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: 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?

You may insert images by copying and pasting below

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).

You may insert images by copying and pasting below

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,

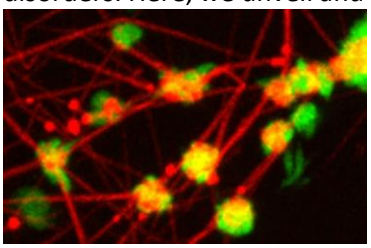


Figure 1. Contracting platelets (green) cause bending and local accumulation of fibrin fibers (red) resulting in dramatic remodeling of the fibrin matrix.

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

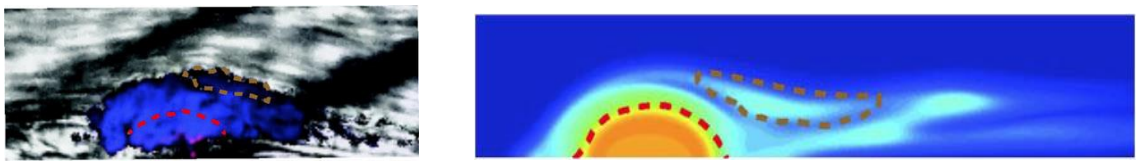


Figure 2. Predictive simulation of blood clot fragmentation dynamics and snapshot from an experimental movie.

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.

You may insert images by copying and pasting below

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*.

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

Click here to email your form to the NIBIB IMAG mailbox

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: David Basanta & Conor Lynch
Institution(s): H. Lee Moffitt Cancer Center & Research Institute
MSM U01 Grant Number: 5U01CA202958
Title of Grant: Multiscale Modeling of Bone Environment in Metastatic Prostate Cancer

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

We are addressing several of the MSM challenges including #3, #8, #9, #11, and #18 with our largest effort pertaining to #9 and #18. The project is proceeding along the lines we proposed in our grant wherein experimental data is used to motivate and parameterize a mathematical models that test novel hypotheses regarding macrophage polarization in bone repair and homeostasis after a fracture. These outputs are then tested in vivo. Our results have provided us with novel insights into macrophage and bone biology that impact our understanding of normal and pathological processes such as bone injury and bone metastatic prostate cancer, the latter being the primary target of our project.

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

You may insert images by copying and pasting below

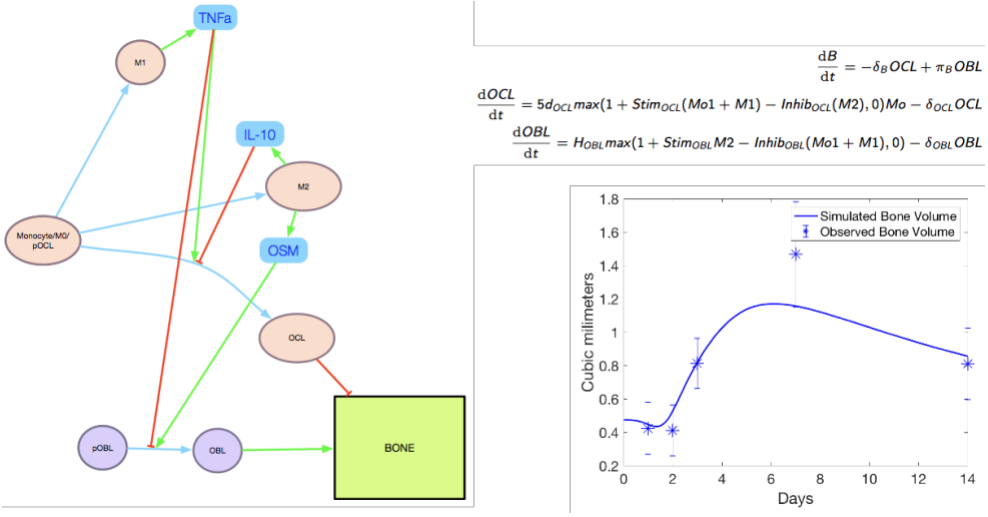
Not at the moment but flow cytometry data is being used to characterize the phenotypes of the myeloid cells involved in bone repair. We anticipate that collaborating with our MSM colleagues that have expertise in machine learning we could identify relevant patterns of macrophage polarization that are indicative of how cancers are progressing in bone or responding to treatment.

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

You may insert images by copying and pasting below

The integration of experimental data with mathematical modeling has allowed us to uncover new biology pertaining both the role of macrophages in the recovery from fractures to the establishment of a 'vicious cycle' in the early stages of prostate cancer metastases in the bone through the interactions between tumor and stroma. We are currently working on enriching our mathematical models with macrophages (at the cellular level, including M0, M1 and M2 phenotypes) as well as several signaling molecules involved in the differentiation and work of macrophages and other bone-resident cells involved in homeostasis and repair. Compared to other organs, little is known about the role of

macrophages in the bone, and even less in the context of cancer. Thus we are laying the groundwork for bone repair with the aim of improving the realism in the model in the case of metastatic cancer. Through the integration of modeling and experiments we have elucidated a number of hypothesis. One such example can be seen in this figure were we explore four different minimal models (of which we only show here one, on the right panel) that could explain M1/M2 impact on bone formation. Using experimental data which we fit into one single ODE (first one in the left), we use the remaining equations to predict osteoclast and osteoblast populations fluctuation over time. We are using a systematic approach to test many of these hypothesis to uncover enough bone biology to motivate our computational bone ecosystem approach.



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

You may insert images by copying and pasting below

1. How to best balance the simplicity that models should bring with the complexity of biology through a rational integration of biological data and hypothesis in multi-modeling frameworks.
2. Models that facilitate the design and application of single or multiple treatments in adaptive therapy based clinical trials.

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

Please list as "Expertise – Name, email"
GU oncology – Julio PowSang, MD, julio.powsang@moffitt.org
Pathology - Jasreman Dhillon, MD, jasreman.dhilon@moffitt.org

Bone biology - Conor Lynch, PhD, conor.lynch@moffitt.org
Mathematical Biology – Alexander Anderson, PhD, alexander.anderson@moffitt.org
Computational Biology – David Basanta, PhD, david@cancerevo.org
Mathematical Biology – Etienne Baratchart, PhD, Etienne@cancerevo.org
Macrophage biology – Lochen Hao,

2018 IMAG Futures Meeting: MSM Consortium March 21-22, 2018

PI(s) of U01 HL122199: James Bassingthwaighte, U Washington; Dan Beard, U Michigan, Ranajn Dash, Med College Wisconsin, Andrew McCulloch, UCSD.

Title: Cardiac Energy Grid

Abstract:

MSM Challenges being addressed: These selected **PAR-15-085 bullets are targets of our research efforts in this U01, the Cardiac Energy Grid:**

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

10) Predictive multiscale models that strongly incorporate uncertainty quantification

6) Multiscale models strongly coupled with standardized protocols for model-driven data collection

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)

18) Predictive multiscale models to improve clinical workflow, standard operating procedures, patient-specific modeling for diagnosis and therapy planning (e.g. image analysis on-line)

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

Our methods are basically biophysical, biochemical, and deterministic, with thermodynamic constraints so far. We are exploring how to use machine learning re alternative pathway fluxes, e.g. where does optimal control play a role in defining cell usage of glucose versus fatty acid for energy production.

Describe significant MSM achievements:

Experiments iterated with modeling analysis:

Efforts have focused on the central aspects of cardiac energy production and utilization with the long term objective being to define the varied routes to cardiac failure. To do this we perform experimental studies in order to define the models for the processes required for to deliver substrates from the blood to the sites of metabolic reactions: the PATHWAYS for glucose, fatty acid, oxygen, nucleosides and ATP.

Putting these together into biologically relevant cardiac model systems characterizes the links among mechanical, electrical, and metabolic models. This allows us to formulate compatible, multi-regional correlated models of the whole heart with the tradeoffs in substrate use versus contractile and electrical activity during differing states of rest and exercise up to maximum exercise in normal activation, as well as with abnormalities of conduction and excitation. Control of substrate choice, of vasomotor state locally, and of force development locally are all dependent on patterns of excitation.

The overall aims are two: (1) To provide a set of reproducible models of central aspects of cardiac metabolism to the research and clinical investigative communities, and (2) To provide a modeling framework for investigations into the conditions for and causes of cardiac failure. The details are expressed as a set of projects categorized by PATHWAYS related to requirements for, and utilization of ATP generation in the heart.

Pathway for Substrate Delivery by Coronary Blood Flow:

Models for blood-tissue exchange, convection, diffusion, permeation, reaction;
Flow-limited exchange for O2, H2O; barrier-limited for most solutes;
Flow heterogeneity: fractal correlation structure; fractal vascular system;
Correlation structure in flows and effects of vasodilators;
Models of vaso-regulatory processes in normoxia and hypoxia;
Pressure-flow autoregulation in the heart;
Role of ATP and Ado in hypoxia and SM response via A2 receptors;
Adenosine vasodilation differs depends on the source: blood versus cardiac cell.

Pathway for Glucose:

Multicapillary transport across endothelium, interstitium and cardiac cell membrane.
Modeling Glut4 regulation (+/- insulin and insulin receptor activation).
Glycolysis, hexokinase, glycogen cycle, to lactate and pyruvate. FDG kinetics for PET studies.
Kinetic models with thermodynamic constraints.
Osmotic responses in strenuous exercise dynamics.
Pentose shunt.

Pathway for Fatty Acid:

Albumin binding affinities and release kinetics.
Endothelial and sarcolemmal transporters; interstitial radial diffusion modeling;
Formation of acyl CoA, DAG, TAG, into vacuoles or lipid droplets; re-acylation from droplet;
Acyl CoA transferase into mitochondria; beta oxidation.

Pathway to CHO and fat oxidation, the TCA cycle:

TCA cycle w/wo aspartate/glutamate shuttle;
Tracer versions of TCA for ^{13}C - glutamate isotopomer analysis; versions for C1 or C2 labeling.

Pathway for Oxygen:

Oxygen inflow/ CO2 excretion: Ventilatory mechanics and alveolar gas exchange
$Hb(O_2)_4$ binding models: Effects of pO_2, pCO_2, pH.
Temperature and density affects on Hb-oxygen binding. Determination of Kd.
Competition: Hb binding with CO, NO
Tutorials for HbO sequence in JSim, later for Matlab, SBML, CellML libraries
Hyperbaric Rx for CO poisoning.
Hypoxia, NO and NO release
Capillary-tissue Exchange of O_2, H_2O, CO_2
    Diffusion of H20 and O2 inside RBC, cell binding sites (muscle Mb)
    Binding and reaction at cytochrome oxidase (Dash)
Oxidative Phosphorylation models, a sequence of them: (Beard05, Beard07, Dash,)

Pathway for Nucleosides and Nucleotides: Experiments and modeling analysis:

Exchange and reactions of adenosine, inosine hypoxanthine, xanthine, uric acid in the heart.
Cardiac purine release in hypoxia.
Modeling PCr-ATP shuttle (myokinase, Cr kinase, mito membrane)
Low flow perfusion causes 5'nucleosidase down regulation and IMP accumulation
Purine salvage: definition, mechanisms, models

ATP use for Excitation-Contraction Coupling and Ionic Balance:

Cardiac action potential and EC-coupling models
Cross-bridge models with accounting for increased axial cooperativity with deoxyATP
Reduced forms for for excitatory spread and arrhythmia susceptibility (long QT)
Applications linking LBBB and metabolic shifts
Heart failure: diminished deltaG is only part of the story!

NOTE (January 2018): At this halfway point in the grant period we have the data for over 80% of the projects listed, about 2/3 of the models are developed fully operational status, about 40% being completed to validation and available for distribution (free) on the model repository at www.physiome.org. Only about 10% have used uncertainty quantitation so far. Tutorials are developed and on this website for the more elementary topics such respiratory mechanics and gas exchange, compartmental analysis, and blood-tissue exchange. There is, for example, a 100-page operators manual for GENTEX, a convection-diffusion-permeation-reaction multipath model for metabolic reaction sequences that in fully-expanded form uses 110,000 differential equations, but can be reduced to one compartment. In the next 2.5 years we expect to have all of the models, and thus a firm base on which to characterize heart failure.

New MSM challenges:

A next challenge in cardiac metabolism/energetics is *protein metabolism.* Protein fluxes are large; the balance between proteolysis and protein synthesis fluctuates with activity. Athletic stresses require long recoveries. The pathway to protein synthesis begins with the signaling and control of mRNA production to supply the recipe for transcription. The influences of environment, organism activities, humoral and neural signals, and cellular state come together drive many cells simultaneously to transcription in a coordinated fashion: the nuclear (or mitochondrial) DNA response to these drivers are guided by the composite set of input signals from all of these levels. Defining these signals and their origins and connections throughout the body's systems is a hugely complex problem.

Expertise:

Engineering: Andrew McCulloch, amcculloch@ucsd.edu; Dan Beard, beardda@umich.edu;
Brian E. Carlson <bcarl@umich.edu>; James Bassingthwaighte <jbb2@uw.edu>;
Mathematics: Brian E. Carlson <bcarl@umich.edu>,
Aiping Liu <apliu@uw.edu>,
Ranjan Kumar Dash <rdash@mcw.edu>,
Computer Science: Herbert Sauro <hsauro@u.washington.edu>,
Maxwell L. Neal <maxneal@gmail.com>,
Clinical Applications: James Bassingthwaighte <jbb2@uw.edu>,
Physiology/Biophysics: Andrew McCulloch, amcculloch@ucsd.edu;
Mike Regnier <mregnier@u.washington.edu>;
Dan Beard, beardda@umich.edu;
Brian E. Carlson <bcarl@umich.edu>;
James B. Bassingthwaighte <jbb2@uw.edu>.

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: Daniel Beard, Ghassan Kassab
Institution(s): University of Michigan, California Medical Innovations Institute
MSM U01 Grant Number: Click or tap here to enter text.
Title of Grant: Coronary Blood Flow: Integrated Theory and Experiments

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, 9

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

You may insert images by copying and pasting below

No

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

You may insert images by copying and pasting below

We have developed a multi-scale modeling framework to simulate coronary vascular physiology, integrating cell-level phenomena (local metabolic demand and vascular smooth muscle physiology) and whole-organ cardiac mechancis. We have used this modeling framework to guide experiments to measure regional myocardial perfusion/demand matching in coronary stenosis, elucidating important mechanisms at play in regional control of myocardial blood flow.

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

You may insert images by copying and pasting below

Click or tap here to enter text.

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

Please list as "Expertise – Name, email"

Click or tap here to enter text.

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

Click here to email your form to the NIBIB IMAG mailbox

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: Silvia Salinas Blemker and Shayn Peirce-Cottler
Institution(s): University of Virginia
MSM U01 Grant Number: 1U01AR069393
Title of Grant: Multi-scale Modeling for Treatment Discovery in Duchenne Muscular Dystrophy

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

We are addressing the following challenges:

1) Next-generation multiscale models that integrate between different scientific fields and predict integrated functions.

   We are addressing this by coupling biomechanical models and agent-based models to predict the integrated, regenerative response of muscle to injury and disease.

2) Novel methods to fuse biological and/or behavioral processes and mechanisms to model outcomes as a result of various interventions.

   We are developing new modeling approaches, along with experimental models of muscle injury and associated tools for automated image analysis of muscle histology, to study muscle degeneration and regeneration as a result of different pharmacological interventions.

3) 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)

   Our multiscale modeling efforts are directly focused on regenerative medicine in the context of skeletal muscle regeneration in the face of muscular dystrophy.

4) Implementing virtual clinical trials with multiscale models to predict outcomes.

   We are using our multiscale models to simulate different interventions on diseased muscle at different ages and stages of disease.

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

You may insert images by copying and pasting below

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

You may insert images by copying and pasting below

The overall goal of our U01 project is to develop and validate multi-scale models that link biomechanical models of human movement, muscle contraction, & muscle micromechanics with agent-based models of muscle inflammation and regeneration in order to predict disease progression in Duchenne muscular dystrophy.

We have made significant strides towards developing the computational framework and establishing protocols for novel experiments to test the models. To date, we have developed a novel agent-based model of muscle degeneration and regeneration, in both healthy and diseased (dystrophic) muscle. We used the model predictions to develop hypotheses and design experiments to tests the effects of an intervention on muscle regeneration following injury. We have also created macro-scale models of both human and mouse locomotion to investigate how relative muscle loads differ between mice and humans and how this difference could give rise to the observation that mouse models of DMD do not have the same phenotype as the human condition. Finally, we have developed simulation interface platforms: the first integrates Opensim simulations of movement (both human and mouse) with finite-element simulations in FEBio, and the second integrates FEBio simulations of muscle contraction with REPast agent-based simulations of muscle regeneration. We are now working to validate these new platforms and integrate into one seamless pipeline.

Further, experimentally, we have developed an entirely new protocol for testing the injury susceptibility of mouse muscles in a way that mimics muscle loading during gait. Further, we have established novel microscopy and image-processing techniques to precisely quantify the extent to which muscles are injured during a contraction – unique data that will empower the computational models.

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

You may insert images by copying and pasting below

In general, it would be very helpful to our community if we could take a leadership role in how best to serve as peer reviewers for multi-scale modeling papers, in particular those that involve agent-based models.

