A Multiscale Model for Platelet Deposition

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Platelet aggregation is an important regulator of hemostatic function in response to a blood vessel injury. Overactivity of platelet aggregation in situations such as atherosclerotic plaque rupture can cause occlusion of the vessel, while underactivity results in excessive bleeding. Several complex biological and physical mechanisms contribute to the growth of a stable platelet mass at the site of injury while limiting the final extent of growth to prevent occlusion. A detailed model of this system would provide insight on the coupling between biological signaling and fluid flow as well as predict strategies for anti- or pro-thrombotic therapy. Patient-specific models would enable predictions of resistances to common anti-platelet therapies such as asipirin and clopidogrel. A multiscale model is built upon patient-specific platelet phenotyping and is compared to patient-specific platelet deposition to collagen in a microfluidic chamber.

The multiscale model has four major modules: lattice Boltzmann (LB), finite element method(FEM), lattice kinetic Monte Carlo (LKMC), and neural network (NN). The NN is trained on a single donor's pairwise agonist scanning (PAS) experiment that measures the rise in intracellular calcium to three main platelet agonists: adenosine diphosphate (ADP), thromboxane A2 (TXA2), and convulxin (CVX). The LKMC method follows the motion of platelets within the fluid due to diffusion and convection. An inhomogeneous radial distribution of platelets is enforced with an inlet boundary condition and by biasing motion within the fluid. Platelet bonding is captured in LKMC through a bonding model that links prediction of intracellular calcium from the NN to bonding kinetics. The concentrations of soluble platelet agonists, which are released from activated platelets, are tracked using FEM. Finally, LB solves for the velocity of the fluid around the growing platelet aggregate. Each module requires information supplied by the other modules in the framework. For example, the NN model requires the time history of agonist exposure for each platelet in the simulation domain, and this information is supplied by the concentration profiles of agonist from FEM and the locations of each platelet from LKMC. The output of the NN model is ultimately the activation state of each platelet, which determines the bonding kinetics in LKMC and the release rates in FEM. The time step of each module determines the relative accuracy of the coupling. Due to the efficiency of the multiscale framework, the entire active zone of the experiment can be simulated in 2 dimensions for multiple patients and drug treatments.

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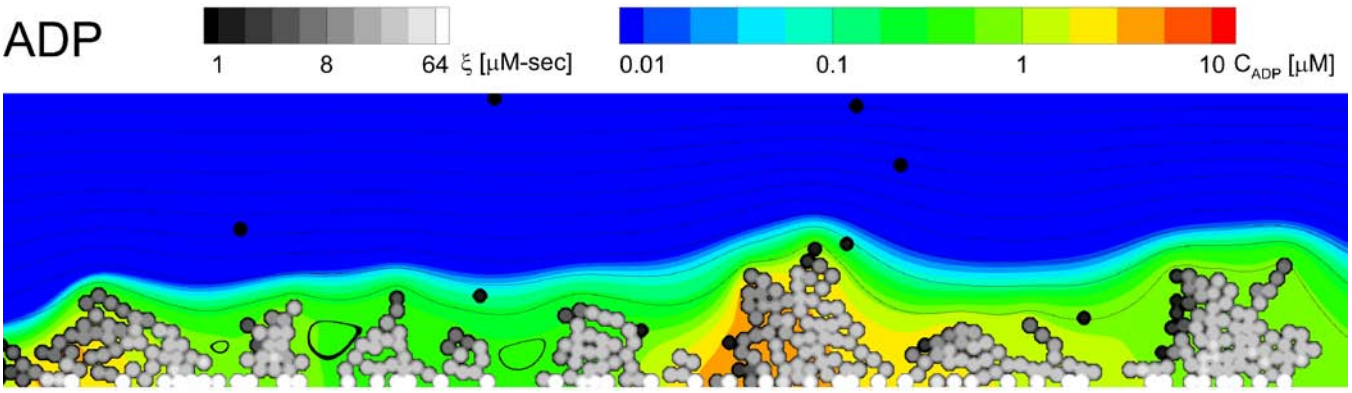

Simulation of platelet aggregation on collagen surface. Circles – platelets (Black – fully unactivated, White – fully activated). Lines – streamlines of the blood flow. Background color – ADP concentration (TxA_2 concentration not shown).