Journal of Theoretical Biology 380 (2015) 367–379

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Numerical validation of a synthetic cell-based model of blood coagulation

J. Pavlova [a], A. Fasano [b,c,d], J. Janela [e], A. Sequeira [a,f,*]

[a] CEMAT, IST, Universidade de Lisboa, Portugal
[b] Dipartimento di Matematica, "U. Dini", Università degli studi di Firenze, Italy
[c] FIAB SpA, Firenze, Italy
[d] Istituto di Analisi dei Sistemi ed Informatica (IASI) Antonio Ruberti, CNR, Italy
[e] Departamento de Matemática and CEMAPRE, ISEG, Universidade de Lisboa, Portugal
[f] Departamento de Matemática and CEMAT, IST, Universidade de Lisboa, Portugal

HIGHLIGHTS

- A simplified mathematical model for blood coagulation is considered including blood slip.
- Numerical simulations have been performed in a 2-D geometry.
- The same results have been obtained as models of higher complexity with no blood slip.
- The influence of blood slip has been emphasized.
- Advantages and limitation of the model have been illustrated.

ARTICLE INFO

Article history:
Received 12 February 2015
Received in revised form
15 May 2015
Accepted 2 June 2015
Available online 12 June 2015

Keywords:
Blood coagulation
Platelets
Biochemical reactions
Mathematical modeling
Slip boundary conditions
Reaction–advection–diffusion equations

ABSTRACT

In Fasano et al. (2012) a new reduced mathematical model for blood coagulation was proposed, incorporating biochemical and mechanical actions of blood flow and including platelets activity. The model was characterized by a considerable simplification of the differential system associated to the biochemical network and it incorporated the role of blood slip at the vessel wall as an extra source of activated platelets.

The purpose of this work is to check the validity of the reduced mathematical model, using as a benchmark the model presented in Anand et al. (2008), and to investigate the importance of the blood slip velocity in the blood coagulation process.

1. Introduction

Blood coagulation is an extremely complex biological process in which blood forms clots to prevent bleeding, followed by their dissolution and, on a longer time scale, by repair of the injured tissue. The process involves different interactions between the blood components and the vessel walls. The biological model used nowadays is the so-called cell-based model (Becker, 2005; Hoffman, 2003a,b) which during the last decade has replaced the so-called cascade model. According to it the coagulation process is subdivided into five phases: initiation, amplification, propagation, termination and fibrinolysis. Each phase develops through a biochemical network including positive and negative feedback mechanisms. A failure at any stage of the process leads to bleeding or thrombotic disorders.

Due to the complexity of the biochemical network, constantly interacting with the blood flow and dependent on platelets activity, mathematical modeling and numerical implementation offer serious difficulties. The literature on mathematical models for blood coagulation has grown at an impressive pace during the last years (see Appiah et al., 2011; Ataullakhanov et al., 1998; Ataullakhanov and Panteleev, 2005; Borsi et al., 2008; Fogelson and Keener, 2010; Leiderman and Fogelson, 2011; Moiseyev et al., 2013; Tanos et al., 2008; Weller, 2010 and the review Fasano et al., 2011).

* Corresponding author at: Departamento de Matemática and CEMAT, IST, Universidade de Lisboa, Portugal.
E-mail addresses: jevgenija.pavlova@gmail.com (J. Pavlova), fasano@math.unifi.it (A. Fasano), jjanela@iseg.ulisboa.pt (J. Janela), adelia.sequeira@math.ist.utl.pt (A. Sequeira).

http://dx.doi.org/10.1016/j.jtbi.2015.06.004
0022-5193/

In our previous work (Fasano et al., 2012) a synthetic model for blood coagulation was proposed. This model studies the clot evolution and its subsequent dissolution combining the action of the blood flow with cellular and molecular processes, and possessing some novelties.

In particular, a coefficient was introduced weighing the contribution of activated platelets, which is obviously a fundamental aspect in the process. Such a coefficient enters as a factor of the reaction rate for the prothrombinase production that implicitly affects all other platelets-mediated chemical reactions, such as those involving prothrombin, thrombin, fibrin, etc. Actually, the amount of the coagulation factors produced and consumed during the clot formation is strongly dependent on the concentration of activated platelets at the injury site, though such a circumstance is frequently ignored in mathematical models.

We also consider the possibility that an additional source of activated platelets at the clotting site may be provided by the blood slip velocity. Therefore, in our view the progressing clot front is capturing not only the platelets being on its way, but also those carried to the clotting site by the slipping flow. Such a mechanism is likely to contribute much more than e.g. diffusion. That provides an explanation of the phenomenon that in different blood vessels, such as veins and arteries, different blood clots structures are observed (Fogelson and Guy, 2008). Let us point out that slip at the vessel wall, though normally disregarded, is a rather natural phenomenon for blood, due to its composite structure. It is well known that a thin erythrocytes free layer is present at the wall (to which a no-slip condition can be imposed), but when treating blood as a homogeneous fluid one must take into account that cells have a finite velocity very close to the wall and this condition is conveniently described as slip.

The simplification of the differential system describing the biochemical cascade reduces model complexity by a large extent. This is particularly important in view of the coupling with a difficult flow problem in variable geometry.