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

Biomedical Engineering (biomechanics, skeletal muscle, finite-element modeling, imaging) – Silvia Blemker, ssblemker@virginia.edu

Biomedical Engineering (microcirculation, muscle, agent-based modeling, in vivo experiments) – Shayn Peirce-Cottler, shayn@virginia.edu

Biomedical Engineering (medical imaging) – Fred Epstein, fhe6b@virginia.edu

Muscle Physiology – Rob Grange, rgrange@vt.edu

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

Click here to email your form to the NIBIB IMAG mailbox

PI(s) of MSM U01: Danny Bluestein, Yuefan Deng, Marvin J. Slepian
Institution(s): Stony Brook University and University of Arizona, Tucson
MSM U01 Grant Number: U01HL131052
Title of Grant: Multiscale Modeling of Blood Flow and Platelet Mediated Thrombosis

Abstract

- **Which MSM challenges are you addressing from the IMAG 2009 Report and how?**

MSM challenges addressed and their implementation:

Challenge (1): We have developed sophisticated particle based methods to describe blood flow in cardiovascular pathologies and the ensuing mechanotransduction processes that may induce the initiation of thrombosis via flow induced platelet activation. A departure from the traditional continuum based approaches used to model such phenomena enabled us to circumvent inherent limitations of continuum based methods to cover the vast range of spatio-temporal scales that are required to describe the complex phenomena of flow induced thrombosis. The MSM methodology developed facilitates the integration of disparate scientific field such as fluid mechanics and cardiovascular disease processes by describing the mechanotransduction processes that couple the two.

Challenge (4): 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.

Challenge (8): Our MSM simulations utilize some of the strongest and fastest HPC resources around the globe, including the Sunway (National Supercomputer Center, Jinan, China), and the XSEDE (TACC on Stampede, and XSEDE on SDSC Comet), TX.

Challenge (9): Our MSM methodology is tightly coupled to extensive *in vitro* experiments with blood recirculating in microchannels using high end video microscopy to capture flow induced platelet shape change, activation, aggregation and deposition, and our hemodynamic shearing devices (HSD). A database of these experimental measurements is used to both validate the simulation predictions and train it, following a rigorous verification and validation (V&V) approach. Additionally, we employ various experimental techniques to establish the mechanical properties of the various cellular and subcellular components of platelets. To that end we have developed an innovative electrodeformation experimental approach to measure platelet stiffness and flexibility without touching the platelets. The data is fed into the MSM models to verify that the model provides a faithful representation of the flowing platelets. Our predictive multiscale models incorporate uncertainty quantification in the coarse graining procedure.

Challenge (15): Our models are used to test development of new anti-platelet therapeutic approaches, such as NLM – novel lipid moieties that modulate platelet membrane and other biophysical properties to make the platelet more shear resistant.

Challenge (16): Spatial scales covered range from macroscopic flow scales to mesoscopic cellular to sub-cellular and molecular atomistic levels (mm to nano). Temporal scales cover the range from milli to pico seconds). This was achieved by developing innovative models integrating Dissipative Particle Dynamics (DPD) with Coarse Grained Molecular Dynamics (CGMD) and developing dedicated Multiple Time Stepping (MTS) algorithms designed to reduce computation time by several orders of magnitude.

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

We are using machine learning to predict the contact area conferred between aggregating platelets under shear flows using inputs extracted from our extensive experimental database. Implementation is via a feedforward neural network with 8 predictors (experimental inputs), two 10 nodes hidden layers- employing a Bayesian regularization algorithm, with the contact area as the output.

- **Significant MSM achievements made (or expected).**

o Better understanding of the complex mechanotransduction processes involved in cellular response to mechanical stimuli, as represented by the vexing problem of flow mediated thrombosis.

o Innovative multiscale algorithms utilizing HPC resources- leading to a true multiscale model depicting blood flow and platelet mediated thrombosis in cardiovascular diseases and in devices. This MSM model is developed following rigorous V&V practices.

o Providing quantitative tools for developing improved pharmacological management of thrombosis by targeting the traditionally ignored mechanotransduction processes, as compared to existing empirics-based treatments.

- **New MSM challenges that should be addressed by the MSM Consortium moving forward:**

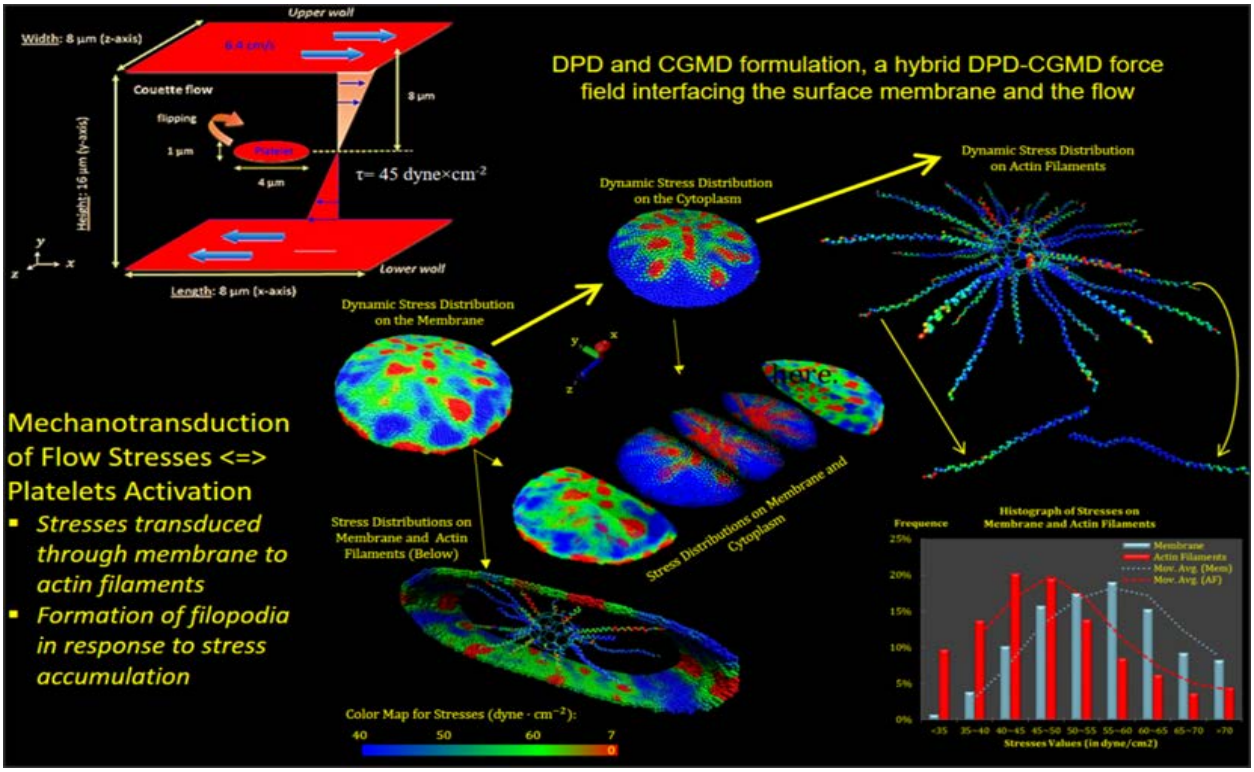
Combining continuum based finite elements simulation methods (e.g., CFD, structural, and FSI) with particle based methods (e.g., DPD, MD) to cover the vast range of scales in biological processes.

- **Expertise of our team (the list below names the PIs only- the combined team has too many expert members to list here, including a Research Asst. Prof., post docs, and graduate students):**

o *Danny Bluestein, Ph.D. Bioengineering- Thrombosis research: developing numerical and experimental methods for elucidating physical forces that regulate cellular function in flowing blood and optimizing thromboresistance in prosthetic blood recirculating devices.* *danny.bluestein@stonybrook.edu*

o *Yuefan Deng, Ph.D., Applied Math. Developing parallel computing algorithms for a wide range of scientific problems. Developing molecular dynamics modeling. A specialist in parallelizing the optimization technique of simulated annealing.* *yuefan.deng@stonybrook.edu*

o *Marvin J. Slepian, MD, Interventional cardiology-* Developing novel *diagnostics and therapeutics for cardiovascular diseases, cell-matrix/material interactions, impact of physical forces on platelet activation and experimental techniques to measure them, innovation in medical devices, extensive clinical and industrial experience.*



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: Kenneth S. Campbell and Jonathan F. Wenk
Institution(s): University of Kentucky
MSM U01 Grant Number: HL133359
Title of Grant: Multiscale modeling of inherited cardiomyopathies and therapeutic interventions

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

Challenge 4, Novel methods to fuse biological and/or behavioral processes and mechanisms to model outcomes as a result of various interventions

Our project goal is to develop a predictive multiscale model of the heart that will improve understanding of familial cardiomyopathies and that can be used to help screen potential new therapies for cardiac disease. Specifically, we are developing, validating, and calibrating a model that uses data quantifying molecular-level myosin function to predict how hearts remodel over time. We will test the computational model initially using data from wild-type mice and from transgenic animals that develop cardiac hypertrophy because of a mutation in a protein that regulates myosin motor function. Additional tests will then be performed using drugs that enhance or inhibit myosin-level contractile function.

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

You may insert images by copying and pasting below

No

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

You may insert images by copying and pasting below

We expect to develop an open-source multiscale model of the heart that spans from millisecond level molecular kinetics to organ-level growth that occurs over weeks and months. We anticipate that our model will be among the first in which cell-level function as well as structure evolves over time in response to genetic and/or pharmaceutical interventions.

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

You may insert images by copying and pasting below

1) Develop standard methods to assess sensitivity to model parameters
2) Develop a database of multiscale models analogous to PubMed or RefSeq

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

Please list as "Expertise – Name, email"

Physiology – Kenneth S. Campbell, k.s.campbell@uky.edu
Engineering – Jonathan F. Wenk, jonathan.wenk@uky.edu
Engineering – Lik Chaun Lee, lclee@msu.edu
Physiology – Christopher Yengo, cyengo@pennstatehealth.psu.edu

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

Click here to email your form to the NIBIB IMAG mailbox

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: William R. Cannon and Jay C. Dunlap
Institution(s): Pacific Northwest National Laboratory, Dartmouth, and Rennsselaer Polytechnic Institute
MSM U01 Grant Number: U01EB022546
Title of Grant: Multiscale Modeling of Circadian Rhythms

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

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

5) Reproducible/reusable multiscale models that will be integrated and adopted into model-poor fields.

6) Multiscale models coupled with standardized protocols for model-driven data collection.

9) Model predictions that drive experimentalists towards systematic testing and validation.

10) Predictive multiscale models that strongly incorporate uncertainty quantification.

16) Novel computational modeling approaches for big data that account for simultaneous sources of data on multiple scales; from biological and physiological measures.

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

You may insert images by copying and pasting below

Yes. Most likely we will be using regression methods to learn regulation points.

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

You may insert images by copying and pasting below

Prediction of metabolite concentrations in the cell, both those free in solution and bound to enzymes. Prediction of reaction rate constants. Prediction of reaction thermodynamics. Prediction of enzyme and pathway regulation. Integration of stochastic and deterministic formalisms for representing reaction networks. Ability to simulate non-steady state dynamics.

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

You may insert images by copying and pasting below

- Modeling complexity – that is, going beyond single steady state situations to model how cells adapt to changing internal and external conditions. Internal conditions may be due to inherent

cycles or oscillations within metabolism or the cell cycle, for instance. Non-equilibrium, non-steady state dynamics.

- Technology that allows us to identify putative drug targets or interventions that take into account that the system is complex and adaptive. Technology that allows us to also predict unintended cellular consequences that are manifest as side-effects of interventions –and how to mitigate these.
    - Metabolism is modeled using constraint-based approaches that only model steady states. Even so-called dynamic constraint-based approaches are simply a series of steady states strung together. There is no adaptivity in these approaches.
    - What happens when one perturbs a metabolic community?
- Machine learning that takes into account physical principles. More often than not, the data is not only noisy with higher uncertainty than precision but it also does not represent a measurement of the underlying processes. The use of physical principles will enable inferences in spite of noisy data.
- Methods to predict regulation from principles (could be combined with inference from data). That heterotrophic central metabolism is generally conserved across metazoans implies that there are common principles for regulation of metabolism. Understanding why cells are regulated – from an operational or dynamic perspective, will lead to predicting how cells are regulated.
- Physical understanding of natural selection. How much physical work/energy is required to replicate different cell types? The work/energy required to replicate is the physical quantity that determines the outcome of natural selection, and hence long-term adaptivity. This is especially important for understanding, predicting and controlling human microbiomes and cancers. But it is also important for brain and tissue repair, as well.
- Models of inter-cellular interactions, from microbiomes to the brain. How do cells turn material and energy gradients into information and knowledge? How do the principles of thermodynamics, control theory and dynamical systems lead to abstractions that become encoded as knowledge? How does perception lead to specific molecular interactions between specific cells/neurons and how do these specific interactions lead to self-awareness?

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

Please list as "Expertise – Name, email"

- *Statistical thermodynamics (physics and math applied to biological systems) – Bill Cannon (William.cannon@pnnl.gov)*
- *Circadian biology and Genetic Engineering – Jay Dunlap (Jay.C.Dunlap@dartmouth.edu), Jennifer Hurley (hurlej2@rpi.edu);*
- *Math, Knowledgebases – Jeremy Zucker (Jeremy.Zucker@pnnl.gov).*

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

Click here to email your form to the NIBIB IMAG mailbox

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: Ross P Carlson, Michael Henson, Luke Hanley, Matthew Fields
Institution(s): Montana State University
MSM U01 Grant Number: 1U01EB019416
Title of Grant: Predictive Multiscale Modeling of Microbial Consortia Biofilms

Abstract

Competitive resource allocation to metabolic pathways contributes to overflow metabolisms and emergent properties in cross feeding microbial consortia

Resource scarcity is a common stress in nature and has a major impact on microbial physiology in medical wounds. This poster highlights microbial acclimations to resource scarcity, focusing on resource investment strategies for chemoheterotrophs, including chronic wound isolates *Staphylococcus aureus* and *Pseudomonas aeruginosa,* from the molecular level to the pathway level. Competitive resource allocation strategies often lead to a phenotype known as overflow metabolism; the resulting overflow byproducts can stabilize cooperative interactions in microbial communities and can lead to cross feeding consortia. These consortia can exhibit emergent properties such as enhanced resource usage and biomass productivity which are both detrimental to patient health. The data presented here connects *in silico* analysis of temporally and spatially resolved consortia physiology with laboratory studies and ties the data together with ecological theories to better understand microbial stress responses and mutualistic consortia functioning.

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

Challenges #1,3,4. The research project integrates data from microbiology, ecology and engineering to model, analyze and predict treatment schemes for multispecies wound biofilms. Monoculture bacterial data is plentiful but data for interacting bacterial species in a spatially resolved biofilm is data poor. The project integrates genome-scale models of individual bacteria with a reaction-

diffusion analysis in a novel framework to provide temporal and spatial resolution of bacterial behaviors in wound biofilms.

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

You may insert images by copying and pasting below

No

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

You may insert images by copying and pasting below

A temporally and spatially resolved biofilm model of a chronic wound has been published. The model is informing the development of the experimental biofilm reactor system to validate the predictions.

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

You may insert images by copying and pasting below

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

Please list as "Expertise – Name, email"

Engineering, microbiology, systems biology, biofilm analysis, microbial consoritia, metabolic modeling: Ross Carlson, rossc@montana.edu; engineering, systems biology, reaction-diffusion analysis, computational biology -Michael Henson, mhenson@engin.umass.edu; microbiology, transcriptomics, microbial ecology, anaerobic biofilms -Matthew Fields, matthew.fields@montana.edu ; analytical chemistry, mass spectroscopy, proteomics, metabolomics -Luke Hanley, lhanley@uic.edu

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

Click here to email your form to the NIBIB IMAG mailbox

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*

PI(s) of MSM U01: Clancy, Colleen E

Institution(s): University of California Davis

MSM U01 Grant Number: U01HL126273

Title of Grant: PREDICTIVE MULTISCALE IN SILICO CARDIO-PHARMACOLOGY

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

7) Implementing virtual clinical trials with multiscale models to predict outcomes

Cardiotoxicity in the form of deadly abnormal cardiac rhythms is one of the most common and dangerous risks for drugs in development. Drug induced cardiotoxicity is one of the leading causes of drug attrition during development and accounts for 22-28% of US post-marketing drug withdrawal. There is an urgent need for new approaches to screen and predict the effects of drugs on cardiac rhythms. Our team is working on a new computer based technology called the "PharmaCoLogic preclinical screening technology" to fill the gap. Our technology will constitute the first solution, to our knowledge, that will allow for computer-based high throughput and low cost predictive screening of preclinical drug effects on the cardiac rhythm. We are developing a novel prototype PharmaCoLogic preclinical screening technology consisting of a multiscale computer-based modeling and simulation approach that predicts how drug interactions with cardiac ion channel targets at the level of the structural interaction and consequent kinetics link to drug induced cardiotoxicity. We expect the initial context of use for the PharmaCoLogic preclinical screening technology to be in the preclinical drug screening efforts to predict proarrhythmia outcomes.

