Multiscale Modeling of Blood Flow and Platelet Mediated Thrombosis: Model Credibility

Peng Zhang[1], Jawaad Sheriff[1], Prachi Gupta[1], Changnian Han[1], Marvin J. Slepian[1,2], Yuefan Deng[1], **Danny Bluestein[1]**

[1]Stony Brook University, Stony Brook, NY, [2]University of Arizona, Tucson, AZ, USA

Start Date: May 1, 2016

Model Utility and Audience

UTILITY:

- Integrated dissipative particle dynamics (DPD) and coarse-grained molecular dynamics (CGMD) approach - bridging the gap between macroscopic transport scales and ensuing molecular events involved in platelet activation
- Predicts changes in platelet morphology upon shear mediated platelet activation, biomechanical transduction, interaction with clotting factors, aggregation with other platelets, and adhesion to blood vessel and device surface

AUDIENCE

- Clinicians and scientists to predict initiation of arterial thrombosis under circulation conditions
- Pharmaceutical manufacturers to develop new approaches for targeting mechanotransduction pathways for pharmacological management of thrombosis
- Cardiovascular device engineers - next generation of devices with better thromboresistance

Model Credibility Plan

VALIDATION OF MODEL PARAMETERS

- Geometrical, rheological, and material properties of coarse grained molecular dynamics (CGMD) platelet model validated using published literature and *in vitro* experiments
- In silico shear-mediated platelet shape change validated with scanning electron microscopy images of platelets exposed in Hemodynamic Shearing Device (HSD)
- Flow-mediated platelet flipping, aggregation, and adhesion models validated with high magnification DIC microscopy and high framerate capture of shear-mediated platelet behavior in microchannels
- Antiplatelet agent-induced membrane fluidity modeling validated using a dielectrophoresis (DEP) setup

UNCERTAINTY QUANTIFICATION (UQ) AND PARAMETER SENSITIVITY ANALYSIS

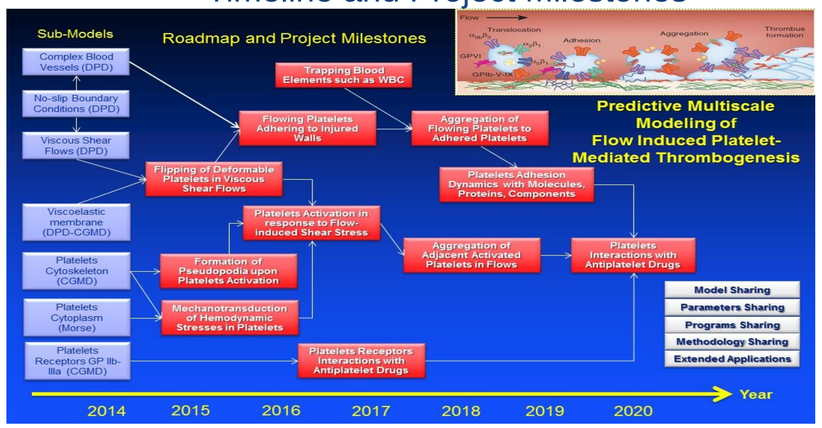
- Identify time-stepping sizes and spatial resolutions for desired accuracy
- Iterative numerical parameter optimization and global parameter sensitivity until convergence
- Predictive ability of simulations using optimal numerical parameters

