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A spatio-temporal model for spontaneous thrombus formation in cerebral aneurysms

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HIGHLIGHTS

- New model numerical for thrombosis formation in cerebral aneurysms.
- Stop of the thrombosis process is an emergent process.
- Low shear-stress threshold for thrombosis initiation validated through an in vitro experiment.
- Application on two spontaneous thrombosis cases.

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ABSTRACT

We propose a new numerical model to describe thrombus formation in cerebral aneurysms. This model combines CFD simulations with a set of bio-mechanical processes identified as being the most important to describe the phenomena at a large space and time scales. The hypotheses of the model are based on in vitro experiments and clinical observations. We document that we can reproduce very well the shape and volume of patient specific thrombus segmented in giant aneurysms.

1. Introduction

Thrombosis is an important physiological process by which the fibrinogen transported by blood is transformed into a solid and stable mesh of fibrin filaments. Usually, the role of thrombosis is to form a plug on an injured tissue to prevent blood hemorrhage, and to allow for tissue remodeling. Thrombus formation may also have detrimental effects, for instance in strokes, when a clot obstructs a blood vessel without being dissolved by natural thrombolysis. In the case of cerebral aneurysms (fragile, bubble-like structures that may appear on cerebral arteries and cause death if ruptured), thrombosis is the healing mechanism by which the aneurysm cavity may be occluded, and the parent artery remodeled.

Spontaneous thrombosis is found more frequently in giant aneurysms than in smaller ones (Whittle et al., 1982; Schaller and Lyrer, 2002; Cohen et al., 2007; Kulcsàr et al., 2011). A recent approach to treat aneurysms is to insert, in the damaged parent artery, a specific type of stents, called flow diverters (FD). By covering the aneurysm neck, the expected role of FD is to reduce

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the flow in the aneurysm sac and to trigger thrombus formation in the cavity. Although this treatment has a good success rate, it still fails to produce the expected results in about 20% of the cases.

The great difficulty to understand the mechanisms leading to thrombosis and predict its occurrence is the interdependence between the biochemical factors, the aneurysm morphology and the blood flow patterns. Computational Fluid Dynamics (CFD) models have been extensively used to provide detailed analysis of flow structures (pressure, velocity, wall shear stress) in aneurysms (see among many others, Sforza et al., 2009; Augsburger, 2009). These numerical simulations do not include any biological processes. However some studies propose an empirical link between flow pattern and thrombus formation. Based on a study with 3 patients, Rayz et al. (2008) reported that regions of thrombus formation correspond to slow flow locations. In a second work, the same authors investigated the effect of the flow residence time (FRT) on thrombus presence. They conclude that aneurysm regions with high FRT and low velocity can be prone to thrombus formation. Note that the authors did not consider any molecular processes to justify their claim. A more bottom-up approach is considered in Ouared and Chopard (2005) and Chopard et al. (2007), where the flow model is augmented with the presence of abstract procoagulant molecules. Despite its simple implementation of the biological response, this model explains very well why spontaneous thrombosis occurs preferably in large aneurysms.

To go one step further, it is necessary to develop more realistic numerical models where, in addition to the flow dynamics, the relevant biochemical molecules involved in the thrombus formation are taken into account, as well as the interactions between each of them and with the rest of the system, typically the endothelial cells and extracellular matrix.

Fogelson and Neeves (2015) published a detailed review on the complex interactions between blood components and the vascular wall involved in thrombus formation. The authors highlighted several major points like: (1) the role of Red Blood Cells (RBCs) in the platelets margination from vessels center to the vessel wall surface. (2) The function of the GPIb-vWF bonds in the platelet adhesion at high shear stress. (3) The effect of the hydrodynamic forces on the extension of vWF and the modulation of its biological activity. (4) The complex network of proteins interactions and the polymerization of the fibrin monomers. (5) The way blood molecules are transported by the flow. (6) The threshold density of Tissue Factor (TF) to trigger coagulation. (7) The fact that when the shear stress decreases, the amount of TF needed to generate the same quantity of fibrin decreases. (8) The role of platelets to limit the clot growth by impeding access to TF and to immobilize coagulation enzymes complexes.