8) Problem-driven multiscale models that require high performance computing (see below for available advanced computational resources): *We have successfully obtained two allocations on the Anton Supercomputer and have recently received an XSEDE allocation.*

18) Predictive multiscale models to improve clinical workflow, standard operating procedures, patient-specific modeling for diagnosis and therapy planning: *We have developed a whole-cell model of Induced Pluripotent Stem Cell-Derived Cardiomyocytes iPSC-CMs) composed of single exponential voltage-dependent gating variable rate constants, parametrized to fit experimental iPSC-CM steady-state and time constant values for all major ionic currents. By optimizing the model parameters to multiple experimental datasets for each ionic current, we have implemented experimentally-observed variability in the driving ionic currents by varying gating parameters and current densities in the model. The resulting population of cells predicts robust inter-subject variability in iPSC-CMs, and is used to relate specific iPSC-CM phenotype variations to proclivity for arrhythmia. This methodology effectively links molecular mechanisms to cellular-level outputs by revealing unique subsets of model parameters linked to known iPSC-CM phenotypes, including proarrhythmic behavior. This study is the first step towards a computational method to integrate clinical and experimental data into a high throughput methodology to link patient-specific genotype-phenotypes relationships, and examine these relationships the presence of pharmacological intervention.*

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

You may insert images by copying and pasting below

N/A

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

You may insert images by copying and pasting below

We have undertaken structural modeling of local anesthetic and antiarrhythmic drug binding to the human cardiac voltage gated sodium channel. The human voltage gated sodium (Na_v) channel, $hNa_v1.5$, is predominantly expressed in cardiac myocytes and is responsible for the rapid upstroke of the cardiac action potential. $hNa_v1.5$ channel plays a central role in congenital and acquired cardiac arrhythmias and has been a key target for drug development. Mutagenesis studies have previously identified key residues in Na_v channels S6 segments from domains III and IV that form a receptor site for binding of local anesthetic and antiarrhythmic drugs. However, the structural details of how these drugs affect Na_v channel function are not well understood. We have now successfully utilized Rosetta computational modeling software to build a homology model of human $Na_v1.5$ in open-inactivated and closed states based on the cryo-EM structures of electric eel $Na_v1.4$ (PDB ID: 5XSY) and American cockroach NavPaS (PDB ID: 5X0M), respectively. We applied the RosettaLigand molecular docking program to study $hNa_v1.5$ channel interactions with local anesthetic and antiarrhythmic drugs, including lidocaine, etidocaine, QX-314, ranolazine, flecainide and GS967. Our lowest energy models have shown that both local anesthetic and antiarrhythmic drugs bind to hNav1.5 via a common receptor site formed by S6 segments from domains III and IV in the central pore. We are utilizing these results now to further advance structural understanding for molecular mechanisms of local anesthetic and antiarrhythmic drug interaction with $hNa_v1.5$ and provide useful insights towards the rational design of novel modulators of ion channel activity for the treatment of cardiac arrhythmias.

Using previously developed homology models to establish methods for computing affinities for drugs and the cardiac Na channel, we carried out two sets of simulations in order to assess the differences in likely binding positions of lidocaine within the open and closed pore modelsParameters for the neutral lidocaine molecule were obtained using generalized CHARMM force field (CGENFF) for drug-like molecules and optimized using standard protocols using experimental observables and quantum mechanical (QM) data as a reference. U*nbiased MD Simulations:* In these simulations, neutral lidocaine exhibits multiple nonspecific binding modes within the pore, below the selectivity filter, and above the activation gate, in both open and closed states. These binding modes were dominated by hydrophobic interactions including a canonical binding site of F1760 between domains III and IV, which was also observed in docking simulations. The probability of lidocaine occupying the top three interaction sites (clusters) over the combined 180ns of unbiased simulation was computed as the fraction of time occupied by lidocaine, per site. In the closed state, lidocaine was almost equally likely to embed deep in the fenestrations between domains III and IV or domains I and IV, but in the open state model it was slightly more likely to embed between domains I and II or domains II or III, however in the open state the lidocaine molecule embedded less deeply into each fenestration with more of the molecule residing in the aqueous pore. In all cases, the van der Waals energetic contribution dominated in the interactions. We also carried out *Biased MD Simulations – Metadynamics:* The energetic bias employed in metadynamics simulations of lidocaine in the pore models of $Na_V1.5$ was sufficient to allow the sampling of lidocaine egress from the pore into bulk water solution in

the open-state model, in which it overcame an energetic barrier of ~10kcal/mol (**Figure 1B**). However, in the closed state model lidocaine remained trapped, sampling other fenestration regions at the top of the pore (**Figure 1A**), below the selectivity filter the selectivity filter (SF), and unable to overcome an anergetic barrier of over ~20kcal/mol to exit from the pore into either the bulk intracellular solution or the intra-membrane space through a fenestration.

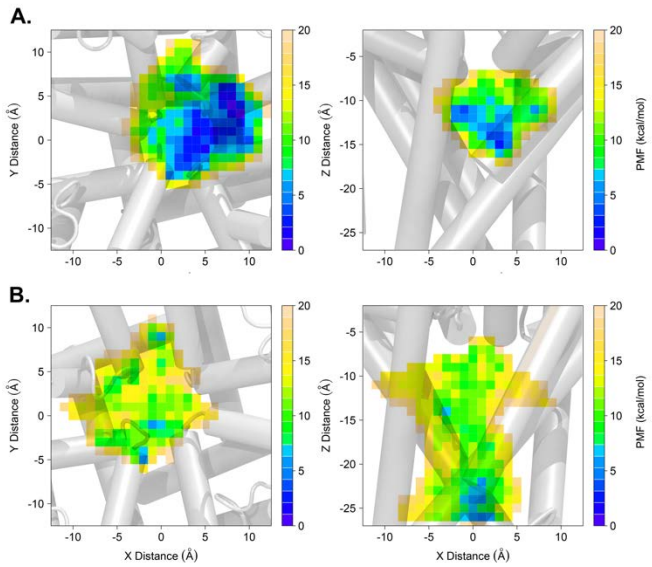


Figure 1. Surface projections of the potential of mean force derived from metadynamics simulations. A. Closed state and **B.** open state models of $Na_V1.5$ overlaid onto potential of mean for surfaces in the x-y plane (left) and x-z plane (right). Enhanced sampling of pore further confirmed interaction with the fenestration regions found in clustering analysis, particularly with the fenestration between domains DIII and DIV.

Interaction of drugs with cardiac ion channels is mediated in large part by the propensity of a drug to passively diffuse into the cell from the extracellular space, and therefore lipid membrane permeation of a drug is a critical factor in its pharmacokinetics. However, at the molecular level, little is known about the specific ionization states, spatial localization, or aggregation patterns of drugs in lipid bilayers, all of which can factor into potency, toxicity, and ability to bind to different sites in cardiac ion channels. Therefore, we developed biomolecular CHARMM force field compatible parameters for a small set of known cardiac ion channel blockers with varying risk propensities for arrhythmogenesis, and used all-atom molecular dynamics simulations to compute kinetics and thermodynamics of their partitioning through hydrated lipid membranes for different drug ionization states. We have developed an approach to determine water-membrane distributions and permeability rates for the drug translocation into the cell, and thus propensities for lipophilic and aqueous access to cardiac ion channel protein targets.

Please suggest any new MSM challenges that should be addressed by the MSM Consortium moving forward. *You may insert images by copying and pasting below*

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

Please list as "Expertise – Name, email"

Atomistic Modeling and Simulation - Igor Vorobyov

Protein, cell and tissue level functional simulation - Colleen E. Clancy

Structural models and de novo modeling - Vladimir Yarov-Yarovoy

Dynamical Systems, Mathematical Analysis- Timothy Lewis

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

Click here to email your form to the NIBIB IMAG mailbox

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: Timothy E. Corcoran and Robert S. Parker
Institution(s): University of Pittsburgh
MSM U01 Grant Number: 1UO1 HL131046-01
Title of Grant: Building Multilevel Models of Therapeutic Response in the Lungs

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

(**11) Mechanistic multiscale models that bridge to the population level to capture more clinical and biological realism for the population**. A key contribution of our proposed work is to bridge Cystic Fibrosis (CF) associated cell-level ion channel malfunction to the individual and population functional assessment of mucociliary clearance (MCC) from the whole lung. At the cell scale, we have human nasal epithelial cell cultures collected from healthy donors, parents of CF patients, and CF patients. The model employs differential-algebraic equations to capture ion transport, fluid trafficking, and electrophysiology to match experimental Ussing chamber assessments for the various patient groups, both individually and as a population. At the organ scale, we have previously constructed lumped-parameter ODE models to capture the MCC and fluid trafficking response of individuals and the patient population during a functional imaging studies.

(18) Predictive multiscale models to improve clinical workflow, standard operating procedures, patient-specific modeling for diagnosis and therapy planning. Using patient-specific models at the systems, and ultimately, cell scale(s), it becomes possible to conduct *in silico* assessments of possible treatment strategies to promote mucus clearance. An example of a present therapy is inhaled hypertonic saline, which is not very durable. Our multi-scale models, calibrated against inhaled normal and hyperosmotic saline, can be used to design an inhalation protocol to target normal hydration levels for CF patients, based on models calibrated to individual patients. Furthermore, we are testing the model with other hyperosmotic therapies (e.g., inhaled mannitol) to assess durability of action and decrease the burden of repeated treatments.

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

You may insert images by copying and pasting below

We are not presently using machine learning methods as part of this project. Other projects in the Parker lab are employing logistic regression, clustering methods (hierarchical, KNN), and other data-

driven approaches with large data sets to identify subpopulation phenotypes and endotypes by grouping patients according to measurable blood or clinical biomarkers.

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

You may insert images by copying and pasting below

We have enrolled 24 subjects (11 controls, 8 CF, and 5 CF parents). These subjects have all had nasal cells collected for culturing and performed a series of lung physiology studies, including our imaging-based assessments of MCC and small molecule absorption (ABS). This data will be used to inform our models. We continue to evolve our generalized, compartment-based model of epithelial cell physiology based on Ussing chamber conditions (a well-defined experimental case) and are now transitioning to the use of a thin-film conditions (more difficult to define but more physiologically relevant). We continue to refine our organ level model to improve both quality of fit to experimental (human imaging) data and the ability to link model parameters to the underlying biology We have also performed a series of experiments comparing the physiology of human nasal epithelial (HNE) and bronchial epithelial (HBE) cell cultures. HBEs have received more use as a disease model in CF and directly illustrate conditions in the lungs but are generally not as accessible as HNEs.

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

You may insert images by copying and pasting below

We have categorized our cell-to-organ-to-organism-to-population work under item (11) from the 2009 IMAG report. It may be more appropriate to make a new challenge heading to span the full range with models grounded in experimental data that capture as much mechanistic understanding as possible at the various scales. The mechanism component, when grounded in observations, would aid linkage across scales by helping direct how smaller-scale models might fit into higher-level models either parametrically or spatially. Models would need to explicitly address the spatiotemporal nature of organ function, while also being tied to a functional/clinical readout that could differentiate healthy and diseased individuals (perhaps also allowing endo/phenotyping of the diseased population into subpopulations based on model-captured differences).

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

Please list as "Expertise – Name, email"

Clinical Imaging/engineering - Timothy E. Corcoran, corcorante@upmc.edu; Engineering / mathematics - Robert S. Parker, rparker@pitt.edu; Cell electrophysiology - Carol Bertrand, cbertra@pitt.edu; Cell physiology and CF Clinical - Michael J. Myerburg - myerburgm@upmc.edu, and Joseph M. Pilewski -pilewskijm@upmc.edu

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

Click here to email your form to the NIBIB IMAG mailbox

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: Yasin Dhaher, PhD/Darryl Thelen, PhD
Institution(s): Rehabilitation Institute of Chicago/University of Wisconsin -Madison
MSM U01 Grant Number: 4U01EB015410-04
Title of Grant: A Multi-Scale Modeling Construct of Knee Mechanics following ACL Reconstruction

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

4) Novel methods to fuse biological and/or behavioral processes and mechanisms to model outcomes as a result of various interventions

8) Problem-driven multiscale models that require high performance computing (see below for available advanced computational resources)

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

You may insert images by copying and pasting below

NO

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

You may insert images by copying and pasting below

1. Developed a frame work on model validation when experimental data is limited and heterogeneous, limited/ heterogeneous data is a key challenge in biomechanics - used the human knee as a model system. (published)
2. Developed a computational framework on employing uncertainty synthesis to inform surgical planning – used ACL reconstruction surgery as a clinical example. (published)
3. Developed a computational construct for coupling across the two different domains in mechanics; deformable and rigid body mechanics – prediction of internal joint variables during functional movement post ACL reconstruction surgery. (published)
4. Developed a computational framework linking motor control and joint mechanics – assessment of neuromuscular training post ACL reconstructive surgery. (published)
5. Established the first attempt to connect tissue level biology with the tissue aggregate mechanics – endocrinological effects on cartilage health after acute joint injury using the human knee as a model system. (partly published; in progress)

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

Better integrate engineering/ modeling approaches with fundamental biology and its approaches. There is a need for more integration between biology (as it is often taught in a Socratic method, and approached using qualitative focused/reductionist methodologies) and engineering/ systems approaches. There is a need for cross-talk on both ends, but often the language and approaches can be inaccessible. The goal is to develop funding mechanisms that enable this cross-disciplinary efforts. These suggestions have been articulated by my colleague Professor Zaman and I to the steering committee as the co-leads of the biomechanics working group.

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

Please list as "Expertise – Name, email"

Mechanical Engineer: Darryl Thelen - dgthelen@wisc.edu

Mechanical Engineer: Yasin Dhaher – y-dhaher@northwestern.edu

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

Click here to email your form to the NIBIB IMAG mailbox

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: Diamond, SL
Institution(s): University of Pennsylvania, Johns Hopkins
MSM U01 Grant Number: U01-HL131053
Title of Grant: Multiscale Systems Analysis of Trauma

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)

#1) Next-generation multiscale models that integrate between different scientific fields:
→ Cardiovascular hemodynamics, immunology, and hematology
#9) Model predictions that drive experimentalists towards systematic testing and validation
→ Prediction of clotting and platelet function testable in microfluidic/well plate or TEG assay

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

High dimensional calcium phenotyping of cellular response used to train neural network model of platelet signaling. Using patient-specific platelets for machine learning.

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

Discovered fundamental new mechanism of platelet downregulation during trauma through high throughput analysis of platelet signaling: Lee MY, Verni CC, Herbig BA, Diamond SL. Soluble fibrin causes an acquired platelet glycoprotein VI signaling defect: implications for coagulopathy. **J Thromb Haemost.** 2017 Oct 5. doi: 10.1111/jth.13863. PMID: 28981200

Discovered fundamental new mechanobiology of shear induced NETosis: Yu X, Tan J, Diamond SL. Hemodynamic force triggers rapid NETosis within sterile thrombotic occlusions. **J. Thromb. Haemost.** 2018 (in press).

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

Strategies for experimental data generation and experimental design that are specifically generated for model development and validation.

Improved annotation, data structures, and data capture for complex, multi-clinician medical interventions such as surgery, resuscitation therapy, anesthesiology.

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

High throughput biology, microfluidics, blood reaction kinetic modeling – Diamond SL.
Machine learning, Data mining, Equation free modeling – Kevrikidis Y.
Numerical methods, Multiscale modeling, Stochastic simulation -- Sinno T.
Trauma Surgery, Patient Medical Informatics, Metabolism – Sims C.

**Save your abstract as "MSM PI Last Name _ 2018 IMAG Futures Pre-Meeting Abstract"*
Click here to email your form to the NIBIB IMAG mailbox

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: David M. Eckmann and Ravi Radhakrishnan
Institution(s): University of Pennsylvania
MSM U01 Grant Number: U01 016027
Title of Grant: *Bridging Multiple Scales in Modeling Targeted Drug Nanocarrier Delivery*

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

#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)

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

You may insert images by copying and pasting below

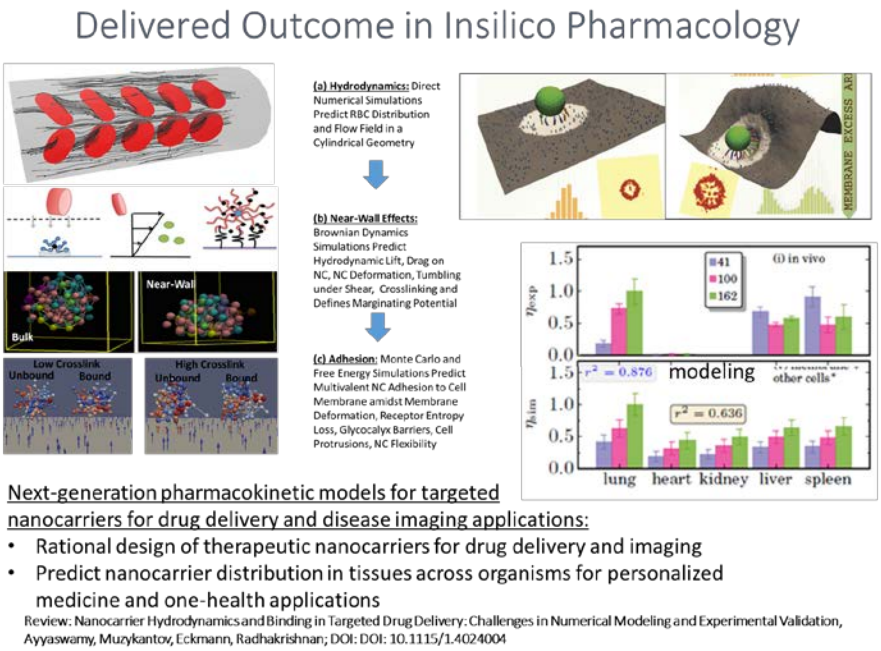
No

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

You may insert images by copying and pasting below

We developed a multiscale and multimodeller computing platform for the design of functionalized nanoparticles (NPs) for applications in disease imaging and targeted drug delivery. (1) At the hydrodynamic scale we capture detailed hydrodynamic interactions of different shaped NPs in the presence of confining boundaries such as blood vessel wall and with adhesion interactions. We include flexible NPs and interactions mediated by red blood cells. (2) At the adhesion scale we capture multivalent interactions between NPs and the cellular surface and include effects of compliance of a live cell membrane, glycocalyx, cytoskeleton, and cell surface heterogeneity. We compute binding avidity (effective association equilibrium constant for multivalent interactions) for rigid and flexible NPs by accounting for enthalpic and entropic terms. (3) At the Pharmacokinetics scale we developed a next-generation pharmacokinetics model to integrate our results from the hydrodynamics and adhesion scales into results for tissue targeting in vivo. We include targeted, untargeted, and clearance mechanisms, as well as use big data repositories (e.g., The Cancer Genome Atlas) to profile molecular expression in a patient specific fashion. (4) We validated our models by comparing each scale of computation separately with independent experiments, and we validated the tissue biodistribution using in vivo measurements. We make predictions for rats and humans based on customizing the

physiological and molecular parameters of our model. Physical and single molecule experiments were conducted to guide the choice of parameters for molecular interactions. The successful comparison and validation were achieved for a diverse range of nanoparticles including rigid spherical particles, flexible biocompatible nanogels, and nanoparticles made through DNA origami. The biomedical applications for our rational targeting platform include lung inflammation, and the actute respiratory distress syndrome.