SHARING OF MODEL ALGORITHMS AND EXPERIMENTAL RESULTS

- Harvard Dataverse (from Year 3). Potential for Google Cloud Platform

Key Experimental Parameters	Key Independent Model Parameters	Adjustable Model Parameters
Properties: μ of plasma: 1.1~1.3 mPa·s at 37°C. Diameter of platelet: 2~5 μm. Aspect ratio: ¼.	γ and r_{cut} in DPD correspond to resultant μ of plasma. Current μ of plasma: 1.12 mPa·s. Diameter: 4 μm. Aspect ratio: ¼.	Increase γ to increase μ of plasma and r_{cut} needs to change accordingly. μ: viscosity.
Shape change (HSD and microchannel + microscopy/SEM): flow rate=> τ: 1~70 dyne/cm²; exposure time: 0~480 sec; pseudopod length: 0.24~2.74 μm; number of pseudopods: 0~5; major axis: 2 ~3 μm; circularity: 0.9~1.0.	Couette flow shear stress: up to 400 dyne/cm² ts_{max} controls growth duration, α controls filopodia growth rate in response to shear stress-exposure time combinations, k_b -aspect ratio (range: 0.2~0.4), circularity (range: 0.8~1.0). r(ts,fb) and σ(ts, fb) controls pseudopod L-length and T-thickness.	Couette flow BCs adjusted for τ: shear stress; $\dot{\gamma}$: shear rate increase/decrease, k_b- change aspect ratio and circularity. r_0 – change pseudopod length L_{max} & T_{max}- converted to model parameter space=> >50 pesudopodia patterns- adjusted to expt. (**multiple dependent parameters change accordingly**).
Flipping experiments in microchannels - real time DIC microscopy (Jeffery's orbit $\phi(\dot{\gamma}t)$): shear stress: 0.2~100 (dyne/cm²); flow rate: up to 17 cm/s.	γ in DPD and ε, σ in LJ potential controls the fluid-platelet interaction. σ – key parameter controlling flipping platelets and their trajectory $\phi(\dot{\gamma}t)$. Flow rate: up to 15 cm/s.	Parameters adjusted according to results from Jeffery's orbit. σ mainly controls the trajectory of flipping platelets. Other sub parameters change correspondingly. $\phi(\dot{\gamma}t)$ is changed accordingly
Platelet stiffness with DEP: E = 1.93~6.88 KPa; ΔL/L: 0~0.2; Poisson's ratio: 0.25~0.35.	Bi-layered membrane: k_b=0.023 N/m, r_0 = 33 nm. Model values: E: from 1.14 KPa to total rigidity; ΔL/L: 0~0.5; Poisson's ratio: 0.37.	k_b adjusted by matching E of experiments. E: Young's modulus, L: axial diameter-deformability of platelet change accordingly.
Micropipette aspiration: γ=(2.9±1.4)×10^{-2} dyne/cm.	Stiffness of membrane controlled by spring force constant k_b. Model value γ from (3.3±0.9)×10^{-2} dyne/cm to total rigidity.	k_b adjusted to match the modulated elasticity of membrane in experiments.γ: shear elastic modulus.
μ of cytoplasm: 4.1~23.9 mPa·s.	Morse potential: control parameters include ε, α and R.	ε mainly controls μ. α takes empirical value (α=7). R- particles average distance.
Modulating membrane fluidity with antiplatelet agents (e.g., (DMSO)-DEP+fluorescence measurements: E, γ change accordingly.	k_b of membrane changed (range 10^{-2} ~ ∞ N/m). Friction factor γ in membrane controls adhesion force strength between interacting particles.	Increase k_b to reflect membrane stiffness. Other parameters adjust accordingly. Platelet deformability adjusted, γ -adhesion properties adjusted to corroborate values for membrane.
Adhesion: microscopy of observed adhesion patterns (vasc. wall-cultured HUVEC + vWF + Fg +fibronectin. Device surface + Fg).	GPIIb/IIIa-vWF binding potential, GPIbα-vWF-GPIbα, f^A- adhesion force magnitude coefficient (time dependent), r_{ij}- inter-receptor distance, n_a- # of receptors, d_c- relaxation distance, vWF multimer, GPIIb/IIIa-Fg binding potential.	Up to 50,000 GPIIb/IIIa and 25,000 GPIb receptors, n_a controls receptor # - model patterns (plt-plt. and/or surface binding and number- r_{ij} adjusted to expt. $r_{ij} < d_c$; r_{ij} –distance between 2 receptors - 2 plts come in contact.).

