Machine Learning in Multiscale Modeling and Validation of In Vitro Experiments of Blood Flow and Platelet Mediated Thrombosis Initiation

PI Grant: Danny Bluestein

Institutions: [1]Stony Brook University, Stony Brook, NY; [2]Sarver Heart Center, University of Arizona, Tucson, AZ.

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Abstract Authors: Peng Zhang[1], Jawaad Sheriff[1], Prachi Gupta[1], Changnian Han[1], Peineng Wang[1], Ziji Zhang[1], Marvin J. Slepian[2], Yuefan Deng[1], and Danny Bluestein[1]

Abstract Text:

Introduction: We developed a multiscale model (MSM) incorporating dissipative particle dynamics (DPD) and coarse-grained molecular dynamics (CGMD), 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* results of platelet motion under flow[1,2], mechanical properties[3,4], and shape change[5], has been expanded to describe shear-induced platelet aggregation[6] and adhesion.

Materials and Methods: We developed three novel machine learning (ML) approaches for image segmentation, modeling in-vitro data and adaptive discretization in massive multiscale modeling. A semi-unsupervised learning method for platelet segmentation with attention to pseudopods and membrane tethers: DIC microscopy images of aggregating and adhering platelets were captured at up to 1000 fps, and processed to obtain platelets' geometrical points as in vitro data. Then, a deep learning network for modeling in-vitro data: the platelets' geometrical data points are meshed to determine contact area between aggregated platelets, and input into a neural network model to predict inter-platelet contact area (Fig. 1). In the training set, we selected shear stresses of 1, 5 and 10 dyne/cm^2. Physics-Informed Learning for Adaptive Discretization in Massive Multiscale Modeling: While MSM sufficiently describes details at disparate spatial scales, no effective algorithm exists for adapting temporal scales to these diverse spatial scales. We developed a novel state-driven adaptive time-stepping (ATS) algorithm that adapts time stepsizes to the underlying biophysical phenomena. Mesoscale DPD blood flow is simulated with μs-timescale and microscale CGMD platelets are modeled with *ns*-to-*ps* timescales. A ML method trains to adapt the time stepsizes. Particle positions and momenta are inputs, and phases are described by the attributes of states from inputs in first two layers- categorized by a neural network and labeled by a two-components vector: time stepsize and state examination frequency. Conceptually, ATS ML corresponds to coarse-graining in time.