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

You may insert images by copying and pasting below

The quantitative description of multiple scales in biological processes are based on theories and models from different fields (e.g, systems biology, continuum mechanics, hydrodynamics). Clinical and health data are heterogeneous ranging from medcial records, imaging data, to molecular profiling. To integrate this diversity, MSM can explicitly focus on heterogeneous multiscale methods or Multimodeller Hyper Models which combine disparate models into one process/simulation framework.

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

Please list as "Expertise – Name, email"

Clinical, Engineering - David M. Eckmann, eckmanndm@uphs.upenn.edu; Engineering, Math – Ravi Radhakrishnan, rradhak@seas.upenn.edu; Pharmacology – Vladimir Muzykantov, muzykant@mail.med.upenn.edu; Engineering, Math – Portonovo Ayyaswamy, ayya@seas.upenn.edu; Engineering – Andrew Tsourkas, atsourk@seas.upenn.edu

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

Click here to email your form to the NIBIB IMAG mailbox

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: C. Alberto Figueroa, Adam L. Dorfman, Seungik Baek
Institution(s): Univeristy of Michigan, Michigan State University, Nationwide Children's Hospital
MSM U01 Grant Number: 5U01HL135842
Title of Grant: Image-based Multi-scale Modeling Framework of the Cardiopulmonary System: Longitudinal Calibration and Assessment of Therapies in Pediatric Pulmonary Hypertension

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

2: Integration of organ-level (cardiopulmonary) and mesoscale-level chemo-bio-mechanical growth&remodeling (G&R) to test and predict responses to drug and acute vasolidatory therapies

3: Modeling principles will be used to generate hard-to-acquire anatomical and hemodynamic data for the human vasculature

4: We've developed models for automatic global and local blood flow regulation which could be used for subject-specific surgical planning

6: Our MS model of the cardiopulmonary circulation has defined a data-acquisition protocol for both Pulmonary Hypertension (PH) and control subjects, for both hemodynamic (short time scales) and tissue G&R simulations (long time scales)

8: Our MS models entail non-linear Partial Differential Equations solved with the Finite Element Method. Therefore, simulations of short and long time scales require access to High Performance Computing

10: We use Bayesian schemes for model calibration. The goal is to obtain robust parameter estimation for patient stratification

15: Our MS model of cardiopulmonary hemodynamics and G&R seeks to explore system-level response to PH therapeutic interventions

18: Our project will develop patient-specific models of the cardiopulmonary system for diagnosis and therapy planning

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

You may insert images by copying and pasting below

Yes. We are currently exploring machine learning methods for automatic image segmenation

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

You may insert images by copying and pasting below

We are currently developing two novel methodological aspects: 1) Definition of a homeostatic state for an entire vascular tree. Previously, this had only been defined for a single vessel. 2) Definition of a formal MS framework to couple short time scale stimuli with long time scale G&R responses

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

You may insert images by copying and pasting below

We are currently developing a protocol to assess form and function in the micro-vasculature of the pulmonary circulation using electron microscopy techniques on both animal and human data. Originally, our project relied on clinical data acquired for the heart and large vessels only. A proper definition and calibration of a MS model of hemodynamics and vascular G&R also necessitates MS data. Thus, bigger emphasis on techniques for MS data acquisition combining different experimental modalities applied to different scales and levels of the model is needed and must be addressed by the MSM Consortium.

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

Please list as "Expertise – Name, email"

Engineering, clinical research: C. Alberto Figueroa, figueroc@med.umich.edu
Engineering, statistics: Seungik Baek, sbaek@egr.msu.edu
Clinical, medical imaging: Adam Dorfman, adamdorf@med.umich.edu
Engineering: Lik Chuan Lee, lclee@egr.msu.edu
Statistics, Engineering: Jongeun Choi, jongeunchoi@yonsei.ac.kr
Statistics, Math: Taps Maiti, maiti@stt.msu.edu
Clinical: Ronald Grifka, rgrifka@med.umich.edu
Clinical: Robert Gajarski, Robert.Gajarski@nationwidechildrens.org

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

Click here to email your form to the NIBIB IMAG mailbox

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*

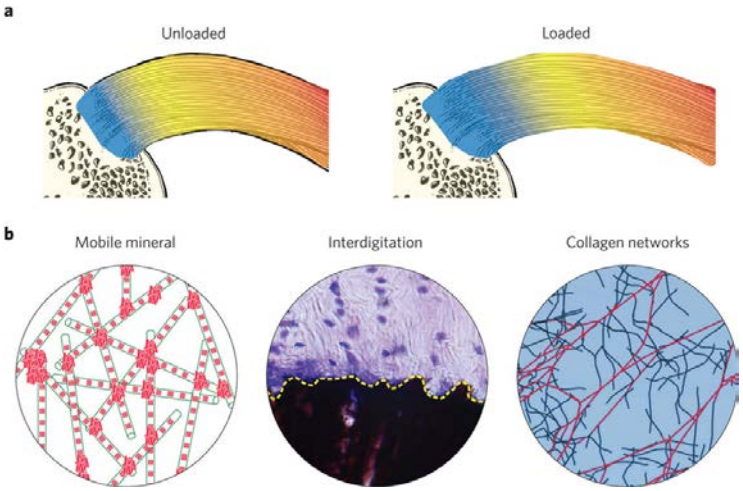
**Save your abstract as "MSM PI Last Name _ 2018 IMAG Futures Pre-Meeting Abstract"*

PI(s) of MSM U01: Guy Genin, Stavros Thomopoulos
Institution(s): Washington University (GG), Columbia University (ST)
MSM U01 Grant Number: U01 EB016422
Title of Grant: Cross-scale interactions between mineral and collagen for tendon-bone attachment

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

Joining of dissimilar materials is a fundamental challenge in engineering. Nature presents a highly effective solution at the attachment of tendon to bone ("enthesis"), e.g., in the rotator cuff - humeral head interface in the shoulder. Pressing needs exist both to understand the mechanics and biology of adhesion and toughening across hierarchical scales in the healthy enthesis, and to reconstitute these in healing. Our work is addressing two challenges from the IMAG 2009 report in the context of attaching dissimilar materials: (5) Reproducible and reusable multiscale models that will be integrated and adopted into model-poor fields (e.g. tissue engineering, regenerative medicine) and (9) Model predictions that drive a community of experimentalists towards systematic testing and validation. Models have been developed from the molecular through the tissue scales, and validated using experimental mechanical testing. These models can now be used to drive the design criteria and implementation of tissue engineering efforts to synthesize tough tendon-to-bone attachments for clinical use.



a, The disordered, energy-absorptive barrier model. Deformation localizes to the enthesis site (blue) due to its high compliance relative to bone (tan), tendon (yellow) and muscle (red). This high compliance arises in part from the character of the tissue at the attachment site, which is now known to behave like a fibrous network. **b**, This tissue is expected to be exceptionally tough relative to the neighboring tissue because of the three known components of disorder at the enthesis site: randomly distributed, mobile mineral (red plates); interfacial roughness (yellow dashed line); and the newly identified disordered fiber arrays (loaded fibres in red; unloaded fibres in blue). From Genin and Thomopoulos, *Nature Materials* **16**, 607–608 (2017).

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

Multiscale failure analysis inherently involves causal inference. We apply causal inference in all of our failure analyses to determine how quantifiable heterogeneity at the nano-, micro-, and meso-scales relate to toughness of tissues. The preliminary results of these analyses show a tradeoff between strength in toughness as certain types of heterogeneity increase.

From the experimental side, we have developed novel computer vision algorithms to assess the processes that lead to failure. These algorithms measure local strain patterns in deforming materials. These methods have been implemented in 2D and 3D and provide, for the first time, a robust method to identify local strain concentrations predictive of local failure.

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

Our recent results suggest that the hierarchical architecture presents cross-scale order for the purpose of strengthening the enthesis against injury, and cross-scale disorder for toughening the enthesis against failure. Understanding the latter represents an important frontier for the field. Initial studies suggest that disorder maximizes the fraction of tissue involved in resisting catastrophic injury-level stresses. Based upon this model, we are developing two new mechano-medicine products for clinical translation: a diagnostic technology to evaluate the degree to which an enthesis is succeeding in physiological strain redistribution, and a repair technology that mimics the mesoscale function of the healthy enthesis by maximizing the fraction of tissue involved in resisting injury-level stresses.

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

MSM has historically focused on understanding and harnessing order across hierarchies. Recent results suggest that order is critical for properties such as strength, flow, and conduction, whereas heterogeneity and disorder are critical for properties such as toughness, mixing, and redundancy. Modeling the latter is challenging and computationally expensive because techniques such as Monte Carlo approaches must be used. A pressing need exists for sound homogenization methods that predict properties of disordered tissues.

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

Engineering (modeling, nano through milliscale) – Guy Genin (genin@wustl.edu)
Engineering (experiments), Regenerative Medicine – Stavros Thomopoulos (sat2@columbia.edu)
Engineering (modeling, nanoscale) – Markus Buehler (mbuehler@mit.edu)
Engineering (modeling, micro through milliscale) – Victor Birman (vbirman@mst.edu)
Engineering (modeling, micro through milliscale) – Pedro Ponte Casteñada (ponte@seas.upenn.edu)
Engineering (experiments, microscale) – Ioannis Chasiotis (chasioti@illinois.edu)
Materials Science (biomineralization) – Alix Deymier (alix.c.deymier@gmail.com)

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: James A Glazier
Institution(s): Indiana University
MSM U01 Grant Number: GM111243
Title of Grant: Development of a Multiscale Mechanistic Simulation of Acetaminophen Induced Liver Damage

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

Our work on experimental quantification and multiscale virtual-tissue prediction of liver toxicity addresses many of the MSM Challenges. The models combine subcellular, cell-level transport, tissue, organ, flow and whole-body models derived from molecular biochemistry, cell biology, fluid-dynamics, immunology, pharmacology and toxicology to model the ingestion, macro-and micro exposure to xenobiotics, intracellular metabolism and damage, and macroscopic tissue level response to cell-level damage [(1) Next-generation multiscale models that integrate between different scientific fields...]. These virtual tissue models include components that are accessible in clinical data (e.g., serum-levels of xenobiotics and metabolites), as well as components which we have had to develop experimental techniques to measure (like the normal and disrupted vascular flow in the liver and cell responses to xenobiotics) [3) Novel methods to fuse data-rich and data-poor scales…]. The liver model is built with a modular structure using standardized model-specification languages (SBML, CC3DML, CompuCell3D Python scripts), and run using open source components to allow reuse and of submodels and the complete models for other purposes. [5) Reproducible and reusable multiscale models that will be integrated and adopted into model-poor fields…]. We have worked extensively to develop histology experimental standards and intravital flow imaging experimental standards to maximize compatibility between model parameter definition and model validation needs and experimental measurements [6) Multiscale models strongly coupled with standardized protocols for model-driven data collection.].

We have begun to systematically generate virtual populations with perturbed model parameters to study the large-scale effects on toxic response of multiple non-pathological small-scale variations in process rates and types (e.g. molecular transport rates, cytochrome profiles, body mass, time of most recent meal…). They also allow a much better understanding of the complex relationship between individual model parameter and structural uncertainty and systemic response. [7) Implementing virtual clinical trials ... 10) Predictive multiscale models that strongly incorporate uncertainty... 11) Mechanistic

multiscale models that bridge to the population level... 17) Multiscale models that characterize the implications of individual-level risks for collective outcomes…].

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

You may insert images by copying and pasting below

We use machine learning in muiltiple areas, for example; (1) estimation and parameter fitting and (2) image processing of intravital and histological microscopy images. In the estimation applications we use neural nets to assist in fine tuning parameters in complex multiscale models based on model outputs across the range of parameter space. For example, we have used a neural net analysis of 2800 simulations exploring a 40 parameter space. The goal of the analysis is to suggest solutions that minimize the RMS error between the model predictions and in vivo human blood concentration of a xenobiotic versus time data. In the image processing domain, we use machine learning and classification to quantify tissue damage areas in histology slides, to segment confocal tissue images and to measure blood flow velocities across large fields of view in the livers of APAP treated mice. The classifiers successfully segmented normal hepatocytes, damaged hepatocytes, vascular space, bile ducts, and vasculature congested with red blood cells. In addition, we have developed continuous, fieldwise measurement of microvascular blood flow in the liver of living mice.

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

You may insert images by copying and pasting below

We were the first group to make extensive use of annotated ODE models in SBML to represent multiple scales in a multiscale model. We used SBML to develop, annotate and model both subcellular metabolic reaction kinetics and whole-body Physiologically based pharmacokinetic model (PBPK). A paper (PMID:27636091) describing the early modeling results was named the "2016 Best Modeling paper" by the Biological Modeling Specialty Section of the Society of Toxicology. In addition, we have initiated a collaboration with the International Organization for Standards (ISO) to dvelop standards in biotechnology ranging from medical, to biological to modeling research. In particular, standards in annotation and sharing of biological data and models.

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

You may insert images by copying and pasting below

- The MSM Consortium needs to better "sell" the utility of computational modeling to the various institutes of the NIH. Other participating government organizations seem to have a better understanding of the potential utility of modeling in their areas but since the majority of the MSM funding seems to be from the NIH, we need to better sell modeling across the NIH institutions.
- The MSM consortium needs to encourage improved methods of annotating and sharing biological knowledge. The modeling community is critically dependent on finding relevant data (wet lab or computational) but the current methods of publication and data sharing are very poor. Note that this is an international challenge that must include non-human health researchers.

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

Please list as "Expertise – Name, email"

Computational biology, physics - James A. Glazier jaglazier@gmail.com
Computaional chemistry, drug discovery - James Sluka, jsluka@indiana.edu
Intravital micrsocopy - Kenneth Dunn, kwdunn@iu.edu
Toxicologist - James Klaunig, jklauni@indiana.edu
Microscopy – Sherry Clendenon, sgclende@indiana.edu

**Save your abstract as "MSM PI Last Name _ 2018 IMAG Futures Pre-Meeting Abstract"*
Click here to email your form to the NIBIB IMAG mailbox

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: Julius Guccione, Ghassan Kassab, Ellen Kuhl
Institution(s): UCSF, California Medical Innovations Institute, Stanford University
MSM U01 Grant Number: 5U01HL119578-04
Title of Grant: MULTI-SCALE LAWS OF MYOCARDIAL GROWTH AND REMODELING

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

Problem-driven multiscale models that require high performance computing

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

You may insert images by copying and pasting below

No

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

You may insert images by copying and pasting below

We have made the first measurements of cardiac myocyte dimensions at multiple time points during the progression of left ventricular pressure overload, volume overload and remodeling due to myocardial infarction.

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

You may insert images by copying and pasting below

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

Please list as "Expertise – Name, email"

Engineering, math, computer science

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

Click here to email your form to the NIBIB IMAG mailbox

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: Michael Henson, Erik Herzog and Yannis Kevrekidis
Institution(s): University of Massachusetts Amherst, Washington University and Johns Hopkins University
MSM U01 Grant Number: U01EB21956
Title of Grant: Multiscale Modeling of the Mammalian Circadian Clock: The Role of GABA Signaling

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

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

The suprachiasmatic nucleus (SCN) is responsible for daily timekeeping in mammals. The SCN consists of approximately 20,000 neurons that coordinate their behavior to produce a coherent overall rhythm. The SCN network is highly heterogeneous with regards to the individual neurons and their connectivity. Neuron level understanding is relatively data rich with experimental methods available to interrogate the molecular mechanisms responsible for single neuron oscillations. By contrast, the network level is poorly understood due to limited data on intercellular communication and network topology. The goal of our modeling effort is to bridge these two disparate scales by combining detailed molecular models of single neurons with sophisticated network reduction techniques based on uncertainty quantification and diffusion maps. The developed methods based on machine learning (e.g. diffusion maps) allow heterogeneity at both the neuron and network levels and enable putative network topologies to be rapidly simulated and compared to our experiments aimed at eludicating the role of GABA signaling across SCN neuron populations. We envision that our work will provide new insights into SCN network organization and be transferable to other importart problems in computational neuroscience problems involving heterogeneous networks.