Timeline and Project Milestones

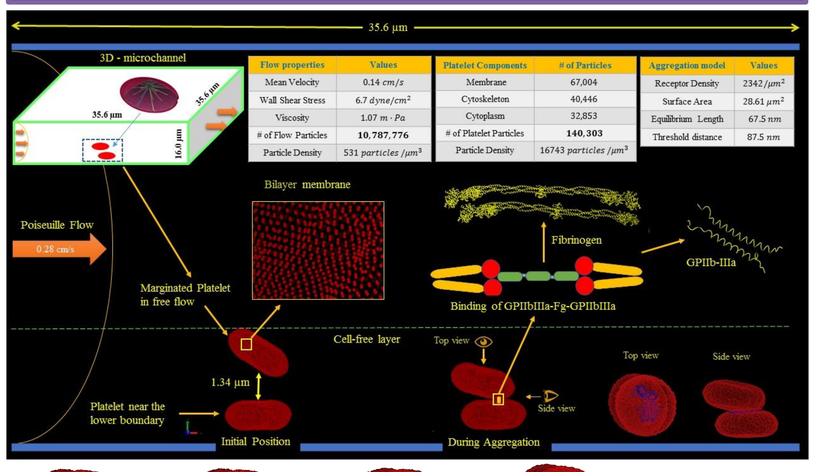


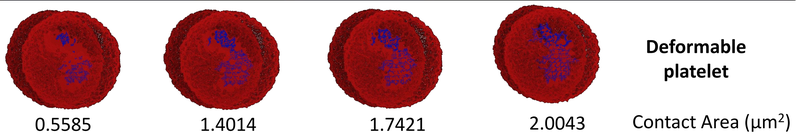
Project Milestones	Months
Top model of DPD of blood flow interfaces with shape change of CGMD platelet model	0-36
Bottom model of CGMD of platelets including components, mechanotransduction	0-30
Modeling platelet mediated thrombosis, including membrane reception and wall interactions	6-54
Experimental validation: platelet shape change, platelet kinematics, adhesion and aggregation	0-54
Developing tools for optimizing multiscale computational efficiencies on HPC resources	6-60

Year 2 Progress

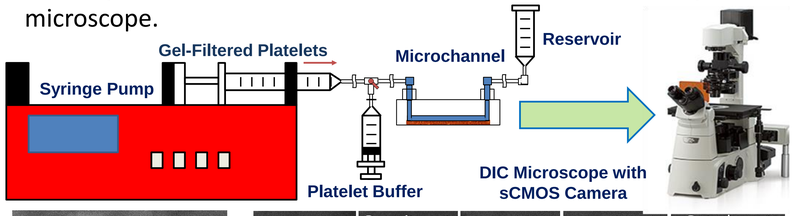
➢ **Platelet Recruitment and Aggregation:** We constructed a molecular-level hybrid force field that combines Morse and Hooke potentials to mimic the binding of **GPIIb-IIIa (αIIbβ3) receptor** and **Fibrinogen** during recruitment aggregation:

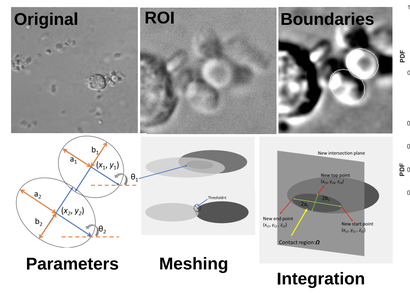
➢ $U_{aggregation}(\boldsymbol{r}) = \sum_{bonds} \frac{f^A}{2r_0}(r-r_0)^2 + \sum_{neighbors} D_0\left(e^{-2\alpha(r-r_0)} - 2e^{-\alpha(r-r_0)}\right)$

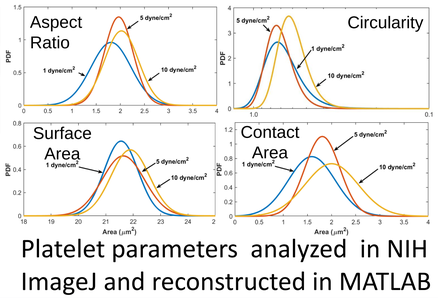




➢ **Experimental Validation:** Platelet recruitment/aggregation events in 100 x 1000 μm microchannels recorded at 100× zoom and 420 fps with Zyla sCMOS camera mounted on a Nikon Ti-Eclipse DIC microscope.

