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

*Pre-Meeting Abstract Submission Form*

*\*Please submit to the NIBIB IMAG mailbox (*NIBIBimag@mail.nih.gov*) by* ***January 8th, 2018***

*\*Save your abstract as “MSM PI Last Name \_ 2018 IMAG Futures Pre-Meeting Abstract”*

**PI(s) of MSM U01: HAUGH, JASON**

**Institution(s): North Carolina State University**

**MSM U01 Grant Number: U01EB018816**

**Title of Grant:** **Multiscale Modeling of Wound Healing**

**Abstract**

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*

**1. Next-generation multiscale models that integrate between different scientific fields (e.g. cardiovascular and neuroscience) and predict integrated functions.**

Our models span the molecular, supramolecular, cellular, and tissue scales of biological complexity and integrate the fields of biochemistry, biophysics, cell biology, and computational biology. Experimental data being generated employ microfabrication and advanced microscopy techniques.

**3. Novel methods to fuse data-rich and data-poor scales to enable predictive modeling.**

At every scale of biological complexity, model development will be guided by new, quantitative measurements, fusing experimental and observational scales that are relatively data-rich (signaling and cytoskeletal dynamics) and data-poor (responses to heterotypic cues and cell migration *in vivo*).

**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).**

Models of wound healing such as ours make contact with all of the examples given: tissue engineering, regenerative medicine, drug and gene delivery, and preventive interventions.

**8. Problem-driven multiscale models that require high performance computing.**

We make use of high performance computing resources to carry out model simulations.

**9. Model predictions that drive a community of experimentalists towards systematic testing and validation**

Progress in the study of wound healing has stalled because of technical challenges. It is considered a messy problem. Models are needed to drive and systematize experimental innovation in the field.

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

*You may insert images by copying and pasting below*

 We are using such methods for analysis of experimental data, but not currently for modeling analysis.

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

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 We have developed and analyzed partial differential equation (PDE), reaction-diffusion models of the phospholipase C (PLC)/protein kinase C (PKC) signaling pathway, which we previously identified as a requisite PDGF chemotaxis pathway; strikingly, we discovered that the lipid second messenger of the pathway, diacylglycerol (DAG), is focally polarized in fibroblasts exposed to a shallow PDGF gradient (~ 5-10% across a cell’s length) in a microfluidic device. Hence, we sought to define a signaling circuit, composed of known interactions and reactions in the pathway, capable of polarization. We found that phosphorylation of myristoylated alanine-rich C kinase substrate (MARCKS) by PKC constitutes a positive feedback that is sufficient for local pathway amplification. The release of phosphorylated MARCKS and its subsequent diffusion and dephosphorylation in the cytosol also serves to suppress the pathway in down-gradient regions of the cell. By itself, this mechanism only weakly amplifies signaling in a shallow PDGF gradient, but it synergizes with other feedback mechanisms. Known feedbacks included in the most recent model are enhancement of PLC recruitment by phosphatidic acid (PA, an intermediate in the metabolism of DAG) and PKC-mediated activation of phospholipase D (PLD, which produces PA by hydrolysis of phosphatidylcholine). We are currently conducting experiments to test specific model predictions.

Motivated by recent evidence indicating that regulation of myosin activity is critical for directed migration of fibroblasts responding to gradients of platelet derived growth factor (PDGF), we develop a particle-based computational platform for simulating actin and myosin dynamics. We then used this platform to simulate a model that accounts for biophysical interactions between filamentous actin and non-muscle myosin II. Our simulations revealed the spontaneous formation of actin asters. We then performed a systematic analysis of model parameters to identify biochemical steps in myosin activity that are good candidates for regulatory control. Finally, we investigated how the model responds in a gradient of PDGF. Interestingly, spatial regulation of motor stiffness led to a time-dependent behavior of the actomyosin network, in which actin asters continue to spontaneously form and dissociate.

**We are developing a hybrid morphodynamic cell model that integrates reaction-diffusion, particle-based, and square-lattice approaches. Importantly, we do not base the cell edge movement on a *globally* defined Hamiltonian and configuration probabilities from the Boltzmann distribution as done in Potts models. Instead, the stochastic dynamics of the cell edge in our model is driven by physically consistent local rules. This has significant benefits for relating model parameters with experimental measurements and interpreting simulation results. Our modular modeling is designed under biologically justifiable assumptions to allow progressive incorporation of structural and regulatory components, building up complexity one step at a time.** In parallel, we developed computational tools, based on stochastic modeling, to analyze time series data for the position of randomly migrating cells. Importantly, our approach allows for the possibility that cells can transition between different migratory states and allows parameters that quantitatively characterize cell movement to be efficiently estimated from experimental data. We applied our methods to two different cell types, MEFs and HeLa cells. Our analysis revealed that for both cell types, randomly migrating cells stochastically transition between distinct states of migration characterized by differences in cell speed and persistence.

We established methods to visualize and track macrophage migration during the inflammatory phase of wound healing *in vivo* and have tested the requirement for the Arp2/3 complex in this process. We are in the process of wrapping up this facet of the project with proposed hybrid (stochastic/continuum) modeling. The simulations will incorporate coarse-grained descriptions of signaling polarization in a partially self-generated PDGF gradient field that will bias stochastic movement of individual cells.

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

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 We have identified three MSM challenges in our research that we think generalize to any physiological system where models integrate molecular, cellular, and higher scales:

1. How to link, in a mechanistic rather than phenomenological way, molecular mechanisms to cell behavior. To what extent is the more mechanistic linkage useful and predictive, in a way that informs molecular interventions?
2. Diversity of cell stimuli. We tend to focus on one or perhaps two aspects of the extracellular environment that drive cell behavior. How do we integrate experiments and modeling to tackle the greater complexity of cues that affect cell behavior/fate?
3. Molecular and cellular heterogeneity in tissues. Tissues are composed of multiple cell types, and in many contexts the cells are in motion and changing their behavior as they differentiate. This presents an enormous yet exciting challenge for modeling.

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

*Please list as “Expertise – Name, email”*

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