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

You may insert images by copying and pasting below

We have used machine learning tools (in patricular, manifold learning/data mining tools like diffusion maps) to obtain compact and parsimonious descriptors of model networks. We just recently started using these tools on SCN models. We have not yet used data driven causal inference tools, but we expect this to occur within the duration of this grant.

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

You may insert images by copying and pasting below

During the first 15 months of the project, we initiated our proposed research on experimental determination of functional GABA connectivity across suprachiasmatic nucleus (SCN) neuron populations, single cell modeling of SCN astroctyes and multicellular modeling of heterogeneous networks of coupled neural oscillators, and development of multiscale computational tools for efficiently coarse-graining and accelerating the simulation of large populations of networked heterogeneous cells. We completed and published the first analysis of the role of astrocytes in the SCN (Tso et al. 2017, Current Biology, 27: 1055-61).

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

You may insert images by copying and pasting below

We believe that MSM consortium would benefit by more focus on common computational techniques rather than the current focus on common application areas.

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

Please list as "Expertise – Name, email"

Circadian biology – Erik Herzog, herzog@wustl.edu*; Neural modeling – Michael Henson,* mhenson@umass.edu*; Multiscale computation/machine learning – Yannis Kevrekidis, Ykevrek1@jhu.edu*

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

Click here to email your form to the NIBIB IMAG mailbox

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: Jeffrey W Holmes
Institution(s): University of Virginia
MSM U01 Grant Number: U01HL127654
Title of Grant: Multiscale Models of Cardiac Growth, Remodeling, and Myocardial Infarction

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

#4 – fusing cell-level models of wound healing and growth with organ-level models of heart mechanics and systems-level models of the circulatory system.

#15 – understanding the mechanisms of action of cardiac resynchronization therapy (CRT), a treatment for heart failure.

#17 – developing predictive models that can be used to optimize CRT in individual patients.

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

You may insert images by copying and pasting below

No.

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

You may insert images by copying and pasting below

The most important achievement to date is developing a flexible framework to couple agent-based models with finite-element models that allows users to vary the spatial resolution of each coupled model independently. Although this is a pretty specific technical development, it is absolutely essential for any investigator who wants to capture cell-level ABMs and tissue-level FEMs of any tissue or organ.

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

You may insert images by copying and pasting below

I would like to see the MSM consortium begin to think about how to educate students (and PIs) in multi-scale modeling. Is everything we do specific to the individual problems and modeling frameworks, or are there some common principles we could start to abstract, articulate, and teach?

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

Please list as "Expertise – Name, email"

Biomechanics and Cardiovascular Physiology – Jeff Holmes (PI), holmes@virginia,edu; Biomechanics and Cardiovascular Physiology – Jeff Omens (subcontract PI at UCSD), jomens@ucsd.edu; Biomechanics, Cardiovascular Physiology, and Finite-Element Modeling – Andrew McCulloch, amcculloch@eng.ucsd.edu; Cardiovascular Physiology and Agent-Based Modeling – Shayn Peirce-Cottler, smp6p@virginia.edu; Biomechanics and Finite-Element Modeling – Kyoko Yoshida, ky2p@virginia.edu; Clinical Cardiology/Electrophysiology – Ken Bilchick, KCB7F@hscmail.mcc.virginia.edu

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

Click here to email your form to the NIBIB IMAG mailbox

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: Dov Jaron
Institution(s): Drexel University
MSM U01 Grant Number: U01 HL 116256
Title of Grant: Multiscale, Transport-Dependent NO Signaling: Cells to Vascular Networks

Abstract

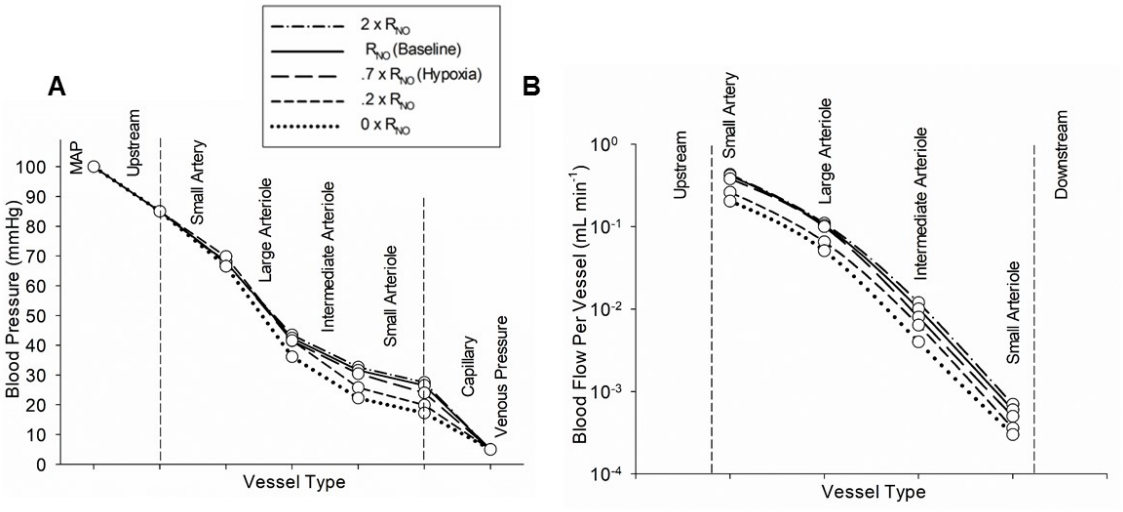
Which MSM challenges are you addressing from the IMAG 2009 Report and how?
https://www.imagwiki.nibib.nih.gov/content/2009-imag-futures-report-challenges
(indicate which challenge (#) you're addressing)

You may insert images by copying and pasting below

Our research is addressing the 9th challenge in the IMAG report: Model predictions that drive a community of experimentalists towards systematic testing and validation.

We are developing several computer models to predict how the shear stress and O2-dependent rate of nitric oxide (NO) production (RNO) affects blood flow and O2-delivery for different conditions. We are also conducting in vivo experiments in the exteriorized rat mesentery microcirculation to measure perivascular NO values simultaneously with arteriolar diameter changes for different experimental conditions. For the spring MSM meeting, we will present results of a dynamic model for changes in vascular diameter, blood flow, and average NO in vascular smooth muscle for a simplified microcirculatory network consisting of dividing small arteries, large arterioles, intermediate arterioles, and small arterioles arranged in a parallel tree. Anatomical information (lengths, initial diameters, width of vascular smooth muscle in the wall, endothelial cell layer thickness, numbers of vessels, etc) are taken from the literature. The model includes passive and active (NO-dependent) components for a myogenic response, as well as shear stress and O2 dependent RNO. The changes in overall blood pressure drop across the network (A) and individual blood flow rates in each vessel type (B) are shown below for 5 different values of RNO, including the case where RNO is zero:

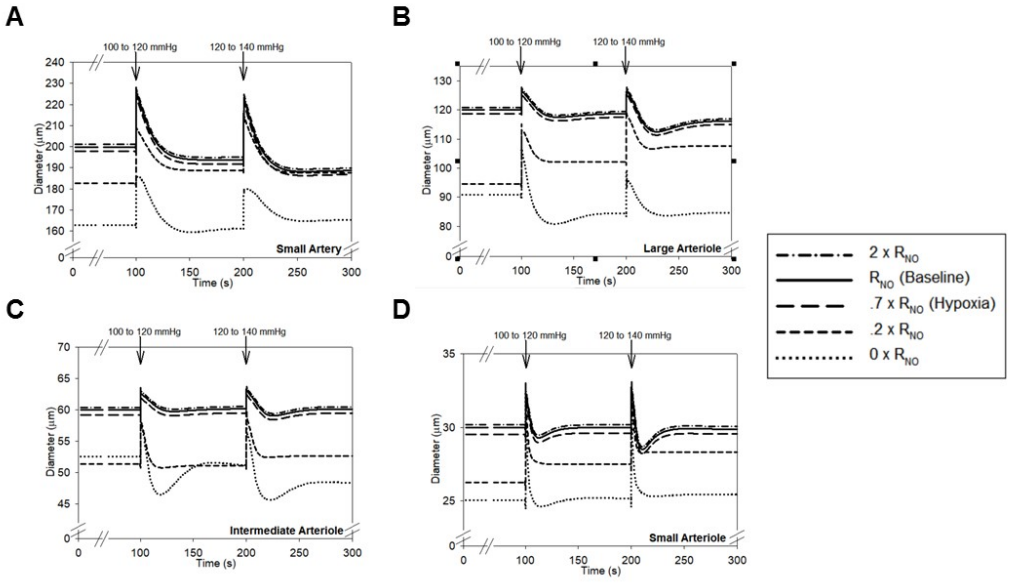
Effect of different values for shear-stress and O_2-dependent endothelial cell NO production (R_{NO}) on the **(A)** blood pressure drop in a simplified microcirculatory network (parallel vessels), with **(B)** individual vessel blood flow distributions. Vertical dashed lines mark the region of vasodilatory control modeled.



Note that the complete absence of NO (dotted lines, zero NO production) predicts the lowest blood pressure at the capillaries, resulting in the lowest blood flow.

The dynamic changes in vascular diameter for these 5 conditions are shown below for each vessel category:

Dynamic responses to step changes in the input MAP for diameters of the **(A)** small artery, **(B)** large arteriole, **(C)** intermediate arteriole, and **(D)** small arteriole for different values of R_{NO}.



We anticipate that our model predictions will help experimentalists design and interpret their studies of the microcirculation in different organs.

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

You may insert images by copying and pasting below

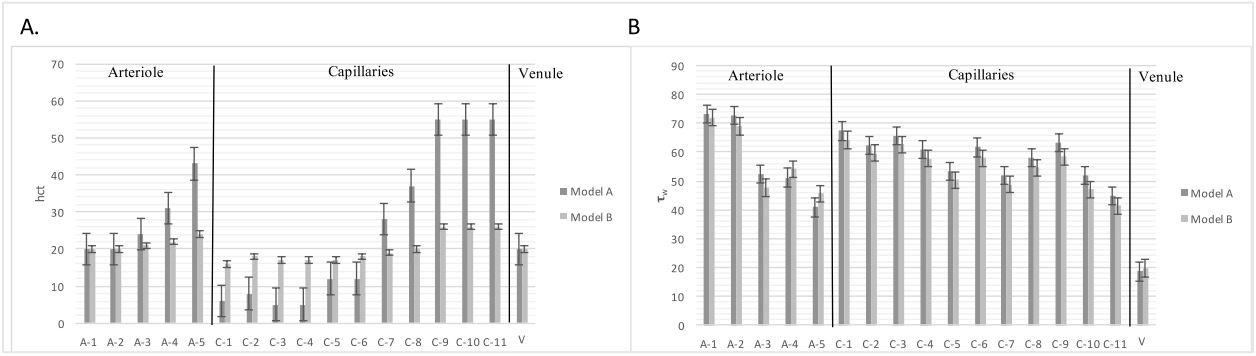
No

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

You may insert images by copying and pasting below

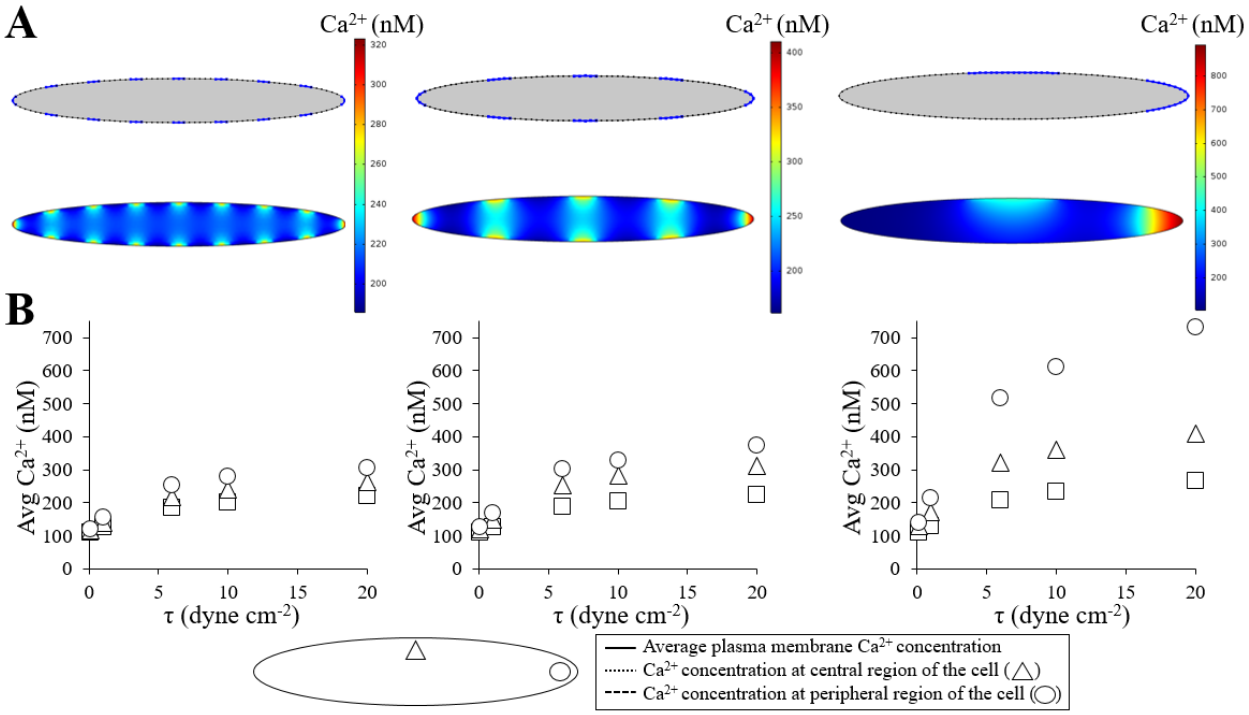
We are also developing other microcirculatory models, including effects of unequal distributions of hematocrit at vessel bifurcations in a hypothetical microvascular unit that includes 5 branching arterioles that feed 11 capillaries. We evaluated 2 different models (A – Pries and Secomb, 2005; B – Gould and Linninger, 2015) that have been proposed in the literature, and found a significant difference between the models which affects downstream values of vascular smooth muscle NO in different branches, as well as differences in O2 delivery. The average differences in hematocrit and wall shear stress in each vessel in the network predicted for the 2 models are shown below:

A. B



We are also developing a cellular model to predict effects of spatial colocalization of endothelial nitric oxide synthase (eNOS) with capacitative calcium channels in the endothelial cell membrane on RNO. The model predicts that heterogeneity of eNOS can produce microdomains in the cell membrane with significantly higher calcium concentrations that elevate RNO. Simulation results are shown below for the

effects of increasing numbers of microdomains on the average calcium concentration:



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

You may insert images by copying and pasting below

There is a paucity of geometric information from which realistic microcirculatory networks can be constructed, as well as limited physiological data for heterogeneity of NO and pO2 in different organs. Our present computational methods using COMSOL software would not be sufficient to solve complex mass transport interactions in a network with heterogenous properties.

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

Please list as "Expertise – Name, email"

Physiology, modeling: Donald G. Buerk, dgb28@drexel.edu; Endothelial cell biology, calcium dynamics: Kenneth A. Barbee, kab33@drexel.edu

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

Click here to email your form to the NIBIB IMAG mailbox

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: David Kaplan, Markus Buehler
Institution(s): Tufts University and MIT
MSM U01 Grant Number: U01EB014976
Title of Grant: Models to predict protein biomaterials performance

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 studies focus on the multi-scale design and modeling of protein polymers as biomaterial systems, including aspects of mechanics, mineralization, dynamic shape change, and related themes. These features relate polymer design to topics of degradability in vivo, mineralization in vivo and the filling of soft tissue defects.

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) – Our studies address the need for hierarchically-based models related to protein biomaterial designs, to meet the needs in the fields of tissue engineering, regenerative medicine and drug delivery. This includes proactive biomaterials with biological signaling (e.g., stem cell differentiation related to osteogenesis) and inhibition of mineralization related to tissues where mineralization is to be avoided due to mechanical needs.

6) Multiscale models strongly coupled with standardized protocols for model-driven data collection – Our multiscale models focus on both validation and prediction of new material behaviors, which then enables model-driven data collection. The integrated modeling-synthesis-characterization paradigm enables us to expand the reach of modeling and experiment in system design.

9) Model predictions that drive a community of experimentalists towards systematic testing and validation – Our models and experimental approaches are being widely disseminated via the consortium web site, as well as via published protocols, publications, and on line venues to try and excite and drive the field toward these needs, their use, and their continued improvement.

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

You may insert images by copying and pasting below

We use machine learning to study protein folding. We develop amino acid text embedding and generating systems to design, build, and test proteins. Based on coherent analogy and similarity between natural language processing techniques and protein structure analysis we aim to establish a mapping table of terminologies to connect these two fields. Public datasets of known material structures, UniProt and RCSB PDB databanks, serve as "text corpuses" to develop machine learning embedding systems that can learn a continuous vector representation of amino acid sequences and preserve biological relational meaning among them, which is similar to the role of the "word2vec" embedding in Neuro Linguistic Programming (NLP).

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

You may insert images by copying and pasting below

We have developed new fundamental strategies to integrate experimental and modeling approaches to address the challenges in biomaterial designs, including specific insights into the role of molecular weight, the impact of domain sizes and distributions within the polymer chains, the impact of hydrophobic/hydrophilic partitioning with the protein domains, and the role of charged termini in terms of how they impact protein polymer assembly and the resulting mechanical properties of the biomaterials that are formed. We have been able to utilize these approaches to bioengineer protein-based biomaterials (e.g., collagens, silks, elastins) with specific goals, including: To predict in vivo degradation of protein-biomaterials based on in vitro models (e.g., silk biomaterials); To predict dynamic material behavior based on specific environmental stimuli (e.g., thermal); To optimize biomaterial interfaces with respect to control (positive or negative) of mineralization; To predict the impact of mutations in collagen chains related to disease state (e.g., *Osteogenesis imperfecta*)

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

You may insert images by copying and pasting below

Increased focus on process simulation/manufacturing.

