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MULTISCALE SIMULATION OF SHEAR-INDUCED PLATELET ACTIVATION: CORRELATING NUMERICAL WITH EXPERIMENTAL RESULTS

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INTRODUCTION

The coagulation cascade of blood may be initiated by shear-induced platelet activation, which prompts clot formation in prosthetic cardiovascular devices and in arterial disease processes. Upon activation platelets undergo complex biochemical and morphological changes. Activated platelets polymerize fibrinogen into a fibrin network that enmeshes red blood cells. Continuum methods fail to capture the smaller scale molecular mechanisms such as the filopodia formation during platelet activation. Utilizing molecular dynamics that can capture and model this is computationally prohibitive. To address these challenges, a multiscale approach may offer an effective means to bridge the gap between macroscopic flow and the cellular scales. We have developed a multiscale model which interfaces nanoscale microstructures of human platelets and mesoscale transport of blood flows, for providing a more accurate flow-induced dynamic stress mapping on platelet membranes and predict their activation and adhesion. Coarse-grained molecular dynamics (CGMD) and dissipative particle dynamics (DPD) have been employed to simulate complex processes at molecular scales, as well as low-to-high Reynolds numbers viscous flow dynamics at mesoscopic scales. Coupling CGMD and DPD systems needs to interface the disparate spatial and temporal scales. Spatial interface is established by a hybrid force field between surface membranes and surround flows, in which microstructural changes of platelets respond to extracellular viscous shear stresses transferred to them [1]. The temporal interface is formulated by a multiple time stepping algorithm, in which three orders of magnitude disparity at microseconds and nanoseconds are handled by four-level integrator [2]. The phenomena of filopodia formation could be mimicked [3]. Additionally, numerical results were directly correlated with differential interference contrast (DIC) microscopy observations of platelets flowing in microchannels [3].

METHODS

We consider two spatiotemporal scale methods: (i) top/microscale using dissipative particle dynamics (DPD) to describe viscous blood fluid flows; and, (ii) bottom/nanoscale using coarse-grained molecular dynamics (CGMD) to describe intra-platelet cytoskeleton, cytoplasm and membrane. CGMD is composed of nonbonded potentials (such as Lennard-Jones (LJ) and Morse) and bonded potentials (such as bonds, angles and dihedrals). Figure 1 shows the multitude of spatial and temporal scales integrated in the multiscale model.

In this model, the top-bottom spatial-scale interface is established by imposing a hybrid force field at fluid-membrane surface interface [1]. This hybrid force field uses stochastic thermostats (top-scale) to maintain the flow's local thermodynamic and exchange momentum between the platelets and the surrounding flow. Simultaneously, it uses hard-core LJ force to provide bounce-back reflection of flow particles on surface membrane, with no-slip achieved by slowing down fluid particles as the fluid particles are getting closer to membrane surface (using the same repulsive term). These repulsive-drag forces fully achieve a no-slip boundary condition between flipping platelets and viscous fluid flows and thus used to evaluate hemodynamic stresses on the flowing platelets membrane, using a force virial stress algorithm.

In addition, the top-bottom temporal-scale interface is improved by using a multiple time-stepping (MTS) algorithm [2]. This algorithm is developed for handling the disparity in integration stepping sizes between DPD and CGMD that requires time stepping at microseconds and nanoseconds, respectively. The new scheme utilized four different step sizes: the fluid system is advanced at the largest step size, the fluid-platelet interface at a middle step size, and non-bonded and bonded interactions of intra-platelet microstructural components at the two smallest step sizes. The 4-level integrator is adjustable to balance the relationship of biomedical accuracy vs. computational complexity.

