A PREDICTIVE MULTISCALE FRAMEWORK FOR SIMULATING FLOW-INDUCED PLATELET ACTIVATION: DNS-DPD-CGMD-MD

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SUMMARY

We present a predictive multiscale framework for simulating flow-induced platelet activation by coupling DNS-DPD-CGMD-MD. Direct Numerical Simulations will be employed for devices and shear flows; Dissipative Particle Dynamics for viscous flows around platelets; Coarse Grained Molecular Dynamics for a biomechanical-based platelet model; Molecular Dynamics for filopodia formation and microtubular rearrangements. A vast range of spatiotemporal scales is covered to model macroscopic devices, mesoscopic fluids and microscale platelets. We validated the platelets properties by correlating simulations with in vitro experiments. This model can be used to predict platelets activation leading to thrombus formation in prosthetic cardiovascular devices and vascular disease processes.

Key words: Predictive Multiscale Modeling, Platelet Activation, Dissipative Particle Dynamics, Coarse Grained Molecular Dynamics

1 INTRODUCTION

The coagulation cascade of blood may be initiated by flow-induced platelet activation, which prompts clot formation in prosthetic cardiovascular devices and vascular disease processes. Upon activation, platelets undergo complex morphological changes. Activated platelets polymerize fibrinogen into a fibrin network that enmeshes red blood cells. Continuum methods fail to capture the molecular mechanisms such as filopodia formation during platelet activation, while utilizing molecular dynamics is computationally prohibitive. A multiscale approach offers a means to bridge the gap between macroscopic flow and the cellular scales.

We’re expanding an existing predictive multiscale model to incorporate a continuum-based approach by combining Direct Numerical Simulations (DNS) with immersed boundary (IB) method for mesoscale blood flow and organs or devices; and a Dissipative Particle Dynamics (DPD) model of viscous flow that interfaces with Coarse Grained Molecular Dynamics (CGMD) model of mechanobiology-based platelets, to simulate their activation via mechanotransduction pathways. This model bridges the gap between macroscopic transport flow-induced platelet activation scales and the ensuing molecular events. Fig. 1 shows the range of multiple spatiotemporal scales in this multiscale computational model. Platelets dynamically change their shapes in viscous shear flows and synergistically activate by a biomechanical transductive linkage chain. The DNS model captures the complex flow field in the macroscale and yields the velocity and pressure profiles that are converted to time-dependent adjustable body forces for the DPD model. The CGMD platelet model is embedded in the DPD blood flow model, with macroscopic dynamic stresses interactively
transferred to the platelet model. Hemodynamic stresses that lead to platelet activation and filopodial formation are mapped on the membrane and simultaneously transmitted to its cytoskeleton. Upon activation, platelets with intracellular constituents evolve as they lose their quiescent discoid shape and form filopodia. Actin filaments that are exposed to the highest stresses undergo filopodial formation. Model predictions are correlated with in vitro results.

Fig.1 A range of multiple spatiotemporal scales that are covered in the multiscale computing framework for simulating flow-induced platelet activation by using DNS-DPD-CGMD-MD

2 METHODOLOGY

Our multiple spatiotemporal methods employ DNS to describe the complex blood flow at the organ/device scale with integrated boundary-fitted curvilinear grids and sharp interface IB [1], DPD to describe viscous blood flow in the cases of stenosis and microchannels [2], and CGMD to model the intra-platelet constituents [3]. Spatially, the DPD-CGMD interface was established by imposing a hybrid force field [4]. A 4-level multiple time-stepping (MTS) scheme was used [5] as an efficient and ultra-scalable numeric solver on top supercomputers [6]. Fig. 2 showed the schematic of the multiscale models for simulating flow-induced platelet activation.

Fig.2 A schematic of the multiscale computing framework

In the mesoscale, we enhanced the conventional DPD formula by adding a Morse-based repulsive term for favorably producing Poiseuille flow of an incompressible fluid through a stenosis where
the compressibility becomes a problem for DPD [2, 7]. We conducted a comparative study to investigate the fluid flow properties of DPD-Morse and DPD fluids through a 67% stenotic microchannel. Our DPD-Morse can extend the conventional DPD to sustain large compression caused by a stenosis.

