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NUMERICAL ASSESSMENT OF DEVICE-RELATED THROMBUS FORMATION TRIGGERED BY THE CONTACT SYSTEM

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SUMMARY

Thrombosis is a major concern in blood-coated medical devices. In the present study, pro-coagulant reactions including the contact activation system are coupled with a fluid solver as well as a recently proposed thrombus formation model. The resulting biochemical/fluid model is applied to a backward facing step configuration, a flow configuration that frequently appears in medical devices. Simulations show that the contact system induces a large concentration of thrombin in the recirculation zone without the need of an a priori knowledge of the thrombus location. Platelets are then chemically activated and generate a thrombus whose both position and growth rate are in good agreement with the experimental data available.

Key words: *Thrombosis, Contact System, Hemodynamics, Reduced kinetics*

1 INTRODUCTION

One of the main problems of blood-contacting devices is thrombus formation which can lead to device malfunction or thromboembolism. Blood clotting in devices is regulated by a series of intertwined biological processes, such as protein adsorption, platelet activity, complement system and coagulation reactions, as reviewed by Gorbet and Sefton [1]. These mechanisms appear due to the presence of the device whose artificial wall lacks the endothelial properties of the vessel. At the material surface, contact activation of factor XII (zymogen of the coagulation cascade) takes place, initiating a cascade of enzymatic reactions [2] that produce thrombin, a key coagulation enzyme that activates platelets and forms fibrin. At the same time, platelet adhesion and activation can also occur at the device surface, as explained by Jaffer et al. [3]. In the last stage of the thrombus formation process, aggregated platelets and polymerized fibrin form a stable clot that may hinder the device performance.

Computational fluid dynamics (CFD) has been used to study the flow in medical devices and evaluate the risk of thrombosis [4]. A straightforward evaluation of thrombosis risk can be performed using specific flow patterns, such as high shear stress yielding to platelet activation [5] or stasis which promotes coagulation [6]. Approaches focusing only on flow properties do not allow to study the biochemical processes, which play a major role in thrombus formation [7]. Thus, more exhaustive methods accounting for platelet activity, the coagulation cascade, clot growth and its interaction with the flow have been developed for thrombus triggered by vessel injury [8], [9]. However, only small computational domains (~100 μm) can be considered due to the complexity of these models. Reduced, low-order models accounting for platelet adhesion, activation (by chemical and mechanical pathways) and clot-flow interaction have been developed (Taylor et al. 2016; Wu et al. 2016). Nevertheless, thrombin produced by the coagulation cascade triggered by the contact system has not been considered in a model of thrombus formation in devices. A model that incorporates the contact activation system and the coagulation reactions until thrombin formation coupled with a realistic representation of flow dynamics is thus needed. This is all the more true as

recent clinical studies have pointed at the contact activation phase as a promising therapeutic target providing an anticoagulant strategy without increasing the risk of bleeding [3], [10].

A first step towards this objective was recently presented by Mendez et al. [11] who implemented a surface-mediated thrombin production model in a general purpose computational hemodynamics framework. The model accounts for the interaction of the blood flow with the contact activation system and the rest of the blood coagulation cascade. The objective of the present study is then twofold:

- 1- couple the framework of [11] to a proper thrombus formation/growth model,
- 2- assess the resulting pipeline by computing a well-controlled configuration relevant to device-induced thrombus formation.

2 METHODOLOGY

The Navier-Stokes equations are solved along with the Convection-Diffusion-Reaction equations for each chemical species. The set of equations writes:

$$\nabla \cdot \mathbf{u} = 0 \quad (1)$$

$$\rho \left(\frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u} \right) = -\nabla p + \mu \nabla^2 \mathbf{u} - \mu F(\varepsilon) \mathbf{u} \quad (2)$$

$$\frac{\partial C_i}{\partial t} + \nabla \cdot (C_i \mathbf{u}) = \nabla \cdot (D_i \nabla C_i) + R_i \quad (3)$$

where \mathbf{u} is the velocity field, p is the pressure field, ρ stands for the density and μ is the dynamic viscosity (both assumed constant-valued). C_i represents the concentration of species i , D_i is the diffusion coefficient and R_i stands for the reaction source term for each of the coagulation factors, as computed from the kinetic model of Chatterjee *et al.* [12] (53 species, 63 reactions rates). In order to initiate the coagulation reactions by contact activation of factor XII, the proper boundary condition introduced by Mendez et al. [11] is used. This condition relates the species diffusive wall flux to the surface reaction rate of factor XII activation. It reads:

$$D_{XIIa} \frac{\partial C_{XIIa}}{\partial n} = -k_s C_{XII} \quad (4)$$

where n is the direction normal to the wall and k_s denotes the surface reaction rate of the $XII \rightarrow XII_a$ reaction. Furthermore, the thrombus evolution is accounted for thanks to the model proposed by Taylor et al. [13] which considers three biochemical species: non-activated platelets (NP), activated platelets (AP) and Adenosine diphosphate (ADP). Mechanical and chemical activation mechanisms are considered in the model. When a platelet is activated, a certain amount of ADP is released and once a threshold concentration of ADP is reached, chemical activation takes place. As in mechanical activation, chemical activation of platelets also releases ADP and an auto-amplification loop is formed. To quantify thrombus growth, the concept of platelet aggregation intensity ε was introduced in [13]. The thrombus frontier corresponds to the surface (line in 2D) where the aggregation intensity reaches a pre-defined threshold value. Production/destruction of ε are also introduced based on the local value of the concentration of activated platelets and viscous shear stress. Finally, the impact of the growing thrombus on the flow is accounted for by considering the thrombus as a porous material and is modeled by adding a Brinkman term in the RHS of the Navier-Stokes equations (see last term of Eq. (2)). The details about the evolution equation of ε and the expression of $F(\varepsilon)$ can be found in Taylor et al., 2016 [13]. The coupling between the approaches developed in [11] and [13] is done by allowing the platelets to be activated by thrombin instead of only ADP. Moreover, given the simplicity of the thrombus model described above, a reduced order kinetic scheme was used for the coagulation cascade which mimics the scheme of Chatterjee *et al.* [12] at lower cost (5 species and 9 reaction rates).

