

A Molecular Model for Platelets at Multiple Scales and Simulations on Supercomputers

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Abstract - a molecular model at multiscale for human platelets is designed and implemented on large-scale supercomputers. The model characterizes the principal physiological functions of key components of single platelet. The organelle zone centralizes as the cytoplasm, the peripheral zone includes the bilayer and exterior coats, and the cytoskeleton zone forms the flow-induced filopodia. It is the first time such a massive model in biomedical engineering is proposed and high-performance computing is the only potential solution for initial-understanding of the model. Algorithmically, a coarse-grained molecular dynamics force field describes the molecular-level interactions in the membrane and cytoskeleton while a Morse potential is applied to the cytoplasm. Together, a coarse-grained stochastic dynamics is applied to simulating the macroscopic viscous fluid flows. Numerical experiments with our model require considerations of large number of particles and the physiological phenomena at multiscale and thus demand development of the-state-of-the-art parallel algorithms, the main thrust of this research.

Keywords - multiscale modeling, platelets, coarse grained molecular dynamics, mechanotransduction, high-performance computing

This research focuses on developing a molecular model for platelets at multiple scales and on performing numerical simulation of the model on supercomputers. The essence of my research involves development of a platelet model and studies of the model numerically. The molecular model for human blood platelets characterizes the principal physiological functions of several key components of a single platelet [1]. As such, the model will require simulations at spatial scales as small as a typical molecule and as big as a complete cell, spanning several orders of magnitude in space and time.

Cardiovascular diseases remain the leading cause of death in the developed world. Thrombogenicity induces stroke, myocardial infarction and pulmonary embolism. Platelets play a key role in hemostasis and are natural to blame for cause of thrombogenicity. However, the mechanotransduction model for platelets is still illusive [2]. To simulate the dynamics accurately and efficiently, multiscale must also be considered. All in all, a more realistic model will require massive computations.

This research will be enabled by the rising power of supercomputing in solving the most crushingly difficult problems in many fields including biomedical engineering [3].

Solving problems will require solutions of models at a wide range of spatiotemporal scales. The rapid growths in size and complexity of application models drive the fastest supercomputers to the limits. Thus, enormous efforts have been devoted to developing, in addition to the accurate models, efficient and innovative algorithms to overcome the challenges of great scalability and total performance for realistic applications such as platelet dynamics [4].

The modeling has been performed on a collection of supercomputer systems including the Seawulf cluster from Stony Brook University, Sunway Blue Light system from National Supercomputing Center in Jinan, China, and Stampede system from Texas Advanced Computing Center. The software package systems I have adapted to perform our simulations include LAMMPS (Large-scale Atomic/Molecular Massively Parallel Simulator), NAMD (Not (just) Another Molecular Dynamics) and VMD (Visual Molecular Dynamics). To facilitate the project, we have designed and developed the in-house software suite called HEMD (Hematological Multiscale Dynamics) for multi-resolution simulations of complex hematological systems.

To address these computational challenges and high-impact applications, this research of multiscale platelet modeling includes the following aims:

A. Modeling the molecular physiology of platelets at multiple scales.

A multiscale particle-based platelet model is developed for accurately describing the mechanics of intra-platelet constituents [5]. The model characterized the principal physiological functions of key intra-platelet components at the molecular level. The cytoplasm zone is modeled as a homogeneous incompressible biofluid, preserving the intra-platelet biofluid viscosity. The peripheral zone resembling the exterior coats is simplified as a viscoelastic bilayer membrane exhibiting the deformation of platelets. The cytoskeleton zone is abstracted as a helical protrusible coil structure enabling the formation of filopodia in response to the rheological stimuli. Algorithmically, a coarse-grained molecular dynamics (CGMD) force field is proposed to describe the molecular-level interactions in the membrane and cytoskeleton components while a Morse potential is applied to the

cytoplasm. In the meanwhile, a coarse-grained stochastic dynamics (CGSD) is applied to simulate the macroscopic viscous fluid flows [6].

