2018 IMAG Futures Meeting – Moving Forward with the MSM Consortium (March 21-22, 2018)

Pre-Meeting Abstract Submission Form

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PI(s) of MSM U01: Mark Alber
Institution(s): University of California Riverside, University of Pennsylvania, University of Notre Dame
MSM U01 Grant Number: U01 HL116330
Title of Grant: Multiscale modeling and empirical study of a mechanism limiting blood clot growth

Title of the Talk: **Combined Multi-scale Modeling and Experimental Study of Blood Clot Contraction and Deformation**

Abstract

Blood clot contraction plays an important role in prevention of bleeding and in thrombotic disorders. In this talk, we unveil and quantify the structural mechanisms of clot contraction at the level of single platelets. A key elementary step of contraction is sequential extension–retraction of platelet filopodia attached to fibrin fibers. In contrast to other cell–matrix systems in which cells migrate along fibers, we will demonstrate that the "hand-over-hand" longitudinal pulling causes shortening and bending of platelet-attached fibers, resulting in formation of fiber kinks. When attached to multiple fibers, platelets were shown in [1] to densify the fibrin network by pulling on fibers transversely to their longitudinal axes. Single platelets and aggregates will be shown to use actomyosin contractile machinery and integrin-mediated adhesion to remodel the extracellular matrix, inducing compaction of fibrin into bundled agglomerates tightly associated with activated platelets. The revealed platelet-driven mechanisms of blood clot contraction demonstrate an important new biological application of cell motility principles.

Recently developed multi-scale discrete worm-like chain model will be used to demonstrate that non-linear mechanical properties of compressed fibrin network can originate from structural re-arrangements of the entire fibrin network, as well as from alterations of individual fibers including fiber buckling, bending and reorientation. Model simulation results support novel hypothesized mechanism of clot contraction [1] and quantify how rearrangement and linkage of fibrin fibers effects network stiffening. The new model was also used to determine how contractile function of platelets, their distribution within the fibrin network and fibrin properties affect mechanical response of a blood clot to applied stresses in blood flow. Lastly, a novel multi-phase computational model will be described that simulates active interactions between platelets and fibrin, to study the impact of various physiologically relevant blood shear flow conditions on deformation and embolization of a partially obstructive clot with variable permeability [2]. Simulations provide new insights into mechanisms underlying clot stability and embolization that cannot be studied experimentally at this time.

References

1. Oleg V. Kim, Rustem I. Litvinov, Mark S. Alber and John W. Weisel [2017], Quantitative Structural Mechanobiology of Platelet-Driven Blood Clot Contraction, *Nature Communication*s 8: 1274. https://www.nature.com/articles/s41467-017-00885-x.pdf.

2. Shixin Xu, Zhiliang Xu, Oleg Kim, Rustem I. Litvinov, John W. Weisel and Mark Alber [2017], Model Predictions of Deformation, Embolization, and Permeability of Partially Obstructive Blood Clots under Variable Shear Flow, Journal of the Royal Society Interface 14: 20170441. http://rsif.royalsocietypublishing.org/content/14/136/20170441.

Which MSM challenges are you addressing from the IMAG 2009 Report and how?
https://www.imagwiki.nibib.nih.gov/content/2009-imag-futures-report-challenges
(indicate which challenge (#) you're addressing)

You may insert images by copying and pasting below

Our work addresses challenges #4,5,8,9:
4) Novel methods to fuse biological and/or behavioral processes and mechanisms to model outcomes as a result of various interventions
5) Reproducible and reusable multiscale models that will be integrated and adopted into model-poor fields (e.g. tissue engineering, regenerative medicine, drug and gene delivery, preventive interventions)
8) Problem-driven multiscale models that require high performance computing (see below for available advanced computational resources)
9) Model predictions that drive a community of experimentalists towards systematic testing and validation

Are you using machine learning and or causal inference methods and how?

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In our work we use inference methods to calculate p-values for statistical significance of experimental data. Typically, we apply a nonparametric Mann-Whitney U-test for analyzing data from blood clotting experiments.

Please briefly describe significant MSM achievements made (or expected).

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1. Blood clot contraction plays an important role in prevention of bleeding and in thrombotic disorders. Here, we unveil and quantify the structural mechanisms of clot contraction at the level of single platelets. A key elementary step of contraction is sequential extension–retraction of platelet filopodia attached to fibrin fibers. In contrast to other cell–matrix systems in which cells migrate along fibers, we demonstrated in our recent paper: Oleg V. Kim, Rustem I. Litvinov, Mark S. Alber and John W. Weisel [2017], Quantitative Structural Mechanobiology of Platelet-Driven Blood Clot Contraction, *Nature Communication*s 8: 1274. https://www.nature.com/articles/s41467-017-00885-x.pdf (authors for correspondence: J.W. Weisel and M. Alber) that the "hand-over-hand" longitudinal pulling causes shortening and bending of platelet-attached fibers, resulting in formation of fiber kinks (see Figure 1). When attached to multiple fibers, platelets were shown to densify the fibrin network by pulling on fibers transversely to their longitudinal axes. Single platelets and aggregates use actomyosin contractile machinery and integrin-mediated adhesion to remodel the extracellular matrix,

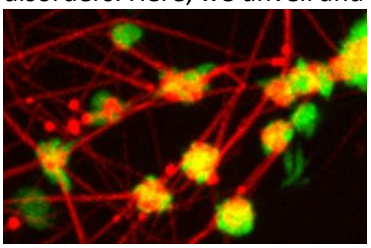

Figure 1. Contracting platelets (green) cause bending and local accumulation of fibrin fibers (red) resulting in dramatic remodeling of the fibrin matrix.

inducing compaction of fibrin into bundled agglomerates tightly associated with activated platelets. The revealed platelet-driven mechanisms of blood clot contraction demonstrate an important new biological application of cell motility principles.

