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MODELING PATHOLOGICAL BLOOD CLOTTING FOR THE DEVELOPMENT OF NEXT-GENERATION ANTICOAGULANTS

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The inherent hemostatic response to vascular injury prevents blood loss, but excessive thrombosis may impede blood flow to vital organs or tissues [1]. As an essential stage of the coagulation mechanism, prothrombin is activated to thrombin. Thrombin is then involved in the activation of blood platelets, the production of fibrin, and an amplification mechanism of the coagulation. As recently shown in [2], in equilibrium prothrombin exists between two forms: “closed” (~80%) and “open” (~20%). The binding of prothrombin to prothrombinase occurs primarily in the closed form, allowing for a slightly more efficient conversion to thrombin. Thus, the ratio between the two forms of prothrombin is a key determinant for blood clotting and an imbalanced ratio may be associated with pathologies.

In this work, we present a mathematical model for the prediction of localized thrombus formation which covers the mechanisms of the human blood coagulation process. Importantly, this model will take into account the impact of the changes in prothrombin open/close ratio on blood clotting upon prothrombin mutations and ligand binding. This aspect is not taken into account by mathematical models currently available in the literature, e.g., as shown in [3].

Within the model, a set of convection-diffusion-reaction (CDR) equations is coupled to the incompressible Navier-Stokes equations. Endothelial injuries/dysfunctions are modeled with boundary conditions to the above equations. We solve our model using a stabilized space-time finite element method [4] and apply this to test cases with realistic blood-flow conditions and vessel geometries.

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