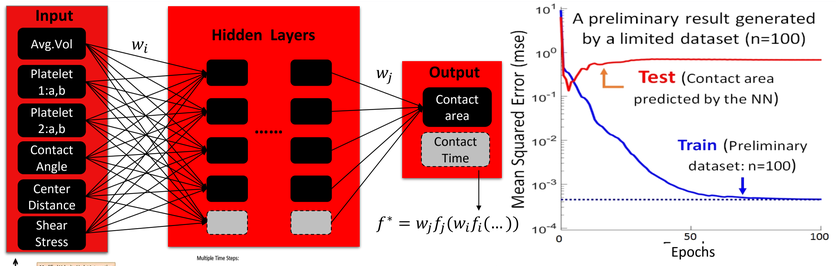


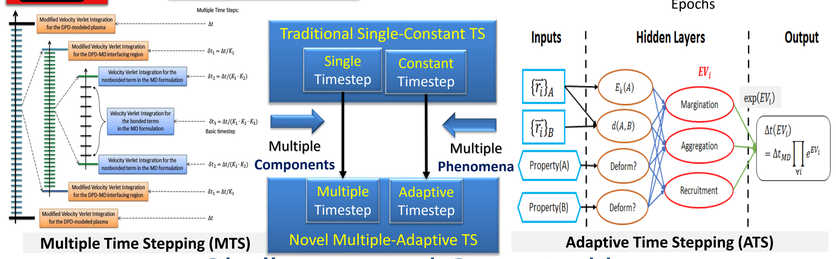




Platelet parameters analyzed in NIH ImageJ and reconstructed in MATLAB

➢ **Machine Learning for Aggregation Prediction/HPC Optimization:** Experimental results train a feedforward neural network (NN) model of contact area. Parallel efficiency optimized with Multiple-Adaptive Time Stepping (MATS).





Challenges and Opportunities

- Lack of techniques to observe platelet deformation, activation, aggregation, adhesion under flow conditions
- Large number of unknown parameters in modeling and simulations
- Adapting discrete particle-based methods (DPD-CGMD) to describe continuum multiscale phenomena
- More Efficient Algorithms on HPC Resources: MTS (Multiple Time Stepping) + ATS (Adaptive Time Stepping)

Uniqueness of Model Credibility Plan

- Utilizes in-house equipment (HSD, DEP, DIC microscopy, and microchannel setup) for validation
- Identifies and quantifies dominant sources of uncertainties, while minimizing global uncertainties from model/computational parameters
- Model parameters interfaced with *in vitro* observations via a database

Requirements for Third Party Evaluation

- Knowledge of LAMMPS molecular dynamics software
- Familiarity with both MD, CGMD and DPD theory
- Familiarity with basics of platelet activation, aggregation, and adhesion
- HPC resources for large multiscale simulations

ACKNOWLEDGEMENTS:

- **NIH** (NHLBI U01 **HL131052**, NHLBI R21 **HL096930-01**, NIBIB Quantum **U01EB012487**. PI: Bluestein, Danny)
- **XSEDE** (**DMS140019** on TACC Stampede, **DMS150011** on SDSC Comet. PI: Zhang, Peng)

PUBLICATIONS:

[1] Zhang, P., et al, *Cellular and Molecular Bioengineering*, 7:552-574, 2014.
[2] Zhang, P., et al, *Journal of Computational Physics*, 284:668-686, 2015.
[3] Zhang, P., et al, *Computer Physics Communications*, 204:132-140, 2016.
[4] Zhang, P., et al, *Journal of Biomechanics*, 50:26-33, 2017.
[5] Gao, C., et al, *Journal of Computational Physics*, 335:812-827, 2017.