# Multiscale Modeling of Blood Flow and Platelet Mediated Thrombosis


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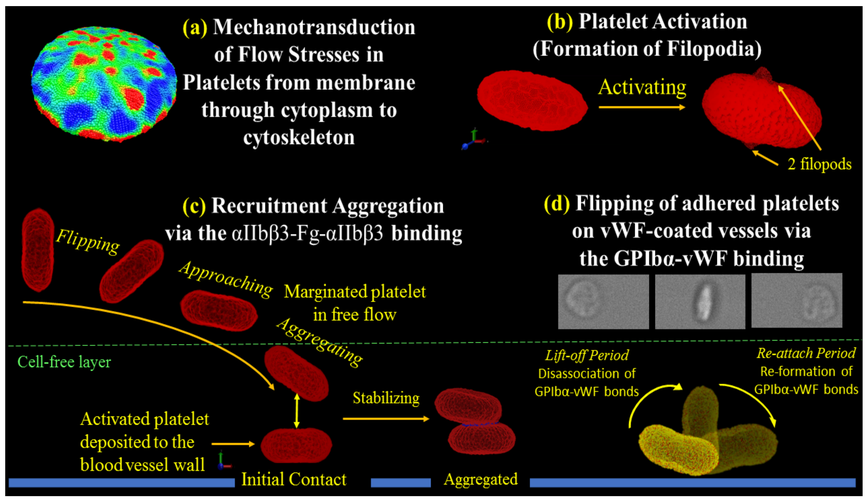
## Project Summary

**INTRODUCTION:** Continuum-based methods fail to cover the vast spatio-temporal scales required to describe complex platelet events comprising flow-induced thrombosis. Our previously developed multiscale modeling (MSM) approach circumvents limitations of such methods by incorporating coarse-grained molecular dynamics (CGMD) and dissipative particle dynamics (DPD) to describe mechanotransduction events triggered by blood flow in cardiovascular pathologies which may induce initiation of thrombosis via flow-induced platelet activation[1-6]. This model, tightly coupled to extensive *in vitro* measurements of platelet motion under flow[1,2], mechanical properties[3,4], and shape change[5], has been expanded to describe early shear-induced platelet aggregation and adhesion. **Machine Learning** methods validate model predictions with in vitro results and adapt temporal scales to diverse spatial scales for efficient simulations.




**MULTISCALE MODEL**: Two Spatial-Temporal scale methods: [1]

(1) Top/microscale using **D**issipative **P**article **D**ynamics (**DPD**) to describe viscous blood fluid flows (viscosity, compressibility);

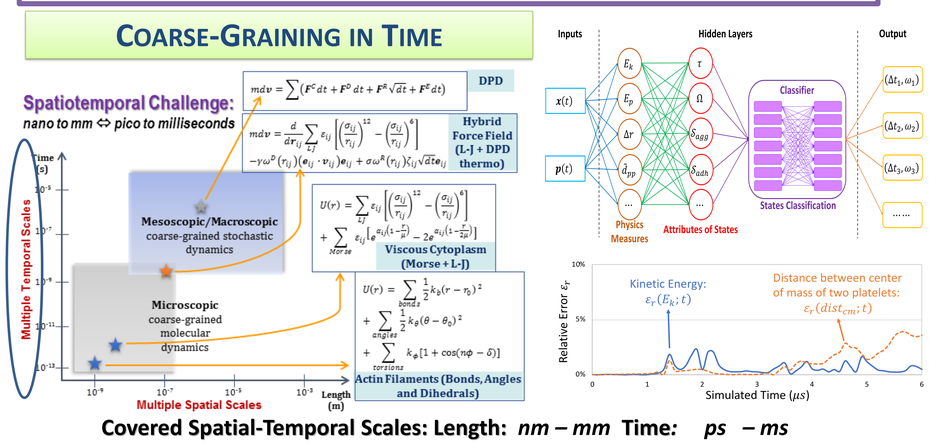
(2) Bottom/nanoscale using **C**oarse **G**rained **M**olecular **D**ynamics (**CGMD**) to describe the platelet membrane, cytoplasm and the cytoskeleton.