Building a fully detailed numerical model which would include all these components, as well as the full coagulation cascade, and could simulate the thrombus formation over the spatial scale of the aneurysms and over temporal scale corresponding to days or weeks is a formidable task, out of reach of current computer technology. For instance, numerical models only implementing the transport of platelets in the presence of the deformable RBCs is already an enormous challenge (Mountrakis et al., 2013, 2015). Appropriate multi-scale methods are thus necessary. Statistical physics teaches us that many microscopic details may be irrelevant when one considers a process at large scale. The results obtained in Ouared and Chopard (2005) and Chopard et al. (2007) clearly show the importance of the spatio-temporal nature of the process, as also emphasized in Fogelson and Neeves (2015). The processes of thrombus start, growth and stop are the result of the presence of the appropriate molecules, at the right place and right time, as transported by the fluid flow. This might be more important than the exact implementation of the coagulation cascade.

In this paper we propose a model to understand the spontaneous formation of a thrombus in a cerebral aneurysm. In Section 2 we identify biochemical components and interactions that must be taken into account in view of the time and spatial scales we are interested in. In particular, in vitro experiments were performed to determine the coagulant factors produced at the aneurysm wall under the flow regime that is observed to be favorable to initiate thrombosis.

Then, in Section 3 we incorporate these factors on a blood flow model. The main components we consider are thrombin, antithrombin, fibrinogen, and fibrin, their mutual interactions, and the response of the aneurysm wall. Other molecules, like platelets are not modeled explicitly, but their role is included in the interaction rules.

In Section 5 an application on two patient-specific aneurysms is performed. It demonstrates the very good predictions obtained from the numerical simulations and illustrates the sensitivity of the process to the production rate of thrombin. Finally this work is concluded and perspectives are given in Section 6.

2. In vitro experiments

In this section we present in vitro experimental results that contribute to the justification of our thrombosis model. Our central hypothesis is that the response of the endothelial cells to low wall shear stress (WSS) flow conditions results into the production of molecules important in the coagulation process, typically Tissue Factor (TF) and its antagonist, the thrombomodulin.

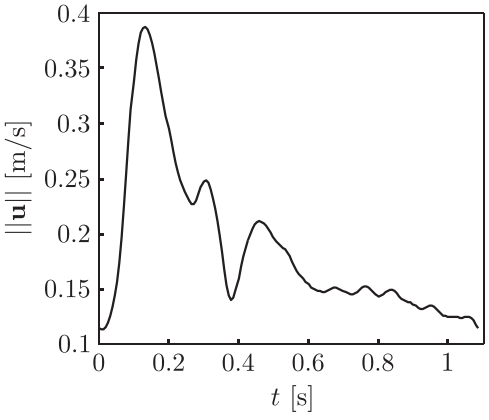

Fig. 2. Average velocity profile over one heartbeat imposed at the inlet of the synthetic aneurysm geometry.

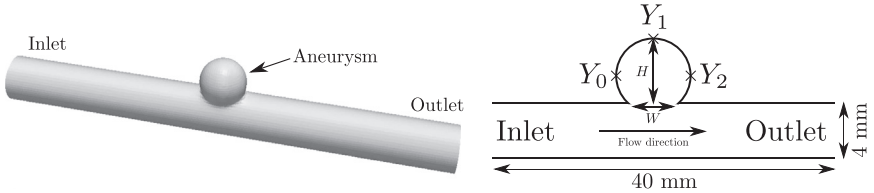

Fig. 1. Synthetic aneurysm geometry with the position of the measurement points Y_0, Y_1 and Y_2. The left panel shows a 2D cut of the geometry, in the mid plane along the parent vessel axis.