B. Relating the biophysics mechanism with the in vitro experiments for an accurate description of platelet mechanics.

A plurality of mechanical, rheological and dynamics properties of the platelet model are studied through extensive computational experiments and directly compared with the in vitro experiments [5]. The cytoplasmic viscosity is correlated with those obtained in the direct measurement of plasmatic viscosity [7]. The elastic deforming properties of the membrane are compared with those obtained in the molecular-scale stretching experiments [8]. The extensible stiffness of actin filaments is compared with those obtained in the in vitro nanomanipulation [9]. Additionally, the dynamics of platelets in the Couette flows is tested against the theoretical predictions (Jeffery's orbit of oblate spheroid in simple shear flows). These extensive experiments enabled the first study of the biophysics mechanism of the platelet model. The results clearly demonstrated that the multiscale platelet model achieved a more accurate prediction of the mechanical and dynamical behaviors of quiescent platelets under flow conditions [6].

C. Predicting the flow-induced platelet-mediated thrombogenicity at the crevice of cardiovascular devices.

The platelet model would be used in several high-impact applications in life sciences [5]. The mechanotransduction of mechanical stimuli (Fig. 2.) for platelets under high shear stresses would be analyzed from qualitatively to quantitatively. With the success of the above steps, we can, for the first time, build a true multiscale platelet model to accurately quantize the platelet activating factor in thrombogenicity [5,10]. In a broader range of impacts in the biomedical, this research helps

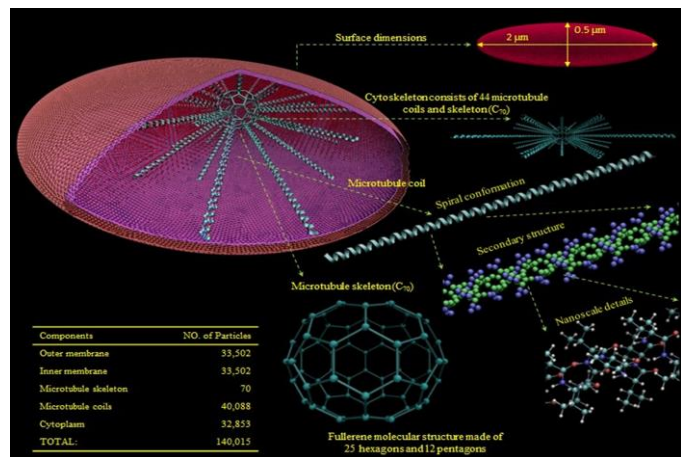


Fig. 1. Multiscale model of human platelets: physical structures and constituents

enable a molecular treatment for reducing the risks in the thrombus-related diseases, facilitate the design and optimization of cardiovascular devices to prevent high-stresses areas, and suggest an accurate mean to evaluate the antiplatelet drugs. This research represents the frontier of combining supercomputing power and computational sciences for resolving the challenges in biomedical engineering.

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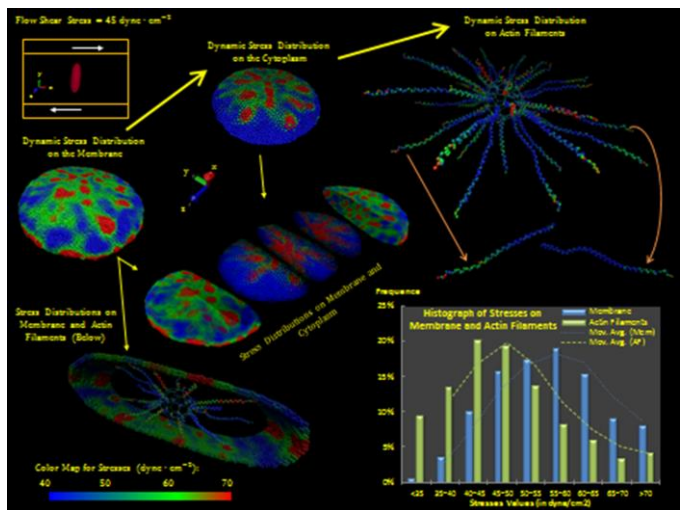


Fig. 2. Mechanotransduction: the dynamic mechanical stress distributions on the membrane, cytoplasm and cytoskeletal architecture (actin filaments)