**ALGORITHMS FOR HPC**: More Efficient Algorithms on HPC Resources:

(1) Simulation Size:
- Platelet model: 140K particles, 8.38 μm$^3$, ρ = 16,708/μm$^3$
- Flow model: 10,787,776 particles, 20K μm$^3$, ρ = 532/μm$^3$
- Total: Flow 10.8M (97%) + 2×Platelets 280K (3%) = **11 Million Particles**

(2) Time Stepping Algorithms: MATS Framework for MSM
- Multiple Time Stepping (**MTS**) Algorithm: **Four-Level** Integrator
- Adaptive Time Stepping (**ATS**) Algorithm: **Event-Driven** Integrator

## COARSE-GRAINING IN TIME





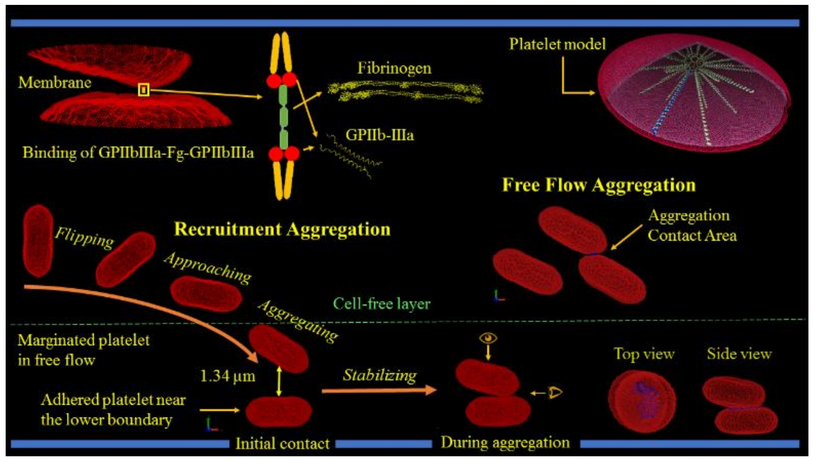


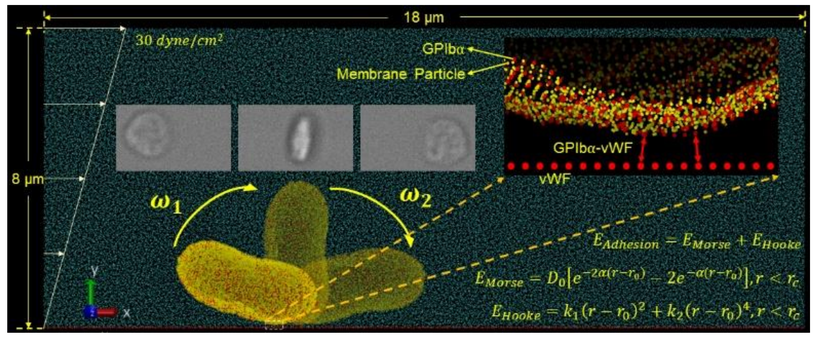
**Covered Spatial-Temporal Scales: Length: *nm – mm* Time: *ps – ms***

## Progress and Milestones

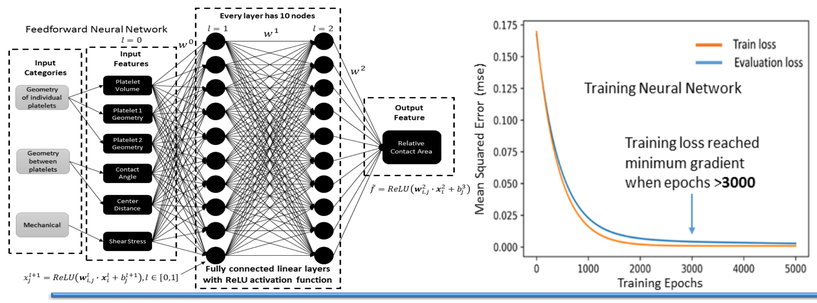
➢ **Platelet Aggregation:** We construct a molecular-level hybrid force field that combines Morse and Hooke to mimic the binding of **αIIbβ3 receptor** and **Fibrinogen** during recruitment aggregation. This force field is parametrized for correlating the morphologic characteristics at aggregation with in vitro results. [6]

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



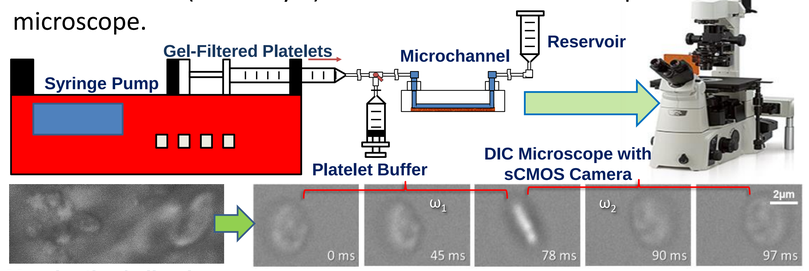




➢ **Prediction Model Using Machine Learning:** In-vitro results are used to train a 2-layer, 10-node feedforward neural network (NN) model.

