

## **Efficient Multiscale Platelets Modeling Using Supercomputers**

This work presents multiscale models and efficient numerical algorithms for analyzing the activation mechanisms of platelets under blood flow conditions at disparate spatiotemporal scales on supercomputers, with applications in initial thrombogenicity studies and medical device optimizations. Modeling the multiscale structures of platelets and the dynamics of their motion in viscous blood plasma require multiple time stepping (MTS) algorithm to optimally utilize the computing resources. This MTS algorithm improves the computational efficiency while maintaining stability and prescribed precisions. Our study of the dynamic properties of flipping platelets adapts the hybridized dissipative particle dynamics and coarse-grained molecular dynamics methods, which resolve the appropriate spatial scales of the platelet and the blood flow, respectively. In addition to the algorithmic strategies, general-purpose graphics processing units are also introduced to speed up the computationally intensive force field evaluations. Examinations of the implementation of the double-punch speedup strategy, i.e., algorithmic MTS and hardware acceleration, reveal significant speedup over single time stepping algorithms and CPU-only solutions. Detailed performance analysis on three representative supercomputers affords the possibility of simulating the millisecond-scale hematology at resolutions of nanoscale platelet and mesoscale bio-flow using millions of particles, the state-of-the-art for the field at the present time.

### **Motivations**

Advances in medical imaging techniques and computational methods have enabled accurate simulations of subject-specific blood flows at the level of blood cell and in complex arterial networks. Those advances in studying blood flow dynamics have in turn improved cardiovascular devices (CVS) design, a process relying heavily on numerical simulations. While the advent of these devices has provided life-saving solutions to millions of patients globally, thrombogenic risk potential of these devices remains an impediment. Thrombosis formation on the surface of these implantable devices is initialized by chain reactions of platelets disorders. Aggregating platelets release factors that promote accumulation of circulating protein called fibrin. A blood clot is a meshwork of platelets and red blood cells woven together by fibrin. Thrombosis is an abnormal localized activation of platelets. Among all pathways that complete such process, evidences show abnormal shear stress at various exposure times or a sudden increase will affect platelet activation. However, quantitative analysis of the platelet shape change is, at best, confined in the laboratory experiments. Successfully computer-modeling such intricate phenomena and analyzing stress field upon platelets activation will help design drugs and implantable blood recirculating devices for fighting vascular diseases. Nevertheless, this task is full of physiological, physical, mathematical and computational challenges.

First of all, physical insights are essential for developing an accurate platelet predictive model with parameters matching laboratory mechanical and thermodynamic blood properties. Secondly, efficient simulations require modeling not just the flow dynamics but process pertinent to flow-induced platelet-mediated blood clotting. As such, multiple scales must be considered to characterize system behavior and the associated powerful and efficient modeling tools must be developed for high-resolution low-cost studies of

complex biological problems. Classical simulation methods are often limited in their applications to certain range of space and time scales. Four length and time scales of classical simulation methods are: (1) scale of continuum models, such as computational fluid dynamics (CFD) in which conservations of mass, momentum and energy govern the fluid motion; (2) scale of mesoscale models, such as Dissipative Particle Dynamics (DPD) in which grouping particles are considered to reduce computational complexity by integrating out particles' internal degrees of freedom; or Lattice Boltzmann Method (LBM) in which fluid consists of fictive particles, and such particles perform consecutive propagation and collision processes over a discrete lattice mesh; (3) scale of molecular dynamics models, the trajectories of actual atoms governed by Newton's equations of motion are studied; (4) scale of quantum mechanics models, quantum effects that produce averaged parameters are considered. For modeling platelet activation, continuum models fail to capture small-scale molecular mechanisms of structure changes and interactions of key players in blood coagulation, however, molecular dynamics that can capture the full dynamics at molecular scales, are impractical due to the demands of astronomical computational resources. A multiscale platelet modeling approach to uncouple macroscopic blood flow and finer features of platelet can offer a compromise for balancing computational accuracy and feasibility. In addition to multiple scale algorithms, implementing them on a particular computing platform for high efficiency is another challenge. The large gap in the space and time scales and algorithm complexities are two major challenges in limiting computing speed. With the unprecedented advances in computer speeds, it's still not practical to simulate one-millisecond hematology phenomena by straightforward porting to supercomputers without massive tuning. Porting simulations to, or developing a new programming model for, novel computer architectures for optimal performance is another aspect of the dissertation work.

Advances are needed to enable breakthroughs in multiscale platelets modeling. These advances include: (1) accurate mathematical models for each scale considered; (2) stable spatial and temporal interfacing methods; (3) robust algorithms that capable of both extracting main features and of quantifying possible errors; and (4) parallel solvers for each model and be scalable to tens of thousands of computer processors, and be portable to heterogeneous architectures.

