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TRANSPORT-REACTION MODEL OF MURAL THROMBOGENESIS

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ABSTRACT

Introduction

Thrombosis is a normal process that occurs after injury. However, thrombosis on an atherosclerotic lesion can lead to heart attack and stroke. Thrombus formation and growth depend on several factors including i) the nature of the thrombogenic surface (at which the thrombus grows); ii) the surface geometry; iii) the biochemistry of blood; and iv) the flow of blood. Previous works have focused on different aspects of coagulation. Few researchers, however, have presented models that couple the effect of biochemical reactions and blood flow on thrombosis. Our objective is to investigate the effect of flow on thrombus growth, including the effects of platelet transport, platelet activation and thrombin production and inactivation.

Model

We modelled a thrombogenic surface with blood flowing over it at a constant shear rate. Our models considered 4 species: resting (non-activated) platelets, activated platelets, thrombin and antithrombin III (ATIII) – see also [1] and [2]. For each species, a diffusion-advection-reaction equation was solved,

$$\frac{\partial C_i}{\partial t} + \mathbf{v} \cdot \nabla C_i = D_i \nabla^2 C_i + R_i$$

where C_i is the concentration of species i, t is time, $\mathbf{v}$ is the blood-flow velocity vector, D_i is the enhanced diffusion coefficient (Brownian motion enhanced by collisions with red-blood cells) and R_i is a reaction rate.

Our model assumptions are as follows. Initially there are no activated platelets. As blood flows over the thrombogenic surface, resting platelets adhere to the surface and activate. Thrombin is produced at the surface of activated platelets. Concentration of thrombin above a critical threshold activates platelets at a rate that depends on thrombin concentration. ATIII binds to thrombin inactivating it. Resting platelets can only attach to portions of the thrombogenic surface that are not covered by platelets. In contrast, activated platelets can attach to both covered and non-covered portions of the surface. Therefore, after complete surface coverage, thrombus growth is regulated by active-platelet adhesion. Simulations of the model were performed using COMSOL Multiphysics.

Results

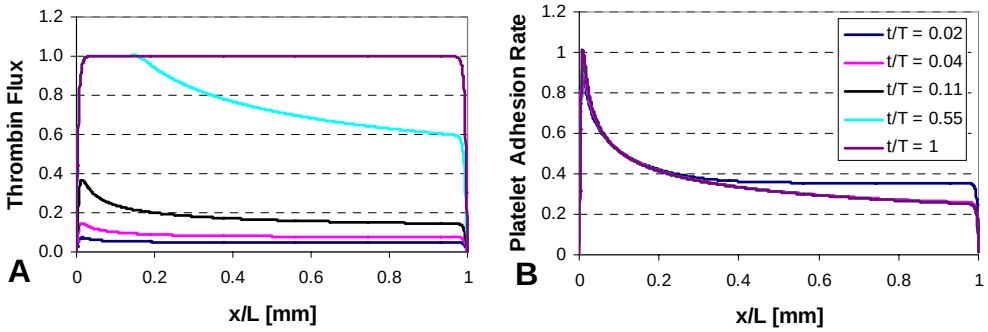

Figure 1: Normalized (**A**) thrombin flux and (**B**) platelet ahesion rate at the thrombogenic surface. x/L represents normalized distance from the beginning of the surface (flow direction from left to right), t is time and T is the time at which the surface is first fully covered.

Our model reproduced the initial stages of platelet adhesion to a thrombogenic surface: i) the initial regime in which platelets adhere at a rate that increases with time and ii) the steady regime in which platelets adhere at a constant rate. The model also captured the increase in platelet adhesion rates that occurs when shear rates increase and initial (systemic) platelet count increases. Platelet adhesion rates and concentration of thrombin-ATIII in the steady regime correlated very well with experimental data obtained from arteriovenous shunts in baboons, e.g. [3].

Simulations of our model showed that thrombin forms a thin concentration boundary layer (~10^2μm) near the thrombogenic surface. Because in our model thrombin activates platelets and activated platelets enable thrombin production, the thrombin and activated-platelet boundary layers had the same thickness. Furthermore, soon after generation of thrombin started at the thrombogenic surface, platelets near the surface activated and the deposition of platelets was soon dominated by activated platelets. As a result, steady activated-platelet adhesion rates were reached before steady production of thrombin was achieved (see Figure 1).

Conclusion

Our model captured the platelet adhesion rates observed experimentally in the steady regime and suggests that thrombin might be produced in excess, explaining the fast initial growth of the thrombus. In the future, we will further develop our model to investigate the effect of flow on other reactions in the coagulation cascade with the ultimate goal of developing a simple and yet accurate model of thrombus growth that might help assessing patient's risks.

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