Our main concern was to focus on the propagation phase of blood coagulation, when the main portion of thrombin is formed. Thus we omit the initial and amplification phases (that in terms of time scales are much shorter), starting after the so-called primary coagulation (platelet driven) and from the moment when a small amount of thrombin and of other activated factors has been already formed.

As a benchmark for our computations the mathematical model proposed in Anand et al. (2008) has been chosen, describing the blood coagulation process from the early stage till the complete blood clot dissolution and combining the biochemistry with the blood flow dynamics. The biochemical differential system in Anand et al. (2008) includes 23 chemical reactions corresponding to the five blood coagulation phases.

According to the reduced model here adopted 10 equations of the benchmark model were replaced by only one virtual equation for prothrombinase production that stands as an output of the amplification phase. Such an approach makes sense only if one is not interested in the evolution of the factors that are omitted, thus the reduced model is not adequate to study the disorders associated to the deficiency or dysfunction of those factors.

Comparison with the benchmark model allows us to provide the missing data for the reduced model, with particular reference to the rate constants appearing in the virtual equation for prothrombinase. Owing to the extremely demanding computational complexity, numerical simulations have been performed in a one-dimensional case.

In consideration of the limited purposes of this first step, we took diffusion as the only transport mechanism, necessarily omitting the action of the blood flow. As a consequence, the contribution of the slipping flow is likewise disregarded, consistently with the fact that the role of platelets is not explicitly included in the benchmark model (Anand et al., 2008).

Once the synthetic model has been suitably tuned, numerical simulations are performed in the two-dimensional case, adding the action of the blood flow and blood slip velocity.

To show the impact of the latter quantity on the evolution of biochemical reactions, these results are compared with the no-slip velocity case, in which the activated platelets concentration is constant.

The outline of the paper is the following. In Section 2 we briefly describe the synthetic and the benchmark models for the blood coagulation process; in Section 3 we give the numerical resolution of the benchmark and synthetic models in the one-dimensional case and provide the initial conditions and unknown parameters for the virtual equation; in Section 4 we show the numerical results in the two-dimensional case considering the impact of the blood slip velocity on the propagation of chemical reactions and compare them with no-slip velocity case. The paper ends with conclusions and some perspectives of future work.

2. Mathematical models for blood coagulation

We start this section by presenting a system of equations that describes two mathematical models for blood coagulation, namely the benchmark and the synthetic models.

We consider an initial-boundary value problem composed of n ($n=13$ in the case of the synthetic model and $n=23$ for the benchmark model) time dependent reaction–advection–diffusion (RAD) equations, mutually coupled through linear and non-linear reaction terms. The system is complemented by initial conditions and (non-)homogeneous Neumann boundary conditions B_i, $i=1,\dots,n$ providing input fluxes at the boundary $\partial\Omega$ of the injury site, see Table 1

$$\begin{cases} \dfrac{\partial [C_i]}{\partial t} = \mathrm{div}(D_i \nabla [C_i]) + R_i - \mathrm{div}(\mathbf{u}\cdot [C_i]) & \text{in } Q_T := (0,T)\times\Omega, \\ D_i \dfrac{\partial [C_i]}{\partial \mathbf{n}} = B_i & \text{on } \Sigma_T := (0,T)\times\partial\Omega, \\ [C_i] = [C_i]^{blood} & \text{for } t=0. \end{cases} \tag{1}$$

Here, $[C_i]$ is the unknown function that describes the evolution of concentration of the coagulation factors in time in the domain Ω, R_i are the reaction terms that depend on the evolution of concentrations $[C_i]$, D_i are diffusion coefficients, $\mathbf{u}$ is the blood flow velocity and $[C_i]^{blood}$ are the initial concentrations.

The authors of Anand et al. (2008) provide a complete list of the required biochemical parameters collected through various laboratory experiments.

In the next section we list the reaction terms for both models and briefly explain the biological meaning of the considered biochemical reactions.

Table 1
Boundary conditions for the benchmark model (Anand et al., 2008).

Coag. factors	Boundary flux terms B_i	Coag. factors	Boundary flux terms B_i
IXa	$\frac{k_{7,9}[IX][TF-VIIa]}{K_{7,9M}+[IX]}\frac{L}{D_{IXa}}$	IX	$-\frac{k_{7,9}[IX][TF-VIIa]}{K_{7,9M}+[IX]}\frac{L}{D_{IX}}$
Xa	$\frac{k_{7,10}[X][TF-VIIa]}{K_{7,10M}+[X]}\frac{L}{D_{Xa}}$	X	$-\frac{k_{7,10}[X][TF-VIIa]}{K_{7,10M}+[X]}\frac{L}{D_{X}}$
XIa	$\frac{\phi_{11}[XI][XIIa]}{\Phi_{11M}+[XI]}\frac{L}{D_{XIa}}$	XI	$-\frac{\phi_{11}[XI][XIIa]}{\Phi_{11M}+[XI]}\frac{L}{D_{XI}}$
tPa	$\left(k^{C}_{tPA}+k^{IIa}_{tPa}+k^{Ia}_{tPA}\right)\frac{[ENDO]L}{D_{tPA}}$		

According to Anand et al. (2008) parameter L represents the thickness of the plasma layer that covers the thrombogenic plane and $[ENDO]$ stands for the surface density of the endothelial cells that secrete tPA.