224c Multiscale Modeling of Receptor-Mediated Platelet Adhesion to Surfaces under Flow

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Platelets are the key participants in thrombotic events that take place following vascular injury. These tiny ellipsoidal-shaped blood cells are recruited to the exposed subendothelial region at the vascular lesion and aggregate to form a hemostatic plug that blocks further blood loss and seals the wound. Initial platelet contact with the exposed subendothelial components at physiological shear rates in arterioles ($500 – 2{,}000\ s^{-1}$) and even at pathological shear rates in stenosed regions ($2{,}000 – 10{,}000\ s^{-1}$) of the vasculature is mediated by the platelet glycoprotein GPIbα surface receptor. The GPIbα receptor binds the A1 domain of collagen-bound von Willebrand factor (vWF), a large multimeric plasma glycoprotein. GPIbα-vWF-A1 tether bond formation is critically important for enabling platelets to initiate binding to the injured exposed subendothelial surface. This tether bond exhibits selectin-like binding kinetics characterized by fast on- and off-rates, high tensile strength, and the requirement of a critical level of shear flow for adhesion to occur.

Platelets bound to the surface via this molecular pair exhibit rolling over the surface in the presence of shear flow; similar to leukocyte rolling. Platelets, however, are far from spherical in shape and appear as flattened ellipsoids. This difference in shape influences the cell's flow behavior near a solid boundary, specifically the manner, frequency, and duration of cell-surface contact, and the magnitude of shear and normal forces acting on the platelet (Mody et al., 2005). Mathematical models of one or more platelets flowing near a surface under linear shear flow, and undergoing reversible binding to a reactive surface, have been virtually non-existent until recently. Such dynamic simulations of platelet adhesion would have immense utility in understanding and modeling healthy and pathological thrombotic phenomena. Very little has been done to date to model the adhesive behavior of an ellipsoidal-shaped cell near a surface because of the limited availability of fluid mechanical equations for flow of an ellipsoid in a bounded fluid. Importantly, previous hydrodynamic studies of spheroidal-shaped particle motion near a wall in shear flow did not consider particle contact with the surface, or the effect of surface contact on subsequent flow behavior.

We have developed a new multiscale simulation which fuses a boundary elements calculation of cellular-scale fluid mechanics, with a stochastic Monte Carlo simulation of the formation and breakage of receptor-ligand molecular bonds. The computational method employed for calculating the rigid body motion of an oblate spheroid-shaped particle in our study is based on the Completed Double Layer – Boundary Integral Equation Method (CDL-BIEM), a boundary element method developed by Kim and Karilla (1991) to solve the integral representation of the Stokes equation. The platelet surface is discretized into 96 elements, with each element comprised of one node at the center and three nodes per edge – totaling 9 nodes per element and 386 nodes per surface. Our fully 3-D computational model incorporates the influence of the proximity of the wall and determines the cell's modified translational and rotational trajectories that result following surface contact. This model was developed along similar lines to the Multiparticle Adhesive Dynamics method used by King and Hammer (2001) to study the effects of hydrodynamic interactions between flowing and bound leukocytes on the adhesive behavior of these cells. When the platelet nears the surface and is within binding range, bond formation between GPIbα and surface-bound vWF is tested. Bonds that form are represented as linear springs with fixed end-points on either surface. The bond forces and torques acting on the cell are a function of the length and orientation of each of the bond springs that bind the cell to the surface, as well as on the physical state of compression and extension. The Fortran 95 random number generator is used to test both bond formation and breakage against their respective probabilities calculated from the instantaneous bond association and dissociation rate. The Bell model parameters for single GPIbα-vWF bond dissociation kinetics as obtained by Doggett et al. (2002) are incorporated into the adhesive dynamics calculations.

Calculations were performed for physiological wall shear rates of 500-4000 s^{-1}. The results demonstrate that platelet flow behavior is quite different from that of spheres. The platelet is found to exhibit three distinct flow regimes, with the dominant flow regime being dependent on its initial height from the surface. These distinct regimes can be found to exist if the platelet axis of revolution has minimal tilt about the x-axis, i.e., the flow is symmetric about the major axis of the platelet that lies in the plane of flow. Only in one of these three flow regimes do platelets exhibit surface contacting. For significant out-of-plane motions the behavior is more complex. With fully 3-D motions the platelets has a greater tendency to repeatedly contact the surface allowing the platelet to sample surface-bound molecules with which it can interact to form tether bonds. The results from adhesive dynamics simulations quantify the frequency of cell collisions with the surface, the capture efficiency, the hydrodynamic forces acting on platelet bonds, their effects on bond formation and breakage, pause times with average number of bonds formed, and the surface distribution of bonds and bond forces. The simulation predictions demonstrate the importance of shear rate and regime of flow in critically determining cell-surface collision frequency and capture efficiency.

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