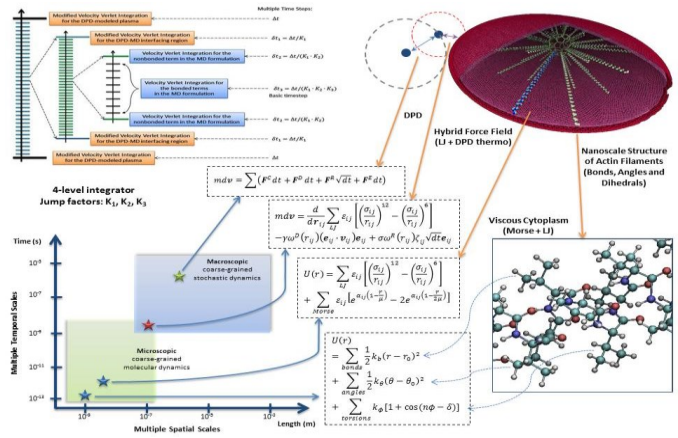

Figure 1: Multiscale Framework for Simulating Platelets in Blood Flows

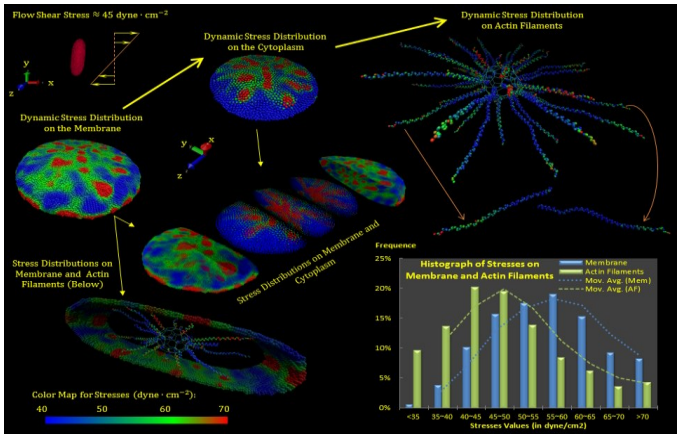

Figure 2: Mechanotransduction of Hemodynamic Stresses in Platelets

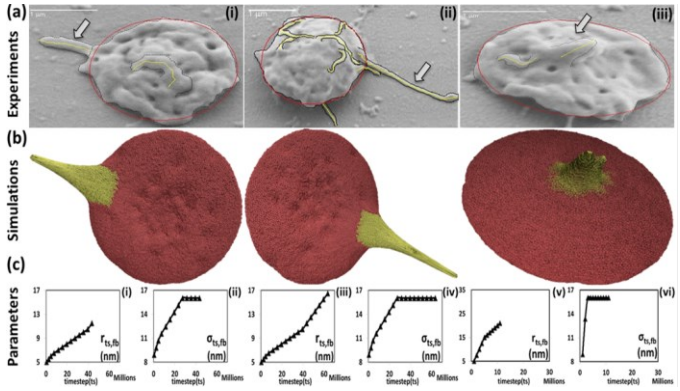

Figure 3: Filopodia Formation Correlating with Experiments

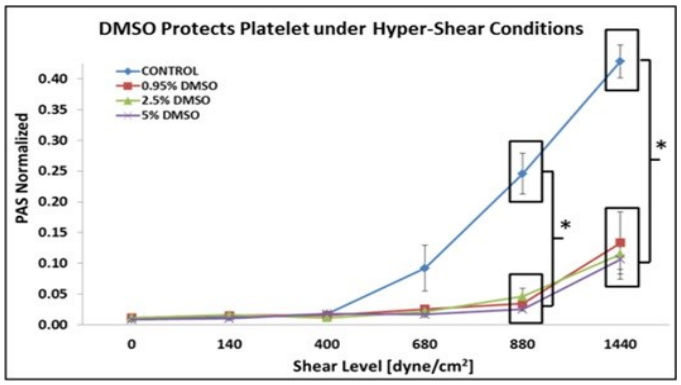

Figure 4: Certain levels of DMSO (2.5-5% v/v) can protect platelets from hyper sheared conditions, using a syringe capillary shearing device (SCSD)

RESULTS

This multiscale model describes nanoscopic mechanotransduction and biophysical characteristics of deformable platelets in complex viscous flows. The membrane was modeled with Young's modulus of 31.2 μN/m, cytoplasmic viscosity of 4.1 mPa·s, single actin filaments stiffness of 56.3±1.0 pN/nm [1, 4]. Fluid-platelet dynamic interaction preserved the dynamic properties of flowing platelet [1] which allows the study of the effects of the mechanotransduction processes of hemodynamic stresses on the flowing platelets (Figure 2). Comparative studies between rigid and deformable platelet models have indicated that rigid models significantly overestimate the stresses on the membrane, which in turn may lead to erroneous predictions of the platelet activation potential under shear conditions. The model also mimicked the formation of filopodia observed during early stage platelets activation [3] (Figure 3). Simulation results compared favorably with in vitro microchannel experiments.

DISCUSSION

Spatial-temporal interfaces have been achieved in the multiscale model, demonstrating the hallmarks of platelets under flow induced shear conditions: flipping trajectories, platelets deformability, viscous blood plasma flows, cytoplasm and elastoviscous membrane dynamics, and formation of filopodia upon platelet activation[1-5]. Flow induced stress information was transmitted to intracellular components. The morphological changes of platelets interactively influenced the surrounding flow field. Dynamical coupling of the micro-nano scales thus allowed the platelets to continuously change their shape during activation in response to the flow induced shear.

We are currently employing several microfluidic techniques and SEM imaging of platelets activated under shear flows to observe their interactions and corroborate our multiscale model predictions. We are also assessing the efficacy of antiplatelet agents in inhibiting shear-induced platelet activation. Work to date has demonstrated most conventional anti-platelet agents have limited efficacy under "hypershear conditions," whereas Dimethyl sulfoxide (DMSO) a polar aprotic solvent capable of modulating platelet membrane fluidity is effective in limiting shear-induced activation and aggregation [6] (Figure 4). We have applied our multiscale approach to model the mechanotransduction process driving the inhibition effect of the membrane fluidity modulation achieved by DMSO [6]. To the best of our knowledge this the first study of its kind.

CONCLUSIONS

Our multiscale approach offers a computationally feasible and highly resolved methodology for modeling platelet activation under shear conditions. Biophysical properties of the deformable platelets are accurately described down to the nanoscales. Hemodynamic stress is mapped on intra-platelet components. Phenomena of filopodia formation are mimicked and correlate with *in vitro* microchannel experiments. This model can be further employed to simulate other processes involved in platelet activation and thrombosis, offering a practical multiscale methodology for solving complex clinical problems at the juncture of biology and engineering.

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