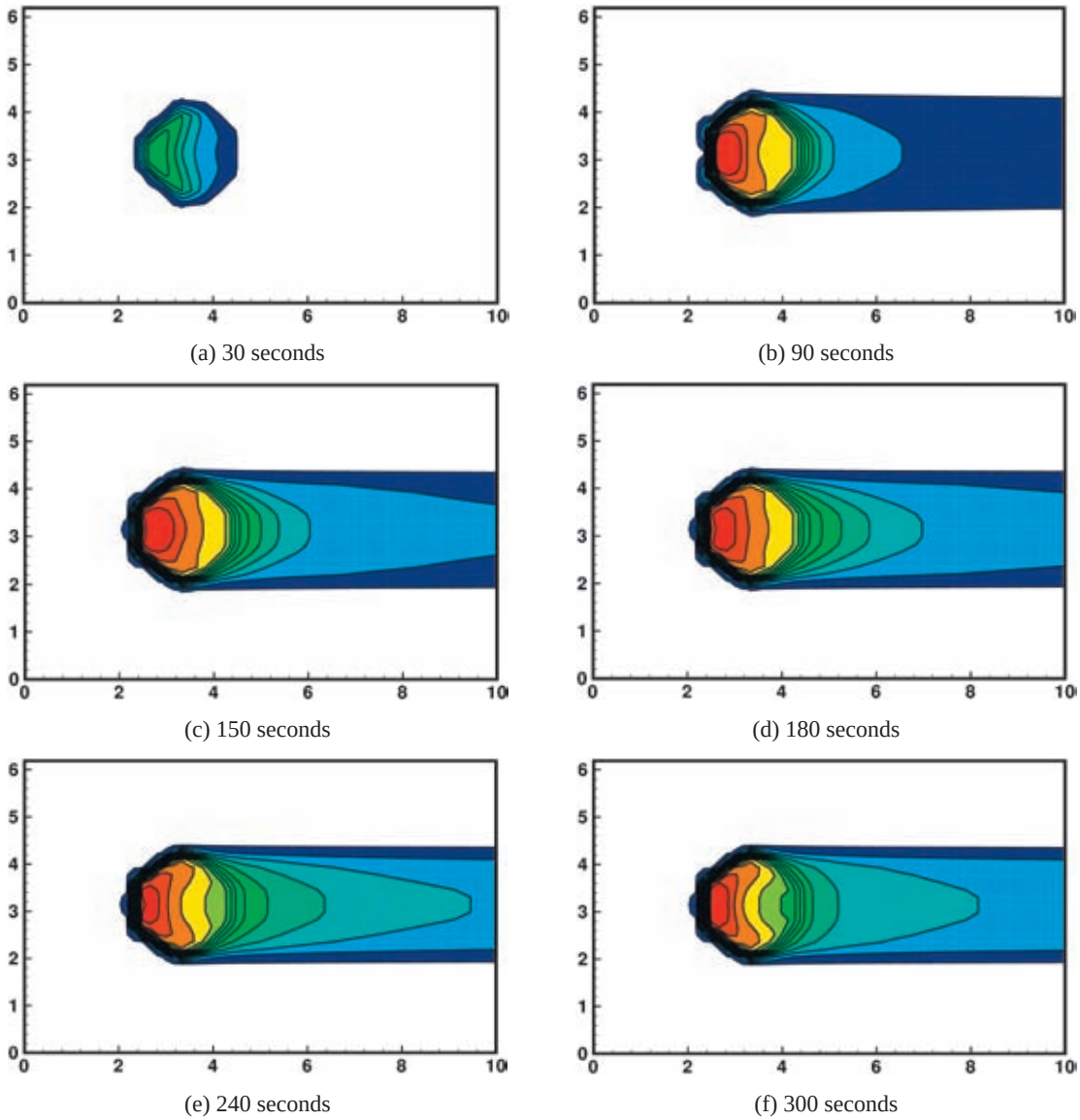
Clot growth can be better observed in Fig.4 which shows surface fibrin concentration contours in the time period *0 – 300s* of clotting. The length scales of both axes correspond to the axial and tangential coordinates, normalized by the vessel cross-section radius. Due to advection, fibrin is transported downstream on the injured vessel wall region and the clot's shape changes its form during the clotting process.



(a) Thrombin [IIa] (b) Fibrin [Ia]

(c) Tissue Plasminogen Activator [tPA] (d) Plasmin [PLA]

Fig. 3 – Time evolution of the concentrations of selected chemical species in the centre of the clotting surface



(a) 30 seconds (b) 90 seconds

(c) 150 seconds (d) 180 seconds

(e) 240 seconds (f) 300 seconds

Fig. 4 – Fibrin concentrations on the vessel wall during the first 5 minutes of clotting

Clot growth and dissolution needs more computational time and is beyond the purpose of the preliminary numerical simulations obtained with this model.

DISCUSSION

Preliminary numerical results of three--dimensional simulations for a simplified version of a model of clot growth and lysis, based on [2,3] and detailed in [6], have been presented here.

The inclusion of additional chemical constituents and their interactions, as those involved in platelets activation and aggregation, should be incorporated into the model to obtain more realistic results. Moreover, the blood flow model used in the simulations only captures its shear-thinning viscosity and could be improved using more complex rheological models. It would be interesting

to incorporate such extensions in the used solvers to obtain numerical results for a more realistic coagulation model that fits physiological experimental data and may be used in clinical applications. This is the object of our current research.

ACKNOWLEDGEMENTS

This work has been partially supported by project PTDC/MAT/68166/2006 and by CEMAT--IST through FCT's funding program.

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