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

Please list as "Expertise – Name, email"

Modeling – Markus Buehler (mbuehler@mit.edu) Protein Bioengineering – David Kaplan (david.kaplan@tufts.edu)

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

Click here to email your form to the NIBIB IMAG mailbox

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*

PI(s) of MSM U01: Dartois, Flynn, Kirschner (contact), Linderman
Institution(s): Univ. Michigan, Rutgers Univ., Univ. Pittsburgh
MSM U01 Grant Number: 5U01HL131072
Title of Grant: Multi-scale systems pharmacology approach to TB therapy

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)

This MSM project integrates computational and biological models that bridge multiple length and time scales with the overall goal of identifying improved antibiotic regimens for TB treatment. Aspects of our project that address the challenges include:

- Unique collaboration of experimentalists and computational modelers in immunology, pharmacology, mathematics and engineering to address a central problem in TB. (challenge #1)
- Our predictive multi-scale model (MSM) bridges multiple physiological spatial and time scales and is aimed at narrowing the design space for antibiotic treatment. Our systems pharmacology approach will for the first time integrate (a) immune and infection processes that occur at multiple scales to produce several granuloma types, (b) bacterial dynamics, including development of resistance and role of the local environment, and (c) antibiotic PK-PD, including penetration into different regions of granulomas, to predict therapy efficacy. Novel heterogeneous agent-based model (ABM) grid will be implemented to capture dissemination of bacteria to airways leading to cavity formation - a major problem in TB patients. (challenges # 5, 15)
- Matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) imaging to capture antibiotic penetration into rabbit, NHP and human granulomas. These samples are spatially data-rich but temporally data-poor, and use of our MSM, along with a novel geographical information systems (GIS) approach to compare images with our *in silico* outcomes for validation, will serve to integrate information enabling realistic and predictive modeling. (challenge #3)
- Novel PET imaging measures of inflammation that correlate with disease status (model validation) (challenge #9)
- Model-driven data collection: PK-PD and resistance data will enable model building and calibration. (challenge #6)

- Novel optimization algorithm approach using high performance computing to identify optimal antibiotic regimens at a single granuloma level. (challenge #8)
- Virtual clinical trials using high performance computing to predict population-level treatment outcomes. (challenges #7, 8)
- Incorporation of uncertainty and sensitivity quantification to identify critical mechanisms that influence drug distribution, resistance development, and treatment efficacy with outcome measures bridging different scales. (challenge #10)
- Predicted "Virtual clinical trial best performer" antibiotic regimen will be tested in NHPs against the standard regimen, i.e. we will make model predictions that drive experimentalists toward systematic testing and validation. (challenge #6)

The detailed mechanistic and physically-based analysis of infection and antibiotic therapy in TB we propose here has never before been attempted. Our goal is to create a MSM with explicit predictive capability regarding antibiotic combinations and regimens, providing a fundamental infrastructure for antibiotic evaluation for TB, a model-poor field. Our interdisciplinary approach will shift current practice, changing an empirical approach based primarily on mouse data to a predictive computational approach, enabling rapid identification of candidate antibiotic regimens out of thousands of possibilities for further testing.

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

In previous MSM-funded work, we applied a machine learning approach to predict biomarkers (Marino, Gideon, Gong, Mankad, McCrone, Lin, Linderman, Flynn, Kirschner, **Computational and Empirical Studies Predict Mycobacterium tuberculosis-Specific T Cells as a Biomarker for Infection Outcome**, PLoS Computational Biology, 2016, DOI: 10.1371/journal.pcbi.1004804, PMID: 27065304). It is not a focus of the currently funded work.

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

1) *Applying optimization algorithms to tuberculosis antibiotic treatment regimens.* Tuberculosis (TB) requires treatment with multiple antibiotics taken over at least 6 months. This long treatment often results in poor patient-adherence, which can lead to the emergence of multi-drug resistant TB. New antibiotic treatment strategies are sorely needed. New antibiotics are being developed or repurposed to treat TB, but as there are numerous potential antibiotics, dosing sizes and potential schedules, the regimen design space for new treatments is too large to search exhaustively. In this work, we propose a method that combines an agent-based multi-scale model capturing TB granuloma formation with algorithms for mathematical optimization to identify optimal TB treatment regimens. We define two different single-antibiotic treatments to compare the efficiency and accuracy in predicting optimal treatment regimens of two optimization algorithms: genetic algorithms (GA) and surrogate-assisted optimization through radial

basis function (RBF) networks. We also illustrate the use of RBF networks to optimize double-antibiotic treatments. We found that while GAs can locate optimal treatment regimens more accurately, RBF networks provide a more practical strategy to TB treatment optimization with fewer simulations, and successfully estimated optimal double-antibiotic treatment regimens. Our results indicate surrogate-assisted optimization can locate optimal TB treatment regimens from a larger set of antibiotics, doses and schedules, and could be applied to solve optimization problems in other areas of research using systems biology approaches. Our findings have important implications for the treatment of diseases like TB that have lengthy protocols or for any disease that requires multiple drugs.

2) *Comparing efficacies of fluoroquinolones in TB granulomas using a multi-scale systems pharmacology approach.* Granulomas are complex lung lesions that are the hallmark of TB. Understanding antibiotic dynamics within lung granulomas will be vital to improving and shortening the long course of TB treatment. Three fluoroquinolones (FQs) are commonly prescribed as part of multi-drug resistant TB therapy: moxifloxacin (MXF), levofloxacin (LVX) or gatifloxacin (GFX). To date, insufficient data are available to support selection of one FQ over another, or to show that these drugs are clinically equivalent. To predict the efficacy of MXF,LVX and GFX at a single granuloma level, we integrate computational modeling with experimental datasets into a single mechanistic framework, *GranSim. GranSim* is a hybrid agent-based computational model that simulates granuloma formation and function, FQ plasma and tissue pharmacokinetics and pharmacodynamics and is based on extensive in vitro and in vivo data. We treat in silico granulomas with recommended daily doses of each FQ and compare efficacy by multiple metrics: bacterial load, sterilization rates, early bactericidal activity and efficacy under non-compliance and treatment interruption. *GranSim* reproduces in vivo plasma pharmacokinetics, spatial and temporal tissue pharmacokinetics and in vitro pharmacodynamics of these FQs. We predict that MXF kills intracellular bacteria more quickly than LVX and GFX due in part to a higher cellular accumulation ratio. We also show that all three FQs struggle to sterilize non-replicating bacteria residing in caseum. This is due to modest drug concentrations inside caseum and high inhibitory concentrations for this bacterial subpopulation. MXF and LVX have higher granuloma sterilization rates compared to GFX; and MXF performs better in a simulated non-compliance or treatment interruption scenario. We conclude that MXF has a small but potentially clinically significant advantage over LVX, as well as LVX over GFX. We illustrate how a systems pharmacology approach combining experimental and computational methods can guide antibiotic selection for TB.

3) *Emergence and selection of isoniazid and rifampin resistance in TB granulomas.* TB remains a global public health challenge, and the number of drug-resistant cases is increasing world-wide. Resistance against isoniazid (INH), rifampicin (RIF), or both (multi-drug resistant TB, MDR-TB) is of particular concern, since INH and RIF form part of the standard 4-drug regimen for active TB disease. While it is widely accepted that suboptimal treatment leads to resistance, it remains unclear how host immune responses and antibiotic dynamics within granulomas (sites of infection) affect

emergence and selection of drug-resistant bacteria. We take a systems pharmacology approach to explore resistance dynamics within granulomas. We integrate spatio-temporal host immunity and bacterial, INH and RIF dynamics into our computational framework, *GranSim*. In this work, we expand *GranSim* to allow simulated bacteria to acquire resistance to INH and RIF, including fitness costs and compensatory mutations. We use *GranSim* to simulate resistance emergence in the absence of treatment, as well as resistance selection during treatment with INH and/or RIF. There are four main findings. First, in the absence of treatment, the percentage of granulomas containing resistant bacteria mirrors the non-monotonic bacterial dynamics within granulomas. Second, drug-resistant bacteria are less frequently found in non-replicating states in the caseum as compared to drug-sensitive bacteria. Third, due to pharmacokinetic and pharmacodynamics differences between INH and RIF, pre-existing INH-resistant bacteria have a stronger influence on treatment outcomes than RIF-resistant bacteria. Finally, under combination therapy with INH and RIF, only a few MDR bacteria are able to significantly affect treatment outcomes, and all drug-susceptible bacteria are eliminated within ~20 days of starting treatment, leaving only drug-resistant bacteria. Taken together, these results indicate that resistant bacteria emerge prior to treatment, and the existence of a few drug-resistant bacteria present at the start of treatment can disrupt efficacy. Overall, our approach allows exploration of resistance at bacterial, granuloma, host and population scales. These methods can be applied toward optimizing treatment regimen design to minimize resistance selection for new and existing anti-TB antibiotics.

4) *Predicting the role of pro- and anti-inflammatory cytokines on granuloma function.* Developing new therapies requires a better understanding of the complex host immune response to infection, including dissecting the processes leading to formation of granulomas, the dense cellular lesions associated with TB. In this work, we pair experimental and computational modeling studies to explore cytokine regulation in the context of TB. We use our next-generation hybrid multi-scale model of granuloma formation (*GranSim*) to capture molecular, cellular, and tissue scale dynamics of granuloma formation. We identify TGF-β1 as a major inhibitor of cytotoxic T-cell effector function in granulomas. Deletion of TGF-β1 from the system results in improved bacterial clearance and lesion sterilization. We also identify a novel dichotomous regulation of cytotoxic T cells and macrophages by TGF-β1 and IL-10, respectively. These findings suggest that increasing cytotoxic T-cell effector functions may increase bacterial clearance in granulomas, and highlight potential new therapeutic targets for treating TB. Using immunotherapeutic approaches together with antibiotics has the highest chance of improving treatment and provides a new route to success.

Published and submitted work to date on this project:

Kirschner D, Pienaar E, Marino S, Linderman JJ. A review of computational and mathematical modeling contributions to our understanding of Mycobacterium tuberculosis within-host infection and treatment. Current Opinion in Systems Biology 3:170-185. http://dx.doi.org/10.1016/j.coisb.2017.05.014. 2017.

Warsinske HC, DiFazio RM, Linderman JJ, Flynn JL, Kirschner DE. Identifying mechanisms driving formation of granuloma-associated fibrosis during Mycobacterium tuberculosis infection. J. Theor. Biology 429: 1-17. 2017.

Pienaar E, Sarathy J, Prideaux B, Dietzold J, Dartois V, Kirschner DE, Linderman JJ. Comparing efficacies of moxifloxacin, levofloxacin and gatifloxacin in tuberculosis granulomas using a multi-scale systems pharmacology approach. PLoS Computational Biology 13(8): e1005650. 2017. https://doi.org/10.1371/journal.pcbi.1005650.

Cicchese J, Pienaar E, Kirschner DE, Linderman JJ. Applying optimization algorithms to tuberculosis antibiotic treatment regimens. Cellular and Molecular Bioengineering 10: 523. 2017. https://doi.org/10.1007/s12195-017-0507-6.

Warsinske HC, Pienaar E, Linderman JJ, Mattila JT, Kirschner DE. Deletion of TGF-β1 Increases Bacterial Clearance by Cytotoxic T Cells in a Tuberculosis Granuloma Model. Frontiers in Immunology 8:1843, 2017, DOI: 10.3389/fimmu.2017.01843

Marino S, Kirschner DE, A multicompartment hybrid computational model predicts key roles for dendritic cells in TB Infection, Academic Editors: Gennady Bocharov, Olga Solovyova and Vitaly Volpert, Computation 2016, 4, 39, DOI: 10.3390/computation4040039, PMID: 28989808.

Pienaar E, Linderman JJ, Kirschner DE. Emergence and selection of isoniazid and rifampin resistance in tuberculosis granulomas. Submitted for publication, 2017.

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

Some of our group has been funded by the MSM mechanism since the origin of the program. We wonder if there is a better way to archive for tutorial purposes or to communicate findings and approaches, i.e. to share the collective expertise of MSM-funded researchers with the next generation of researchers. While there are many wonderful examples of models in published works from the community, and some attempt at a central repository of models, there is little in the way of a higher-level introduction to the field. This could be accomplished via a book and/or summer schools.

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

PI -Dartois – pharmacology, imaging. (dartoiva@njms.rutgers.edu)
PI -Flynn – immunology, primates, microbiology. (joanne@pitt.edu)
PI -Kirschner – mathematics, computation, modeling. (kirschne@umich.edu)
PI -Linderman – engineering, computation, modeling. (linderma@umich.edu)
Consultant-Russ Butler- spatial geography and GIS (russ.butler@adu.edu)

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

Pre-Meeting Abstract Submission Form

PI(s) of MSM U01: R. Laubenbacher, B. Mehrad
Institution(s): UConn Health, University of Florida
MSM U01 Grant Number: 1U01EB024501-01
Title of Grant: Modular design of multiscale models, with an application to the innate immune response to fungal respiratory pathogens

Abstract

This project addresses Challenge 5) *Reproducible and reusable multiscale models that will be integrated and adopted into model-poor fields.* An important obstacle to the reproducibility of models is the complex and changing nature of computing environments. Reusability of multi-scale models is often limited by the complexity of the code base, which makes modifications difficult. Model adoption is often limited by barriers to use. This project addresses these challenges through the development of a highly modular software architecture that minimizes dependencies among submodels, and packages submodels, together with their complete computational environment, within lightweight software containers that facilitate modular design. The model is coupled with a user interface that allows a non-modeler to use the model for exploratory computational experiments. The biomedical application area is the innate immune response to respiratory fungal infections, a disease type for which there is no extensive modeling environment available. The model will integrate high-throughput molecular data, tissue-level data, as well as organism-level measurements.

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

No

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

We have made progress in defining the lung tissue geometry to be used, and a prototype implementation of our earlier tissue-level model in the new architecture paradigm. Furthermore, we have collected transcriptomics data from several of the relevant immune cell types.

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

MSM should support training and education projects.

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

Math and biology – R. Laubenbacher, laubenbacher@uchc.edu
Biology and math – B. Adhikari, badhikari@uchc.edu
Medicine, math, and computer science – R. Posner, rposner@uchc.edu (clinical)
Computer science – A. Hosny, abdelrahman@axware.co
Scientific visualization – W. Schroeder, will.schroeder@kitware.com (industry)
Pulmonary immunology – B. Mehrad, Borna.Mehrad@medicine.ufl.edu (clinical)

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: Gianluca Lazzi, Theodore W. Berger
Institution(s): University of Utah, Salt Lake City, University of Southern California
MSM U01 Grant Number: GM104604
Title of Grant: Predictive Modeling of Bioelectric Activity on Mammalian Multilayered Neuronal Structures in the Presence of Supraphysiological Electric Fields

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)

#1: We integrate biochemical processes with intra- and extracellular electrical activity;
#4: We developed novel methodologies to combine extracellular field and intracellular membrane potentials in response to external stimulation
#8: Our hippocampal multiscale model does require a high-performance cluster for parallelization of massive amounts of calculations
#9: Multiscale models are used as to predict the effects of drugs for multiple pathologies of the nervous system (in-silico drug discovery)
#18: In the context of drug discovery, our modeling platform can be used to evaluate outcomes of individualized treatments

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

Yes, we use a data-driven input-output (IO) modeling approach as a solution to the scale linking problem. We run simulations using detailed (computationally heavy) mechanistic models, and use the responses obtained to build and calibrate IO models capable of efficiently extracting the functional properties of the corresponding mechanistic models, but with a considerably smaller footprint. These IO models are then used as highly efficient surrogates to constitute the building blocks of the multi-scale model, thereby making possible simulations that comprise a large number of functional units.

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

We successfully developed computational/methodological bridges that model bioelectric responses of neuronal tissue to electrical stimulation. These methodologies enable integration of multiple dimensions: (i) the integration of multiple natures (electrical field generated by a stimulating electrode, electrophysiological neuronal responses and biomolecular mechanisms), (ii) of multiple spatial dimensions (from nanometer to millimeter scales) and (iii) of multiple temporal dimensions (from

short-term (msec/sec) to long-term (minutes/hours) processes). These methodologies also enable integration of mechanistic (hypothesis-driven) and input-output (data-driven) models to realize efficient large-scale simulations while preserving meaningful nonlinear dynamics.