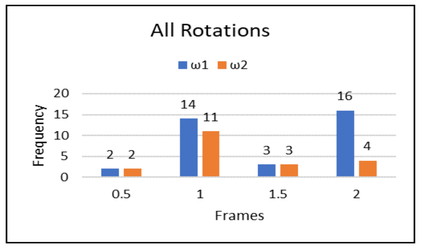



➢ **Platelet Adhesion:** Experimental Validation

Gel-filtered platelets with and without red blood cells (RBCs) are perfused through 100 × 1000 μm microchannels pre-coated with von Willebrand factor (100 μg/ml) at shear stresses 5-30 dyne/cm$^2$. Adhesion events are recorded at 100× zoom and 1000 fps with a sCMOS camera (Andor Zyla) mounted on a Nikon Ti-Eclipse DIC microscope.




**Platelet parameters analyzed in NIH ImageJ and Nikon NIS Elements to provide inputs for machine learning and simulation models:**
- Rotation angle
- *Time for full rotation (180°)*
- *Platelet major/minor diameters*
- *Platelet surface area*
- *Translocation velocity*
- *Shear stress (dyne/cm$^2$)*




**Number of frames for lift-off ($\omega_1$) and falling ($\omega_2$) periods at $\tau_w$=6.7 dyne/cm$^2$ t($\omega_1$)= 16.35 ± 5.14 ms and t($\omega_2$)= 13.62 ± 4.16 ms (n = 30, *p*>0.05, 91.49 fps).**

**Preliminary results indicate that t($\omega_1$)>t($\omega_2$), with implications for rates of vWF-GPIbα bond formation and breakage under flow conditions. Ongoing experiments extend this analysis to $\tau_w$=30 dyne/cm$^2$ and 1000 fps.**

## Addressing the CPMS Ten Simple Rules

| | |
|---|---|
| **Rule 1. Define context** | Models are designed to reflect platelet properties and dynamics found in disease- and device-associated blood flow |
| **Rule 2. Use appropriate data** | Parameters and input variables are based on published and in-house in vitro observations. If any parameters cannot be validated , other model variables are monitored to ensure accurate reflection of platelet biology |
| **Rule 3. Evaluate within context** | Simulations are performed under physiological and pathological shear stresses relevant to blood vessels and blood-recirculating cardiovascular devices, with appropriate blood properties (i.e. viscosity, temperature). |
| **Rule 4. List limitations explicitly** | Numerical simulations are accurate in the context of published data and in-house in vitro observations. We do not make Further limitations are the capacity of the software to model biological observations and \HPC resources |
| **Rule 5. Version control** | All experimental data are traced by their creation date and generators. All DPD-CGMD files track the creation date. |
| **Rule 6. Document adequately** | Simulation codes/model markups are tracked and shared among the simulation group. All experimental data are stored in a video/spreadsheet database and shared among all team members via Stony Brook's Google Drive service |
| **Rule 7. Disseminate broadly** | We are exploring sharing simulation software and data/experimental data broadly via the Google Cloud Platform. These items are also presented during regular meetings and national/international conferences. |
| **Rule 8. Get independent reviews** | Our algorithms and experimental data will be shared with fellow IMAG researchers with similar work (i.e. Drs. Alber and Karniadakis) for independent evaluation. |
| **Rule 9. Test competing implementations** | We test the efficiency of various iterations of our DPD and CGMD codes to select the most appropriate model parameters. Due to the uniqueness of our approach, we do not have an external algorithm for direct comparison. |
| **Rule 10. Conform to standards** | While there are no set standards for our platelet-based experiments, we follow commonly followed practices for blood/platelet preparation, microscopy, and statistical analysis as published in relevant experimental journals. |

**CONCLUSIONS:** Our computationally affordable, highly resolved, and validated multiscale modeling approach provides a potentially predictive platform to describe shear-induced activation, aggregation, and adhesion in shear flow down to the nanoscales. Ongoing simulations and experiments currently evaluate aggregation events with multiple platelets and incorporate GPIbα-vWF interactions for adhesion at moderate to high shear stresses. Our validated models can be used to test development of new anti-platelet therapeutic approaches that modulate platelet membrane and other biophysical properties to make the platelet more shear resistant. We are utilizing MSM to analyze the impact of clinically relevant shear forces generated via a range of devices and pathologies to predict cellular responsiveness driving thrombosis.

BioFluids Lab @ Stony Brook U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- **XSEDE** (**DMS150011** on SDSC Comet, Zhang, Peng)



**PUBLICATIONS:**

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