### **Major Results**

In order to achieve above goals, I engage in developing a computational methodology that will efficiently simulate the millisecond-scale hematology with heterogeneous supercomputing. The main contributions and major results of this work are as follows:

#### **(1) Multiscale Models**

A multiscale model for solving this multicomponent biological problem is developed and implemented for simulation on supercomputers [1-3]. In this model, three simulation domains are identified: platelet domain, blood flow domain and interfacing domain. For platelet domain, the microscopic method using coarse-grained molecular dynamics (CGMD) is employed to emulate components of platelets such as pathogenic membranous morphology and cytoskeletal filaments. Compared with full molecular dynamics (MD) simulations, the CGMD model that reduces the degree of freedoms can save computational time. For

blood flow domain, the mesoscopic method using dissipative particle dynamics (DPD) is employed to address the bulk transfer of viscous blood flows in arterials with adjustable flow Reynolds numbers. Through massive supercomputing and parameterizing experiments, the mechanical properties such as platelet membrane viscoelasticity, flow compressibility and viscosity can be resembled by model parameters. For interfacing domain, to mimic friction between platelets surface membranes and surrounding blood flows, we proposed a hybrid force field containing the stochastic and random terms from DPD and Lenard-Jones potential from MD. The hybrid force field parameters are determined by matching the platelets flipping trajectory with analytical solution in Couette flow velocity field. The Couette flow stress field is designed to emulate the shear stress range of stenotic vessels where thrombogenicity is most likely to happen. The details of multiscale model are demonstrated in “multiscale fluid-platelet model” section in poster.

### (2) Multiple Time-Stepping Algorithm

In order to accommodate the multiple spatial scales in our platelet model, adaptive multiple time-stepping (MTS) algorithm with four-level integrators to connect the corresponding temporal scales is developed [4]. The four-level integrator can be adjusted via three loop factors to optimize accuracy and computing speeds, resulting in huge speedup of computation while maintaining stability and accuracy. The schematic diagram and pseudo code of four-level multiscale multiple time stepping is shown in “Speedup Strategy I” section in poster.

### (3) GPGPU Acceleration

The MTS algorithm we developed reduces computational costs but without lowering the communication costs proportionally. The basic idea of a multiple time-stepping scheme is to compute the more costly non-bond and long-range forces only once per long time step. In each step, there are two kinds of inter-processor communication: (1) the atom coordinates exchange after they are updated and (2) the forces exchange after every force evaluation. The latter is reduced at the same rate at which the force evaluation is reduced by the MTS algorithms and this step can be eliminated if Newton’s 3rd law is ignored among neighbor bin. Unfortunately, the former cannot be reduced because the updated atom coordinates can only be exchanged in the innermost loop in order to update velocities for the next step. When computation time is reduced, the unchanged communication costs, resulting in a higher communication-to-computation ratio, start to ruin scalability. A way out of this dilemma is the increased computational workload for local computations. We exploit a double-punch speedup strategy, i.e., the algorithmic MTS algorithm and GPGPU acceleration[5]. Porting intensive computation workloads to systems with accelerators help reduce the inter-process communication costs on CPU-only systems. Practically, our multiscale simulations are performed with the open source LAMMPS and its GPU package for hybrid high-performance computers. We have made the following adaptations: (1) implement our no-slip boundary conditions between the flows and blood vessels (for CPUs); (2) implement our multiple time stepping algorithm for multiscale platelet modeling (for CPUs and GPUs); and (3) implement the DPD-CGMD hybrid force field (for CPUs and GPUs). Though LAMMPS starts to support some simulations on Intel Xeon Phi coprocessors recently, the code is still

unavailable to support all of necessary functions on the co-processors for our multiscale simulations. We are making progress on porting our package of multiscale simulations to Intel Xeon Phi coprocessors.

#### (4) Performance Analysis

Carefully investigating the performance of multiscale simulations on the state-of-the-art supercomputers will assist us in maximum delivery of performance [6]. We characterize and analyze the performance of multiscale platelet-mediated simulations on three supercomputers: Tianhe-2, Stampede and CS-Storm (a high-density multi-accelerator system). Two configurations of the CS-Storm platform are tested: one with 8 NVIDIA K40m GPUs and 2 Intel Xeon E5-2670 v2 2.5GHz CPUs (264GB memory) and the other with 16 K80 GPUs and 2 Intel Xeon E5-2680 v3 2.5 GHz CPUs (132GB memory). We perform three problem-specific benchmark cases. The smallest system contains 0.68 million particles, forming a single platelet that flips in a viscous flow. This system is used for parameterization and observation of micromorphological changes for platelet. The middle system contains 2.7 million particles forming 4 platelets. This system is suitable for validating the inter-platelet and platelet-vessel interactions. The largest system contains 10.9 million particles forming 16 platelets. This system helps study the initial stage of clot processes involving multiple platelets. The performance results manifest the possibility of simulating the millisecond-scale hematology at resolutions of nanoscale platelets and mesoscale bio-flows using millions of particles. Performance results can be found in section "Performance Results on Supercomputers" in poster.

#### Conclusions and Future Work

Multiscale models, numerical algorithms, and advanced hardware will enable solution of new classes of problems in science, engineering, and medicine. My research is at the center of such development. Future work is to build larger platelets aggregation simulation system to predict blood clotting mechanics, rheology, and dynamics, to better understand thrombosis pathologies. Achievement of such goal will enable efficient predictive simulations for initial thrombogenicity study and may provide a useful guide for exploring mechanisms of other complex biomedical problems at disparate spatiotemporal scales.

#### References

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