MODEL CREDIBILITY PLAN

All proposed multiscale simulations will be validated using extensive data collected from experiments performed in the PI/Co-PI (DB, MJS) laboratories and experimental data from literature (refer to our Data Management Plan describing the databases created). Model parameters will be compared with experimental results for validation and/or iterative adjustment until differences between the model predictions and the experimental data is minimized or eliminated. Major phenomena that will be modeled include shear mediated platelet shape change, platelet flipping in microchannels, adhesion onto endothelium/subendothelium and device surfaces, platelet stiffness as measured with dielectrophoresis (DEP) or micropipette aspiration, and modulation of platelet membrane fluidity with antiplatelet agents. The table below lists key experimental and model parameters, and how the latter will be adjusted should there be a substantial difference between them:

Key Experimental Parameters	Key Independent Model Parameters	Adjustable Model Parameters
Properties: μ of plasma: 1.1~1.3 mPa·s at 37°C[229]. Diameter of platelet: 2~5 μm. Aspect ratio: ¼.	γ and r_{cut} in DPD correspond to resultant μ of plasma[230]. 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/cm^2; 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/cm^2. ts_{max} controls growth duration, α controls filopodia growth rate in response to shear stress-exposure time combinations[193], 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 parameters dependent on key parameters and change accordingly***).
Flipping experiments in microchannels - real time DIC microscopy (Jeffery's orbit $\phi(\dot{\gamma}t)$): shear stress: 0.2~100 (dyne/cm^2); flow rate: up to 17 cm/s.	γ in DPD and ε, σ in LJ potential controls the fluid-platelet interaction[230]. σ – key parameter controlling flipping platelets and their trajectory $\phi(\dot{\gamma}t)$. Flow rate: up to 15 cm/s.	Parameters are adjusted according to results from Jeffery's orbit. σ mainly controls the trajectory of flipping platelets. Other sub parameters change correspondingly[230]. $\phi(\dot{\gamma}t)$ 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[231].	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 correspondingly.
Micropipette aspiration[207]: 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[232]: 4.1~23.9 mPa·s.	Morse potential[233]: 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 strength of adhesion forces between interacting particles.	Increase k_b to reflect membrane stiffness. Other parameters adjust accordingly. Platelets deformability adjusted, γ -adhesion properties are adjusted to corroborate experimental 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 when 2 plts come in contact.).

Uncertainty quantification (UQ) and parameter sensitivity analysis (SA5): Multiple sources of uncertainties arise from interfacing vastly different algorithms at different scales on heterogeneous computer architectures and sizes, namely, parameters characterizing the platelets/flow at various scales, reductionist model assumptions, numerical uncertainties due to truncation and runoff errors, and experimental data errors (the latter are referred to under Statistics in the proposal). We will perform, individually and collectively, a careful minimization of the uncertainties. Adaptive optimization of the computational speeds and modeling accuracies is the central goal of our multiple time-stepping schemes− a key element of our multiscale approach. Error minimization will be achieved with the following steps (i) UQ at each scale to identify time-stepping sizes and spatial resolutions for achieving desired accuracy (ii) training numerical experiments for parameter optimization and local and global parameters sensitivity analysis will be performed iteratively till convergence to optimal parameters will be achieved (iii) simulations using the optimal parameters will be tested by their ability to predict the experimental data. A practical multiscale modeling approach for achieving validity and accuracy while minimizing computing efforts, has long been a challenge for computational scientists. Applied to multiscale modeling of flowing platelets, analysis conducted in our validated studies suggest a 100 folds gain in computing efficiency over conventional methods without losing accuracy[1-4].

Independent 3rd party evaluation: Sharing our modeling tools is integral to this project (details in the proposal). To further enable others to gain confidence and adopt them to their corresponding multiscale simulation needs, starting in the 3rd year a special budget was allocated for a 3rd party evaluation. By then we will simulate and validate several benchmark cases. Quantitative metrics will be created (derived from the parameters table above) and utilized to prove the credibility of our model. It will be used by us to demonstrate the model credibility to the 3rd party evaluator, and possibly reproduced by the evaluator in specific benchmark cases (either using our resources- some readily available to the HPC community, or independently). We will work closely with the PO and SO's and IMAG project scientists to identify appropriate groups in the MSM Consortium to perform this independent evaluation.