2. We recently developed a multiscale, discrete worm-like chain model, and calibrated the model using our experimental data from Kim et al. Biomaterials 2014 on compressed clot viscoelasticity and structure. The model will be used to study how microscopic network structural and mechanical features, including fiber stiffness, orientation and length distributions, impact macroscopic characteristics of the clot, such as elastic and loss shear moduli of the fibrin network, its compressive strain and densification. We already demonstrated using model simulations that non-linear mechanical properties of compressed fibrin network originated from structural re-arrangements of the entire fibrin network, as well as from alterations of individual fibers including fiber buckling, bending and reorientation. Experimental measurements of elastic and loss shear moduli of fibrin networks revealed dual softening-hardening transitions as the networks were exposed to compressive loads, with softening occurring at small and intermediate compressive strains, whereas hardening developing at larger degrees of compression. Simulated results revealed very good agreement with the rheometer experimental data and support our hypothesized mechanism of stress propagation through the network and quantify how rearrangement and linkage of fibrin fibers effects network stiffening. The paper on these results will be submitted for publication shortly. The developed multi-scale model will also allow us to study interactions between platelets and fibrin network inside of a blood clot. In particular, we will examine how the contractile function of platelets, their distribution within the fibrin network and fibrin properties affect mechanical response of the clot to applied stresses in blood flow and clot stability. To calibrate the model we will use our experimental data recently published in Kim et al. Nat Comm., 2017, 8(1):1274.

3. We developed in our recent paper: Shixin Xu, Zhiliang Xu, Oleg Kim, Rustem I. Litvinov, John W. Weisel and Mark Alber [2017], Model Predictions of Deformation, Embolization, and Permeability of Partially Obstructive Blood Clots under Variable Shear Flow, *Journal of the Royal Society Interface* 14: 20170441. http://rsif.royalsocietypublishing.org/content/14/136/20170441, a novel two-dimensional multi-phase computational model is introduced that describes active

interactions between the main components of the clot, including platelets and fibrin, to study the impact of various physiologically relevant blood shear flow conditions on deformation and embolization of a partially obstructive clot with variable permeability. Simulations provide new insights into mechanisms underlying clot stability and embolization that cannot be studied experimentally at this time. In particular, model simulations, calibrated using experimental intravital imaging of an established arteriolar clot, show that flow-induced changes in size, shape and internal structure of the clot are largely determined by two shear-dependent mechanisms: reversible attachment of platelets to the exterior of the clot and removal of large clot pieces. Model simulations predict that blood clots with higher permeability are more prone to

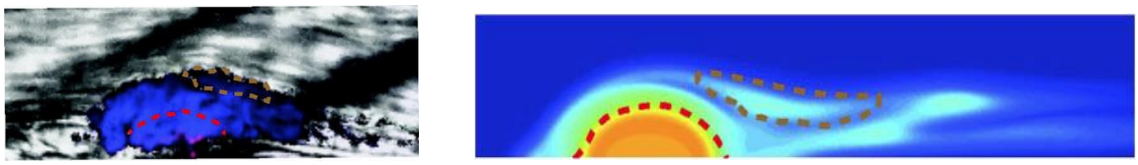

Figure 2. Predictive simulation of blood clot fragmentation dynamics and snapshot from an experimental movie.

embolization with enhanced disintegration under increasing shear rate. In contrast, less permeable clots are more resistant to rupture due to shear rate dependent clot stiffening originating from enhanced platelet adhesion and aggregation (see Figure 2). We are now running model simulations to predict risk of thromboembolism based on the data about composition, permeability and deformability of a clot under patient specific local haemodynamic conditions.

Please suggest any new MSM challenges that should be addressed by the MSM Consortium moving forward.

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1. Coarse-graining approaches including coarse-grained versions of molecular dynamics models and sub-cellular models. 2. Model reproducibility. 3. Molecular-to-cellular link. Role of the heterogeneity in both of cell types and of the cell microenvironment. Connection to omics data. 4. Rigorous description of coupling in space and time. Similar to matching asymptotic methods in PDEs. 5. Influence of multi-scale modeling on different biomedical fields. Applications of the models upstream to identify likely failures of new treatments. 6. Precision vs personalized medicine.

What expertise are on your team (e.g. engineering, math, statistics, computer science, clinical, industry) and who?

Please list as "Expertise – Name, email"

Computational and Mathematical Biology, Applied Mathematics, Mathematical and Computational Modeling – Mark Alber, malber@ucr.edu, and Zhiliang Xu, zhiliangxu@nd.edu; Biophysics, Cell and Molecular Biology – John Weisel, weisel@pennmedicine.upenn.edu; Biochemistry - Rustem Litvinov, litvinov@mail.med.upenn.edu; Bioengineering, Mechanical Engineering, Applied Physics and Mathematics – Oleg Kim, oleg7kim@gmail.com; olegkim@ucr.edu; Image reconstruction and analysis, computer science –Danny Chen, *dchen@nd.edu*.

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