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

You may insert images by copying and pasting below

Development of standardized strategies for multiscale models, modeling methodologies, and computational approaches

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

Please list as "Expertise – Name, email"

Electrophysiology *- T. W. Berger,* berger@usc.edu*, D. Song,* dsong@usc.edu*, M. Humayun,* humayun@med.usc.edu*.* ***Engineering*** *- G. Lazzi,* lazzi@usc.edu*, T. W. Berger,* berger@usc.edu*, D. Song,* dsong@usc.edu*, J-M. C. Bouteiller,* jbouteil@usc.edu*, K. Loizos,* ky.lo45@gmail.com*, G. Yu,* geneyu@usc.edu*.* ***Math*** *- G. Lazzi,* lazzi@usc.edu*, T. W. Berger,* berger@usc.edu*, D. Song,* dsong@usc.edu*, J-M. C. Bouteiller,* jbouteil@usc.edu*, K. Loizos,* ky.lo45@gmail.com*, G. Yu,* geneyu@usc.edu*.* ***Statistics*** *– D. Song,* dsong@usc.edu*.* ***Computer science****, Dong Song,* dsong@usc.edu*, J-M. C. Bouteiller,* jbouteil@usc.edu*, K. Loizos,* ky.lo45@gmail.com*, G. Yu,* geneyu@usc.edu*.* ***Drug discovery*** *– J-M. C. Bouteiller,* jbouteil@usc.edu*, T. W. Berger*, berger@usc.edu*.* ***Industry****, G. Lazzi,* lazzi@usc.edu*, T. W. Berger,* berger@usc.edu*, J-M. C. Bouteiller,* jbouteil@usc.edu*.* ***Visualization****, C. Johnson,* crj@utah.edu*,* ***Clinical****, T. W. Berger,* berger@usc.edu *, D. Song,* dsong@usc.edu*, M. Humayun,* humayun@med.usc.edu

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

Click here to email your form to the NIBIB IMAG mailbox

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

Pre-Meeting Abstract Submission Form

PI(s) of MSM U01: W. Jonathan Lederer, M. Saleet Jafri, Carmen A. Mannella
Institution(s): University of Maryland School of Medicine, George Mason University
MSM U01 Grant Number: 1U01HL116321
Title of Grant: Multiscale Spatiotemporal Modeling of Cardiac Mitochondria

Abstract

Which MSM challenges are you addressing from the IMAG 2009 Report and how?

Mitochondria regulate production of ATP from the breakdown of substrate in response to cellular signals linked to the cell's metabolic demands. This process is central to many important questions in the cardiovascular, neuroscience, cell biology, and molecular biology/biochemistry fields (#1). The environment of the mitochondria within the cell can see large spatiotemporal fluctuations in these signals (calcium, ADP, NADH). This project seeks to combine multiscale modeling with experiment to understand the dynamic regulation of mitochondrial function. Mitochondrial function is thought to be tightly linked to the organelle's crista nanoarchitecture. However, protein localization and signaling in nanocompartments within mitochondria are difficult to measure, making this a data poor scale. Leveraging information from physiological measurements of whole mitochondria and the cellular (data rich) environment through modeling enables us to explore these data poor scales (#3). The predictions of the model will inform which are the important experiments to do to constrain critical features of the models (#6, #9). The modeling computations will require high performance computing resources due to the computational complexity of the problem (#9). Platforms will be chosen that facilitate model sharing.

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

No

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

We have developed a multiscale model of mitochondrial crista structure and mitochondrial function, and have run simulations on Virtual Cell to enable sharing. We have gathered a variety of cardiac muscle mitochondrial structures that we can use to study the effect of crista structure on functions related to bioenergetics and calcium transport.

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

There are challenges in enabling and encouraging Multiscale Experimental Data Collection that could be a topic of discussion; we can further improve how we share modeling and algorithmic expertise, so we can benefit more from each other's work.

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

High Performance Computing, Computational Modeling, Bioinformatics – M. Saleet Jafri, sjafri@gmu.edu; Cellular Imagining, Mitochondrial Physiology, Biophysics – W. Jonathan Lederer, JLederer@som.umaryland.edu; Electron Microscopy, Mitochondrial Biology – Carmen Mannella, CMannella@som.umaryland.edu

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

Click here to email your form to the NIBIB IMAG mailbox

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: Bruce Y. Lee
Institution(s): Global Obesity Prevention Center at Johns Hopkins University
MSM U01 Grant Number: 121364
Title of Grant: Virtual Baltimore Lab: A Computational, Multi-Scale Model for Obesity Solutions

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

14) Models that provide innovative characterizations of interactions between individual-level behaviors, cognition, or affective processes and group-, market-, or population-level outcomes

15) Models to explore underlying mechanisms of individual-, community-, or population-level preventive or therapeutic interventions

16) Novel computational modeling approaches for big data that account for simultaneous sources of data on multiple scales; from biological and physiological measures, to social and psychological variables, and to environmental or contextual or societal level factors

17) Multiscale models that characterize the implications of individual-level risks for collective outcomes, or the implications of systemic risks for individual behaviors and outcomes

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

You may insert images by copying and pasting below

We develop agent based simulation models and follow the different types of outcomes and when particular outcomes occur, we perform systematic sensitivity analysis to determine cause and effect.

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

You may insert images by copying and pasting below

Our GOPC Systems Science Core is working in concert with a wide variety of decision makers and has developed an agent based model (ABM), VPOP – Virtual Population for Obesity Prevention, to explore the impact of obesity and a variety of obesity-related policies and interventions. As detailed in a publication in *Health Affairs*, we developed and used an ABM, in conjunction with the Aspen Institute's

Project Play, of all youth in the US to evaluate the impact of increasing physical activity of different proportions of youth. Results showed that maintaining 2017 recommended levels of physical activity participation (31.9%) in youth would result each year in a net present value of $1.1 trillion in direct medical costs and $1.7 trillion in lost productivity over the course of their lifetimes. Improving physical activity participation by as much as 18.1% (e.g., raising the percentage of youth who exercise to 50%), would avert $8.1 billion in direct medical costs and $13.8 billion in lost productivity. Increasing the proportion of children who exercised to 75% would avert $16.6 billion and $23.6 billion, respectively. Our team also developed a VPOP model of Washington DC to explore the impact of crime on physical activity, as detailed in a publication in *Obesity*. We developed an ABM of wards 5, 7, and 8 in Washington, DC to quantify the impact of crime and crime reduction on physical activity location accessibility, leisure-time physical activity (LTPA) and obesity among African-American women. Our simulations show that crime may serve as a barrier to LTPA. For example, reducing crime so more physical activity locations were accessible (increasing from 10% to 50%) decreased the annual rise in obesity prevalence by 2.69% among African-American women. Reducing crime and increasing the propensity to exercise through multi-level interventions (e.g., economic development initiatives to increase time available for physical activity and subsidized health care) may decrease obesity prevalence. Crime prevention strategies alone can help prevent obesity, but combining such efforts with other ways to encourage physical activity can yield even greater benefits. As described in a publication in the *American Journal of Preventive Medicine*, our GOPC has already developed ABMs of Baltimore City, Philadelphia, and San Francisco to evaluate the impact of point-of-purchase SSB warning labels, SSB consumption, and subsequently overweight and obesity prevalence among adolescents. San Francisco passed the Sugar Sweetened Beverage Warning label ordinance and Baltimore considered the mandate as well. For this study, SSBs were defined as a non-alcoholic beverage that contains added caloric sweetener. Experiments showed that implementing SSB warning labels at all SSB retailers lowered obesity prevalence among adolescents in all three cities. Point-of-purchase labels with 8% efficacy (e.g., labels reducing the probability of SSB consumption by 8%) resulted in the following percent changes in obesity prevalence (Fig. 2): Baltimore: -1.69% (95% range: -2.75, -0.97; $p<0.001$,); San Francisco: -4.08% (95% range: -5.96, -2.2; $p<0.001$); Philadelphia: -2.17% (95% range: -3.07, -1.42; $p<0.001$). Sensitivity analyses explored the impact of varying key parameters such as literacy rate, SSB warning label efficacy (e.g., the threshold at which the label no longer significantly reduces obesity and overweight prevalence), retailer compliance with implementing the label, and the types of establishments that utilize the label.

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

You may insert images by copying and pasting below

The MSM consortium ought to focus efforts on making multiscale models understandable and accessible to decision makers.

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

Please list as "Expertise – Name, email"

Clinical – Bruce Y. Lee brucelee@jhu.edu ; Industry – Bruce Y. Lee; Computational modeling – Bruce Y. Lee, Atif Adam aadam1@jhu.edu , Marie Ferguson marie.ferguson@jhu.edu , Sindiso Nyathi

snyathi@jhu.edu ; Behavior and Physiology – Tim Moran tmoran@jhmi.edu , Community Intervention and Medical Anthropology – Joel Gittelsohn jgittel1@jhu.edu ; Computer science – Daniel Hertenstein dherten1@jhu.edu , Mario Solano Gonzales msolano3@jhu.edu , Molly Domino mdomino3@jhu.edu

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

Click here to email your form to the NIBIB IMAG mailbox

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: Ching-Long Lin
Institution(s): University of Iowa
MSM U01 Grant Number: NIH U01 HL114494
Title of Grant: An integrative statistics-guided image-based multi-scale lung model

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

(The challenges that we have addressed and have been addressing are #3, 4, 8, 9, 11, and 15.)
Accurate prediction of airflow distribution and aerosol transport in the human lungs, which are difficult to be measured in vivo but important to understand the structure and function relationship, is challenging. It is because the interplay between them spans more than two orders of magnitude in dimension from the trachea to alveoli. Our research focuses on developing the techniques and strategies for modeling lungs both within and between subjects, viz. subject-specificity versus generalization from individuals to populations, with both exhibiting multiscale characteristics. For "within subjects" modeling, a computed tomography (CT)-derived subject-specific computational fluid dynamics (CFD) lung model is developed. The model is essential in linking and predicting local structural and functional interactions in individuals. For "between subjects" modeling, machine learning is employed to identify homogeneous sub-populations (clusters), among healthy and diseased populations, aiming to bridge individual and population scales. The three major challenges that we have overcome are inter-subject variability (due to, for example, gender, age and height), inter-site variability (due to scanner and imaging protocol differences), and definition of novel quantitative CT (QCT) imaging-based metrics at multiple scales (due to alterations at different disease stages) needed for machine/deep learning. Use of the cluster membership to guide subject-specific CFD analysis enables an examination of the cluster-specific structural and functional relationships toward precision medicine.

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

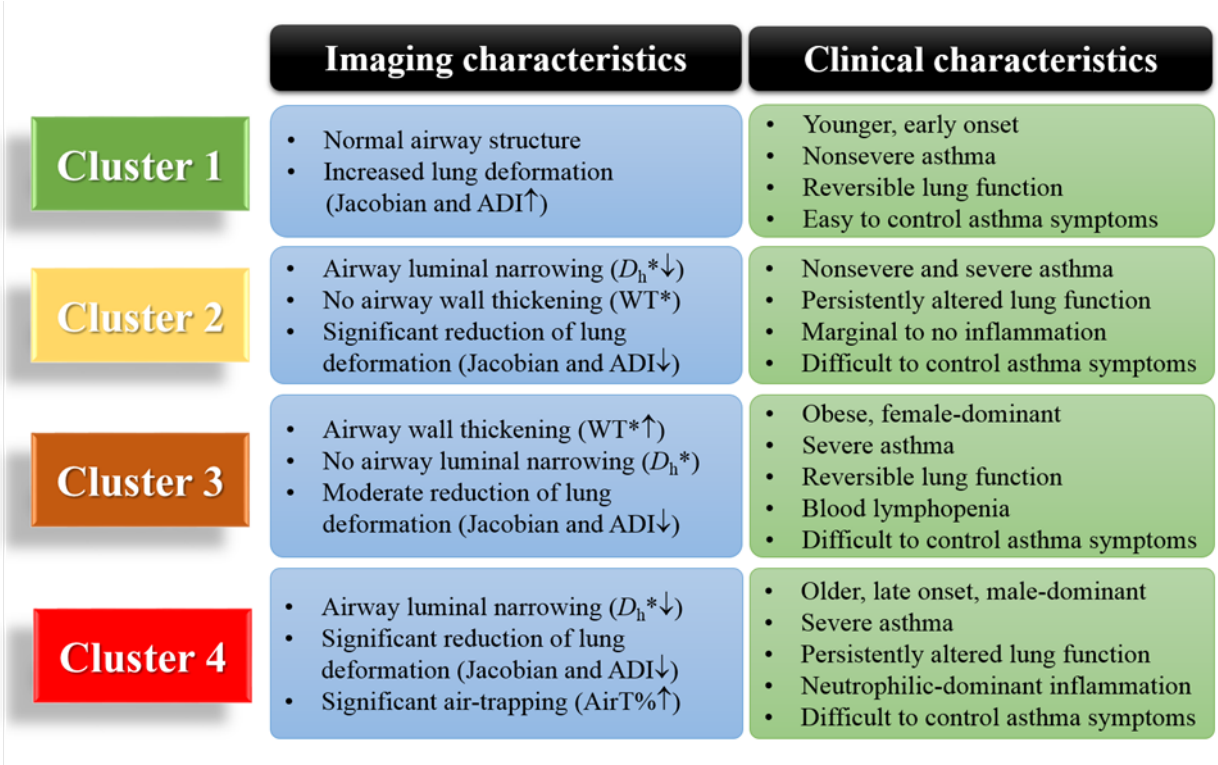
You may insert images by copying and pasting below

Yes, we developed a multiscale-imaging based cluster analysis (MICA) for analysis of asthmatic populations (J Allergy Clinical Immunology (JACI) 2017 Sep; 140(3):690-700). We employed an unsupervised machine learning technique (clustering) for grouping sub-populations of patients. Recently we further enhanced MICA for analysis of a chronic obstructive pulmonary disease (COPD) cohort.

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

You may insert images by copying and pasting below

The clinical and phenotypic characteristics of asthma vary between patients. Thus categorizing asthma sub-groups may be valuable for guiding subject-specific therapy. With the multicenter imaging data, we performed an imaging-based cluster analysis, and found unique differences in the airways and parenchyma of the patients in these clusters. Four distinct asthmatic phenotypes were derived using MICA (see Figure below taken from our JACI paper). The imaging-based clusters demonstrated differences in clinical characteristics including asthma severity, gender, onset of asthma, pulmonary function, inflammatory biomarkers, as well as responses to asthma questionnaires. The study concludes that the new asthma sub-groups may provide better treatment targets in the future, and a framework to possibly identify subpopulations within other chronic lung diseases.



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

You may insert images by copying and pasting below

Employment of cutting-edge deep learning techniques and development and validation of predictive models based on longitudinal data.

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

Please list as "Expertise – Name, email"

Engineering – Ching-Long Lin, ching-long-lin@uiowa.edu, Radiology – Eric A. Hoffman, eric-hoffman@uiowa.edu, Bioengineering - Merry Tawhai, m.tawhai@auckland.ac.nz, Physiology and clinical -John Newell, john-newell@uiowa.edu, Statistics – Kung-Sik Chan, kung-sik-chan@uiowa.edu

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

PI(s) of MSM U01: William W. Lytton

Institutions: SUNY Downstate; Northwestern University; Yale

MSM U01 Grant Number: EB017695; MSM also supported by R01MH086638, R01EB022903

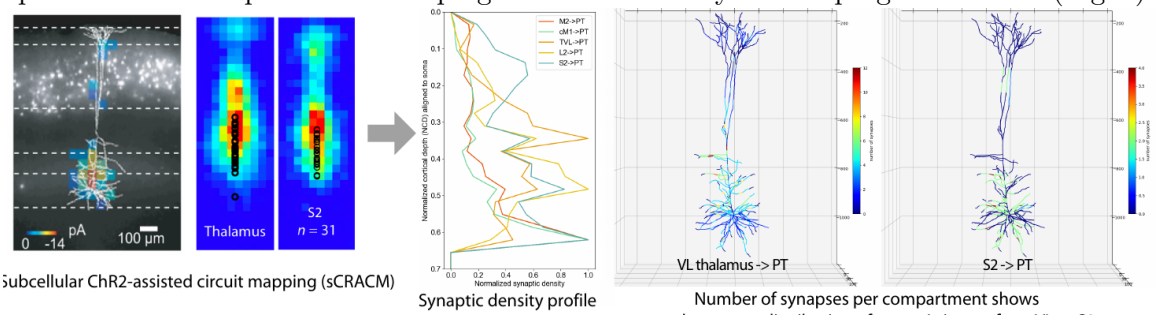
Title of Grant: Microconnectomics of neocortex: a multiscale computer model

Which MSM challenges are you addressing from the IMAG 2009 Report?

#1 Next-generation multiscale models that integrate between different scientific fields We have been developing the tools to bridge the gap between chemophysiology, traditionally handled by computational system biology and electrophysiology, the traditional focus of computational neuroscience.[5]
#3 Novel methods to fuse data-rich and data-poor scales to enable predictive modeling We have fused genetic algorithm (GA) to model dynamics at the cell level[9] with GA for dynamics at the network (tissue) level in order to fill in data-poor dendritic based on somatic and network dynamical measures.
#4 fuse biological and/or behavioral processes and mechanisms to model outcomes as a result of various interventions We have worked at the interface of neural dynamics and behavioral measures by looking at the relation of gamma activity to information transfer and by evaluating the interaction between ion channel and network factors in the context of a memory network.[8]
#5 Reproducible and reusable multiscale models All of our published models are available in the neural model database (modeldb.yale.edu).
#6 Multiscale models coupled with standardized protocols for model-driven data collection We have developed techniques to extract data from optogenetic synapse localization techniques (sCRACM) to build a model with synapses at identified dendritic locations (Fig. 1).
#8 Problem-driven multiscale models that require high performance computing
We have been developing new techniques for providing our mixed ODE/PDE/event-drive simulations on HPCs.[1, 2, 3, 4, 7] Working with the San Diego Supercomputer Center, we received the 2017 HPCwire Reader's Choice Award for "Best Use of AI." (hpcwire.com/2017-hpcwire-awards-readers-editors-choice)
#15 Underlying mechanisms of therapeutic interventions Our dystonia paper provided an example of how multi-drug multi-target pharmacotherapy could be predicted in ways that could never be done in animal trials due to combinatorial explosion.[6] This represented a new collaboration with another clinical neurologist/modeler with expertise in dystonia (Dr. Sanger).