In the nanoscale, we built a mechanobiology-based platelet model by describing key constituents and biophysical properties [3, 8]. We modeled a bilayer membrane, ellipsoid based discoid shape, rigid filamentous core, gel-like cytoplasm using the Morse potential [7], and filamentous actin. An \( \alpha \)-helix structure was used to mimic a protrusable actin filament.

We validated our numerical method by correlating numerical simulations and model predictions with in vitro platelet activation experiments. Purified platelets [8] were prepared from whole blood obtained from consenting healthy donors of both genders. Platelets were exposed in a Hemodynamic Shearing Device to different shear stress-exposure time combinations up to 50 dyne/cm\(^2\) and 4 min, respectively. Platelet samples were fixed with 2% glutaraldehyde, mounted on poly-L-lysine coated glass slides, and dehydrated through an ethanol series prior to imaging with scanning electron microscopy. We particularly examined the average number of visible filopods per platelet, circularity of activated platelets, and the position, length and the aspect ratio of the filopods.

Fig 3: Mechanotransduction of the hemodynamic stresses and filopodial formation for flow-induced activated platelets in shear flows (2 filopods for activated platelet)

Fig 4: Morphological comparison between numerical model (a) and in vitro results (b-d) [9, 10].

3 RESULTS AND CONCLUSIONS

Our multiscale model describes the biophysical properties for platelets down to the nm-length and ps-time scales [3]. Membrane Young’s modulus is 31.2 \( \mu \)N/m and shear elastic modulus is 33.0±9.0 \( \mu \)N/m. Cytoplasm viscosity is 4.1 mPa·s. Actin filament stiffness is 56.3±1.0 pN/nm.

Using this model, we simulated the flow-induced platelet activation (Fig. 3). We assessed shear stress accumulation for flowing platelets during a flipping period. When platelets were flipping in the viscous blood flow, dynamic stresses were mapped on the membrane and transmitted to the cytoskeleton, with simultaneous accumulation of the mapped stresses over the period. This emulated the effect of mechanotransduction process of dynamics stresses in platelets. Filopodial formation is applied to actin filaments that are exposed to the highest stresses.

We correlated the morphological changes for activated platelets between the numerical simulations (A) and the in vitro results (B-D) (Fig. 4). The morphological details of our platelet model is shown in Fig. 4A. Fig. 4B is an SEM image for cytoskeleton reorganization, while Fig. 4C is the surface of activated platelets [9]. Fig. 4D is the rendered view of a tomographic volume for a filopod [10].
We correlated our numerical results for flow-induced platelet shape change with in vitro results. We counted the average number of visible filopods per platelet, the circularity of activated platelets, and the position of filopods of varying lengths. The in vitro results show that the average number of visible filopods is 2-3 per platelet, and their lengths ranged between 0.5 to 1.0 μm. The long filopods grew mostly on the edge of a platelet, while the filopods on the center were short. The majority of activated platelets preserved their ellipsoid shape and their circularity had no significant change. Our model assembled 44 actin filaments so it was capable of imitating enough visible filopods. In addition, our model also agreed with the preservation of the discoid shape and reflected the position of the short and long filopods.

Our simulations do not only agree with the in vitro results but also suggest new testable predictions. Our results reveal that (i) decreasing membrane stiffness plays an essential role in promoting the formation of long filopods. In addition, (ii) increasing numbers of longer filopods, for highly activated platelets, strongly correlates with microstructural rearrangement and mechanical properties. We show that a platelet needs to sustainably increase its protrusive force to grow a longer filopod and requires a stronger cytoskeleton to support more filopods growing radially outward. In this, a stronger structural arrangement and a stiffer mechanical property are supportive.

Our approach is the first computationally affordable numerical method for simulating the platelet activation by highly resolved mapping of mechanical stresses on the cytoskeleton in dynamic flow. Biophysical properties of a platelet are accurately described down to nm-length and ps-time scales. The viscous flows are described at μm-length and ns-time scales. Phenomena of filopodia formation are mimicked and correlate well with in vitro results. This model can be further employed to model the initiation of thrombosis in blood flow and study the effects of modulating platelet properties to enhance their shear resistance via mechanotransduction pathways.

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REFERENCES