The framework described above was applied to predict the thrombus growth in a backward facing step geometry (BFS) inspired from the experimental configuration of Taylor *et al.* 2014 [14]. The

flow equations were solved thanks to the in-house CFD solver YALES2BIO (imag.umontpellier.fr/~yales2bio/) already used by Mendez et al. [11].

3 RESULTS

The flow configuration considered is presented in Figure 1 which also displays a typical map of thrombin concentration after convergence. Note that this result corresponds to the case where the thrombus generation/growth model is switched off. This allows illustrating how the coagulation cascade initiated by the contact system is able to produce thrombin behind the BFS, where the characteristic flow time scale is large enough to allow chemistry to dominate. In the other regions of the flow domain, any thrombin production is washed out before accumulation can occur. Note that the boundary condition Eq. (4) is applied uniformly over all the walls in Fig. 1. This contrasts with conventional in-vivo models in which the reactions are initialized at user-defined injury sites.

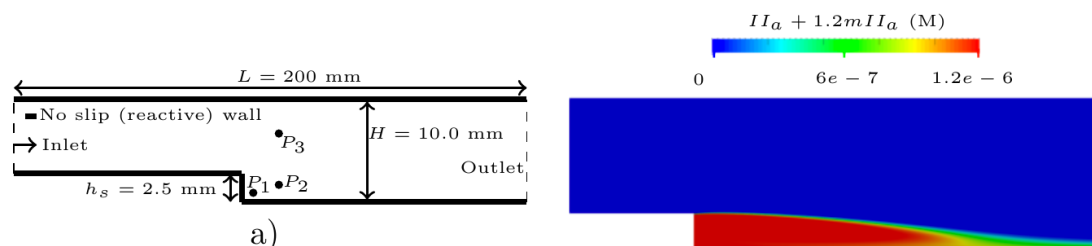


Figure 1: Schematic of the BFS configuration (left) and concentration of thrombin in absence of thrombus formation modeling (right).

When the thrombus generation/growth model is switched on, the computation predicts blood clotting behind the BFS, as observed in the experimental data of Taylor et al. [14]; this is illustrated in Figure 2.

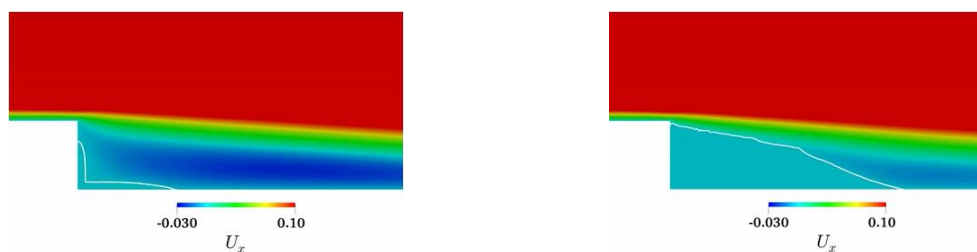


Figure 2: Longitudinal velocity component after 5 (left) and 20 (right) minutes. The white line is the boundary of the thrombus.

Figure 3 shows that the computed growth of the thrombus is in good agreement with both experimental and computational data. Note however that the evolution of the thrombus is mostly independent (not shown) on the amount of activated platelets injected at the inlet of the flow domain. Indeed, the platelets activation is very efficiently triggered by the thrombin issued by the contact system. This contrasts with the previous study of Taylor et al. 2016 [13] where the background concentration of activated platelet shows a large influence on the non-normalized results.

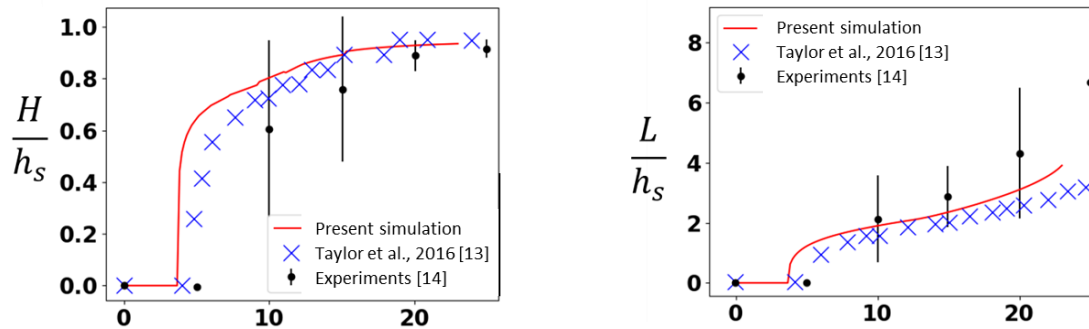


Figure 3: Time evolution of the length (left) and the height (right) of the thrombus behind the BFS.

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