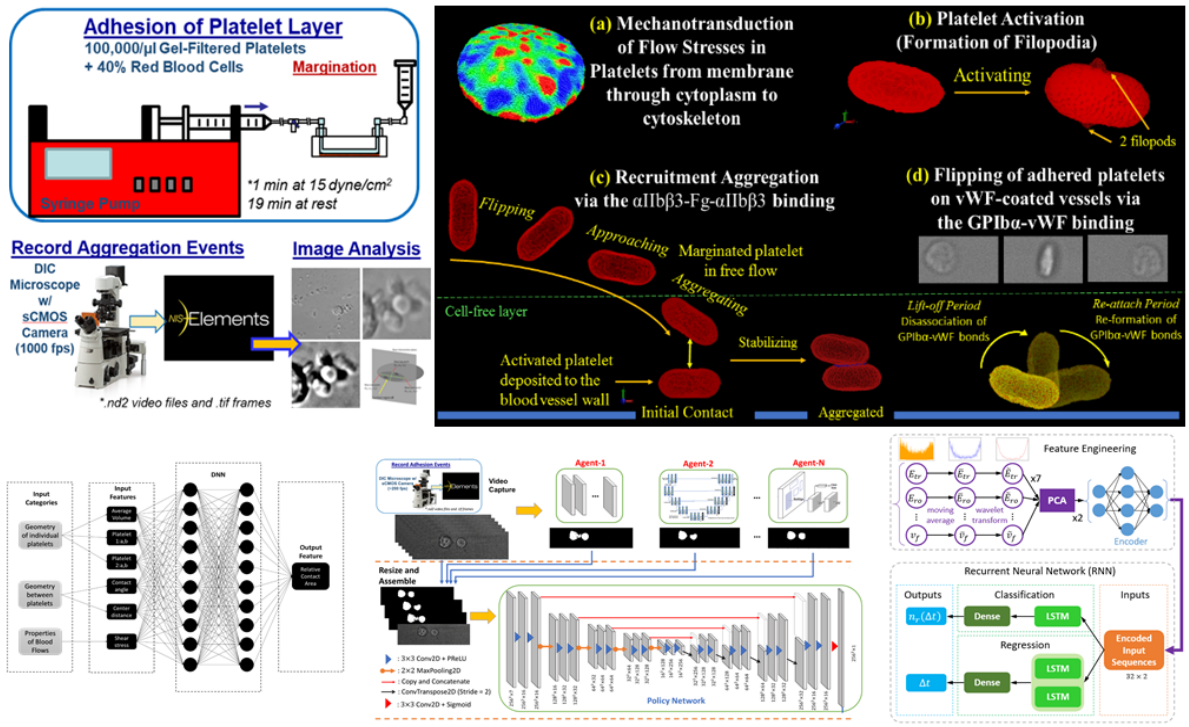

Figure 1: In vitro platelets adhesion experiments; MSM of mechanotransduction, platelet activation, recruitment aggregation and adhesion; and three machine learning schemes: (i) a deep learning network for predicting contact area between aggregated platelets; (ii) an unsupervised learning network for platelet segmentation with attention to pseudopods; and (iii) a recurrent learning network for more efficient massive multiscale simulations

Results and Discussion: Our model describes biophysical properties of platelets down to nanoscales, with membrane Young's modulus of 31.2 μN/m and cytoplasm viscosity of 4.1 mPa·s. Mean normalized contact area model predictions and in vitro results (0.094±0.021 and 0.092±0.021, respectively) suggest that our ML-1 model accurately predicts the contact area for aggregated platelets, and is used in our multiscale modeling to validate the in silico results. The ATS algorithm was compared with traditional single time-stepping (STS) algorithm, along time of kinetic energy of two platelets (Fig 1, ML-2). The results in both algorithms are consistent with each other. Computing times using ATS for different phases were cut by 20~75%.

Conclusions: Our computationally affordable, highly resolved, and validated multiscale modeling framework provides a potentially predictive platform to describe flow shear-induced activation, aggregation, and adhesion down to the nanoscales. Our novel ML models can be used to validate simulation predictions and also can improve the modeling efficiency. Ongoing simulations and experiments evaluate aggregation events with multiple platelets and incorporate GPIbα-vWF interactions for adhesion at moderate to high shear stresses. Our framework can be used to test new anti-platelet therapeutic approaches that increase platelet shear resistance.

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References: [1] Zhang, P., et al, *Cell Mol Bioeng*, 7:552-574, 2014. [2] Gao, C., et al, *J Comput Phys*, 335:812-827, 2017. [3] Zhang, P., et al, *J Biomech*, 50:26-33, 2017. [4] Zhang, N. et al, *J Comput Phys*, 257:726-736, 2014. [5] Pothapragada, S., et al, *Int J Numer Meth Biomed Engng*, 31:1-16, 2015. [6] Gupta, P., et al, *Cell Mol Bioeng*, 12:327-343, 2019.

Table: 10 Simple Rules of Model Credibility Gained

Rule 1. Define context clearly	Our DPD-CGMD models are designed to reflect platelet properties and dynamics under shear stresses found in blood flow through diseased vessels and cardiovascular devices.
Rule 2. Use appropriate data	We ensure that all parameters and input variables are based on published and in-house in vitro observations. If any parameters cannot be validated (due to lack of available data or techniques), other model variables are monitored to ensure accurate reflection of platelet biology. Machine learning models are developed to validate in silico predictions with in vitro sparse and noisy data.
Rule 3. Evaluate within context	Numerical simulations are performed under physiological and pathological shear stresses relevant to blood vessels (normal/diseased) 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 conclusions beyond the experimentally validated conditions. Further limitations are due to capacity of the software to model biological observations and limitations of the HPC resources used.
Rule 5. Use version control	All experimental data are traced by their creation date and record the experimenters' names. All DPD-CGMD files track the creation date.
Rule 6. Document adequately	Simulation codes/model markups and changes within are tracked and shared among the simulation group. All experimental data are stored in a database (currently in video and spreadsheet format) and shared among all team members, allowing interfacing with numerical software. Protocols are shared and updated via Stony Brook's Google Drive services.
Rule 7. Disseminate broadly	Simulation software and data/experimental database is currently shared via Google Drive, and we are exploring sharing 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	Within our group, we test the efficiency of various iterations of our DPD and CGMD codes to select the most appropriate model parameters (i.e. Morse potential, bond force parameters, etc.). 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.