Multiscale Modeling of Flow Induced Thrombogenicity With Dissipative Particle Dynamics and Molecular Dynamics

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Introduction

Thrombogenicity in cardiovascular devices and in cardiovascular pathologies is associated with shear-induced activation of platelets resulting from pathological flow patterns generated by them. Flow induced platelet activation process poses a major modeling challenge as it covers disparate spatiotemporal

scales, from flow scales to cellular and subcellular scales. This challenge can be resolved by a multiscale approach that couples the macroscopic effects of flow and stresses to a microscopic mechanotransduction platelet model. We developed a molecular dynamics (MD) based fine-grained nano-to-micro platelet multiscale model that depicts resting platelets and simulates their characteristic shear stress-exposure time activation and the ensuing pseudopodia formation, and compared it to in vitro measurements of activated platelet morphological changes after exposure to prescribed flow-induced shear stresses, such as the core axis and pseudopodia formation width and lengths.

Materials and Methods

Schematic of the platelet model (Fig. 1(a)) imitates geometrical and mechanical properties of three main platelet components: (a) two-layered bonded structure representing the phospholipid platelet membrane bilayer; (b) rigid filamentous core (Figs. 1(b) and 1(c)) and filament bundles representing a cytoskeletal structure; and (c) homogeneous particles representing the cytoplasm filling the gap between the cytoskeleton and the membrane. These components were represented by particles interacting with elastic forces and Lennard–Jones potentials. The dynamic simulation of the pseudopodia formation was performed in nanoscale molecular dynamics (NAMD) and was achieved by controlling the equilibrium length of the bond ($r_{ts,fb}$) and Lennard–Jones potential parameter ($\sigma_{ts,fb}$) between filament bundle particles at simulation timestep (ts). Experiments were conducted using gel-filtered platelets (GFP) exposed in a hemodynamic shearing device [1] to combinations of five shear stress levels ranging from 1 dyn/cm² to 70 dyn/cm² and exposure times. Platelets samples were withdrawn every minute up to 4 min, fixed with 1% paraformaldehyde, placed on poly-L-lysine coated slides, subjected to an ethanol dehydration series, and coated with 20 nm gold particles prior to scanning electron microscopy (SEM, LEO 1550) imaging.

Results and Discussion

By tuning the elastic force ($r_{ts,fb}$) and Lennard–Jones potential ($\sigma_{ts,fb}$) parameters of the model in vacuum, we dynamically simulated the pseudopodia formation. SEM images were analyzed using the MATLAB Image Processing Toolbox, where major and minor axis lengths of the platelet core were obtained from a curve-fit ellipse. Pseudopod thicknesses and lengths were obtained by measuring the distance between the coordinates of protrusion boundaries and its central axis, respectively. The dynamic simulation results achieved by the end of prescribed elapsed times were validated by experimental measurements of pseudopod length and thickness in platelets exposed to flow-induced shear stress for these specified exposure times (Figs. 1(d)–1(i)).

Conclusions

The results illustrate the simulation of platelet pseudopodia formation from a resting platelet using a 3D model with human platelet dimensions. We introduce an implicit inverse map between the input controlling parameters and the defining geometric features of the pseudopodia. To the best of our knowledge, our model is the first to successfully simulate platelet structure and its *dynamic* response to mechanical stimuli in such detail. The current model will be coupled with a triple-scale nano-micro-continuum multiscale model that will enable simulation of flow-induced platelet activation, aggregation, and adhesion leading to platelet mediated thrombosis.

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Fig. 1 (a)–(c) 3D cell model geometry of the simulated platelet. Platelet boundary coordinates from SEM images at (d) 1 dyn/cm²—4 min, (e) 70 dyn/cm²—4 min, and (f) 70 dyn/cm²—0 min, with ((g)–(i)) corresponding simulation results.

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Reference

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