Are you using machine learning and or causal inference methods and how? We use machine learning techniques (Genetic Algorithms) to adjust parameters according to our fitness functions at cell and tissue levels. As noted, we won an HPC AI award for this.

Please briefly describe significant MSM achievements made. We have developed novel techniques for developing network circuitry from optogenetic data (Fig 1):

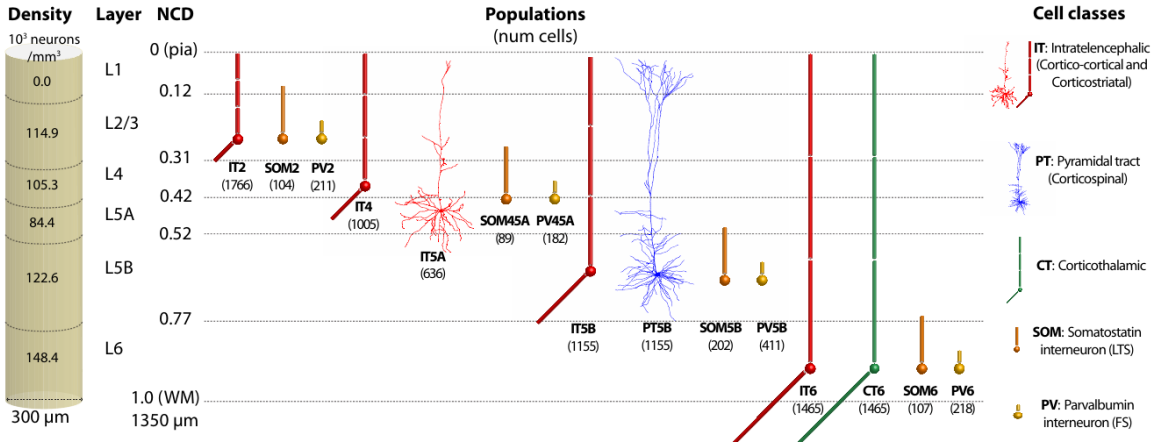


Subcellular ChR2-assisted circuit mapping (sCRACM)

Synaptic density profile (dendritic density corrected)

Number of synapses per compartment shows complementary distribution of synaptic inputs from VL vs S2

We have developed one of the few neocortical network models based as far as possible on a set of coherent datasets – data from one species, one strain, one age group, one cortical area; (however, some parameters are being set from prior estimates or measurements; Fig 2).



Please suggest new MSM challenges moving forward:
Providing interfaces/meshing between high-level top-down phenomenological models of behavior with low-level bottom-up models of basic physiology.

What expertise are on your team?
Clinical/Simulation – William Lytton, bill.lytton@downstate.edu
Machine Learning/Simulation – Salvador Dura-Bernal, salvadordura@gmail.com
Neurophysiology/Neuroanatomy – Gordon MG Shepherd, gmgshepherd@gmail.com

[1] Salvador Dura-Bernal, Amit Majumdar, Samuel A Neymotin, Subhashini Sivagnanam, Joseph T Francis, and William W Lytton. A dynamic data-driven approach to closed-loop neuroprosthetics based on multiscale biomimetic brain models. In IEEE, editor, *IEEE Interanationl Conference on High Performance Computing 2015 Workshop: InfoSymbiotics/Dynamic Data Driven Applications Systems (DDDAS) for Smarter Systems, Bangalore, India*, 2015.

[2] Z Lin, C Tropper, Y Yao, RA Mcdougal, MN Patoary, WW Lytton, and ML Hines. Load balancing for multi-threaded pdes of stochastic reaction-diffusion in neurons. *J Simulation*, 11:267, 2017.

[3] Zhongwei Lin, Carl Tropper, Robert A McDougal, Mohammand Nazrul Ishlam Patoary, William W Lytton, Yiping Yao, and Michael L Hines. Multithreaded stochastic pdes for reactions and diffusions in neurons. *ACM Transactions on Modeling and Computer Simulation (TOMACS)*, 27(2):7, 2017.

[4] WW Lytton, AH Seidenstein, S Dura-Bernal, RA McDougal, F Schürmann, and ML Hines. Simulation neurotechnologies for advancing brain research: parallelizing large networks in NEURON. *Neural Comput*, 28:2063–2090, 2016.

[5] RA McDougal, ML Hines, and WW Lytton. Reaction-diffusion in the NEURON simulator. *Front Neuroinform*, 7:28, 2013.

[6] SA Neymotin, S Dura-Bernal, P Lakatos, TD Sanger, and WW Lytton. Multitarget multiscale simulation for pharmacological treatment of dystonia in motor cortex. *Front Pharmacol*, 7:157, 2016.

[7] S.A. Neymotin, A.M. Mathew, C. Kerr, and W.W. Lytton. *Computational Neuroscience of Neuronal Networks*. Springer Verlag, New York, 2012.

[8] SA Neymotin, RA McDougal, AS Bulanova, M Zeki, P Lakatos, D Terman, ML Hines, and WW Lytton. Calcium regulation of HCN channels supports persistent activity in a multiscale model of neocortex. *Neurosci*, 316(1):344–366, 2016.

[9] SA Neymotin, BA Suter, S Dura-Bernal, GM Shepherd, M Migliore, and WW Lytton. Optimizing computer models of corticospinal neurons to replicate in vitro dynamics. *J Neurophysiol*, 117:148–162, 2017.

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: Terence D Sanger, Simon F Giszter
Institution(s): University of Southern California, Los Angeles; Drexel University, Philadelphia
MSM U01 Grant Number: U01 EB021921 02
Title of Grant: MULTISCALE MODELS OF NEURAL POPULATION CONTROL IN SPINAL CORD

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 and predict integrated functions-

Our project long term seeks to integrate neurophysiological single unit recordings and circuit knowledge with high level behavior and biomechanics states to produce system behavior predictions in terms of stochastic dynamics probabilities, using stochastic dynamic operators (SDOs) identified at the single unit scale.

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

Our methods permit high resolution models at the single neuron recording scale to be integrated with higher scale and coarser brain region, and behavior level state variations to create enhanced predictions of outcomes from the neural ensemble data.

#4 Novel methods to fuse biological and/or behavioral processes and mechanisms to model outcomes as a result of various interventions-

Our methods can incorporate many scales of information and predictions of dynamics changes after intervention.

#10 Predictive multiscale models that strongly incorporate uncertainty quantification-

Our method based on Stochastic Dynamic Operators inherently incorporates uncertainty quantification in dynamics predictions, potentially using information on several scales.

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

You may insert images by copying and pasting below

We employ SDOs to capture system information and make predictions based on neural firing. These predictions can scale from high level (e.g., likelihood of a complex behavior or avoidance of a high risk state) to neural to neural local statepredictions that begin to relate directly to neural circuit causality. We have explicitly begun to explore the use of SDO methods as a 'circuit breaking' technique to identify neural connectivity locally within neural recording of circuits.

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

You may insert images by copying and pasting below

We have used the SDO methods to predict electromyographic recordings. We have used the analysis to predict from model neural data, the downstream outcomes in spinal motor behavior. We have used the SDO framework to show we can identify circuit causality within model spinal circuits conforming to the state of the art knowledge of organization.

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

You may insert images by copying and pasting below

We believe it will be important to expand SDO application to optical recording data where individual spikes are not recorded but rather a convolution of spiking processes and calcium dynamics produces the recorded signal events. This will support larger scale applications of the methods.

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

Please list as "Expertise – Name, email"

Clinician, Mathematician, Bioengineer- Terence Sanger, MD PhD, tsanger@usc.edu; Neuroscientist, Bioengineer - Simon Giszter, PhD, sgiszter@drexelmed.edu; Engineering, Statistics - Maryam Abolfath-Beygi, PhD, mabolfat@usc.edu

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

Click here to email your form to the NIBIB IMAG mailbox

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: Michael Saunders (and subcontracting PI Bernhard Palsson)
Institution(s): Stanford University (and UC San Diego)
MSM U01 Grant Number: U01GM102098
Title of Grant: Multiscale Molecular Systems Biology: Reconstruction and Model Optimization

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)

General-purpose software tools for numerical optimization (#3,#5,#6).

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

Not directly, but machine learning is a very special case of optimization.

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

quadMINOS enables the solution of genome-scale models of Metabolism and macromolecular Expression (ME models). It is incorporated into the COBRA Toolbox 3.0.

quadMINOS has led to cobraME, ecoliME, and solveME software developed by Laurence Yang and colleagues at UC San Diego under subcontracting PI Palsson.

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

You may insert images by copying and pasting below

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

Please list as "Expertise – Name, email"

Numerical optimization – Michael Saunders, saunders@stanford.edu

Numerical optimization – Ding Ma, dingma@stanford.edu

Numerical optimization – Ron Estrin, restrin@stanford.edu

Molecular biology modeling and numerical optimization – Laurence Yang, laurence.yang@gmail.com

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

Click here to email your form to the NIBIB IMAG mailbox

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: James Schwaber, Rajanikanth Vadigepalli
Institution(s): Thomas Jefferson University
MSM U01 Grant Number: HL133360
Title of Grant: Multiscale Model of the Vagal Outflow to the Heart

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

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

You may insert images by copying and pasting below

We have employed a combination of transfer function and ordinary differential equation-based models of the closed loop cardiovascular control circuits. Going forward we are considering hybrid models containing ODE and agent-based descriptions of individual neurons and neuronal populations, with parameters largely derived from targeted neurophysiological and organismal physiological experiments.

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

You may insert images by copying and pasting below

We developed a new computational model of the closed loop cardiovascular control through a multi-input multi-output control network in the brainstem. We explored how the neuronal adaptation in the brainstem contributes to the maintenance of cardiovascular homeostasis following cardiac injury. We are incorporating multi-scale signaling and electrophysiological descriptions of brainstem neurons in this closed loop control systems model.

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

You may insert images by copying and pasting below

Develop freely accessible and rigorous didactic/training resources on various MSM methods and illustrative applications

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

Please list as "Expertise – Name, email"

Neuroscience – James Schwaber, James.Schwaber@jefferson.edu

Systems Engineering, Bioinformatics – Rajanikanth Vadigepalli, Rajanikanth.Vadigepalli@jefferson.edu

Clinical Trainee – Jonathan Gorky, Jonathan.Gorky@jefferson.edu

Physiology – Robert Rogers, NeuroRegalia@hotmail.com

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

Click here to email your form to the NIBIB IMAG mailbox

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: Timothy W. Secomb
Institution(s): University of Arizona, Massachusetts General Hospital
MSM U01 Grant Number: 1U01 HL133362-01A1
Title of Grant: Multiscale modeling of cerebral blood flow and oxygen transport

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

This project aims to develop next-generation multiscale models that integrate different scientific fields, specifically cardiovascular and neuroscience, and predict integrated functions (challenge 1). The computational approach uses high performance GPU-based parallel computing (challenge 8). The work combines experimental and modeling expertise, so that the models will create testable hypotheses leading to new investigational studies (challenges 6 and 9).

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

You may insert images by copying and pasting below

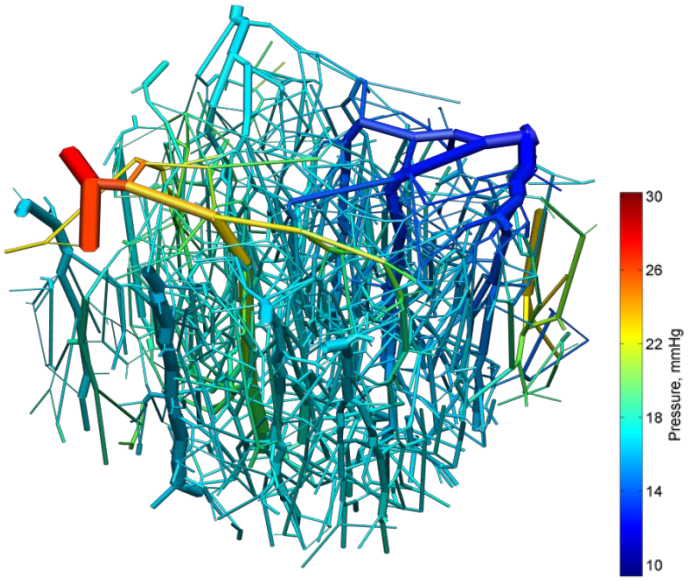
No

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

You may insert images by copying and pasting below

Advances in 3D multimodal imaging of microvascular network structure, blood flow and oxygen levels allow us to obtain spatially and temporally resolved data in tissue regions containing thousands of vessel segments. The goal of our project is to gain quantitative understanding of the relationship between neural activation, blood flow and tissue oxygenation in the brain cortex, using multiscale theoretical models for blood flow, oxygen transport and flow regulation in networks of microvessels, together with data from in-vivo microscopic imaging. This requires: (1) image analysis, conversion of 3D intensity maps into connected network structures with information about segment geometry; (2) flow estimation, based on the physics of network flows, limited measurements of individual flow rates in the given network, and empirical information on flow distribution properties; (3) analysis of oxygen transport, including estimation of boundary conditions on inflowing vessels; (4) simulation of flow regulation (neurovascular coupling), and assessing the roles of the mechanisms involved. Significant progress has been made on all these aspects and work is ongoing. Figure shows vascular network

containing 3572 segments and 3130 nodes, from mouse cerebral cortex. Overall dimensions of region are 609 × 609 × 662 µm. Cortical surface is at the top. Color coded for segment blood hydrostatic



pressures in mmHg.

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

You may insert images by copying and pasting below

Click or tap here to enter text.

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

Please list as "Expertise – Name, email"

Math modeling, numerical computation - Tim Secomb, secomb@u.arizona.edu. Brain imaging - Sava Sakadzic, sava.sakadzic@mgh.harvard.edu, David Boas, dboas@bu.edu.

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

Click here to email your form to the NIBIB IMAG mailbox

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: Eric Sobie and David Christini
Institution(s): Icahn School of Medicine at Mount Sinai and Weill Cornell Medical College
MSM U01 Grant Number: HL 136297
Title of Grant: Multiscale modeling to map cardiac electrophysiology between species

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

6) Multiscale models strongly coupled with standardized protocols for model-driven data collection

Our combined experimental and computational approach is identifying which experimental protocols are most useful for inferring model parameters

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

We are demonstrating the power of validating models through the use of systematic protocols and showing how un-validated models can fail

11) Mechanistic multiscale models that bridge to the population level to capture more clinical and biological realism for the population

Simulations are performed in heterogeneous populations, and the experimental protocols are helping us to quantify the links between molecular-level heterogeneity and functional or phenotypic heterogeneity

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

You may insert images by copying and pasting below

Yes, we have used machine learning algorithms for classifying drugs into dangerous and safe classes based on simulation results and for automatically constraining parameters in models.

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

You may insert images by copying and pasting below

We have published or submitted for publication several manuscripts. One of these, currently under review, describes a methodology to translate drug responses across cell types. This work will be presented at the meeting, and can be summarized as follows: Quantitative mismatches between

human physiology and experimental models can be problematic for the development of effective therapeutics. When the effects of drugs on human adult cardiac electrophysiology are of interest, phenotypic differences with animal cells, and more recently stem cell-derived models, can present serious limitations. We addressed this issue through a combination of mechanistic mathematical modeling and statistical analyses. Physiological metrics were simulated in heterogeneous populations of models describing cardiac myocytes from adult ventricles and those derived from induced pluripotent stem cells (iPSC-CMs). These simulated measures were used to construct a cross-cell type regression model that predicts adult myocyte drug responses from iPSC-CM behaviors. We found that: (1) quantitatively accurate predictions of responses to selective or non-selective ion channel blocking drugs could be generated based on iPSC-CM responses under multiple experimental conditions; (2) altering extracellular ion concentrations is an effective experimental perturbation for improving the model's predictive strength; (3) the method can be extended to predict and contrast drug responses in diseased as well as healthy cells, indicating a broader application of the concept. This cross-cell type model can be of great value in drug development, and the approach, which can be applied to other fields, represents an important strategy for overcoming experimental model limitations.

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

You may insert images by copying and pasting below

None to suggest at present.

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

Please list as "Expertise – Name, email"

Biomedical Engineering -- Eric Sobie, eric.sobie@mssm.edu, Biomedical Engineering -- David Christini, dchristi@med.cornell.edu, Applied Physics, Trine Krogh-Madsen,trk2002@med.cornell.edu; Physiology -- Francis Ortega, Biomedical Sciences -- Jingqi Gong

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

Click here to email your form to the NIBIB IMAG mailbox

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: Rajanikanth Vadigepalli, Jan Hoek
Institution(s): Thomas Jefferson University
MSM U01 Grant Number: EB023224
Title of Grant: Modeling Multiscale Control of Liver Regeneration

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

#5 Reproducible and reusable multiscale models that will be integrated and adopted into model-poor fields

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

You may insert images by copying and pasting below

We are employing ordinary differential equation-based approaches to develop a model of cellular and molecular network driving liver regeneration. We are utilizing nonlinear optimization methods to identify parameter values based on fit to available data as well as model parsimony considerations.

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

You may insert images by copying and pasting below

Thus far, we have developed a network model that incorporates functional state transitions of multiple liver cell types. Model simulations and analysis led to predictions on previously unknown state transitions of hepatic stellate cells. Our initial single cell gene expression assays support this model prediction, but also pointed to additional cell states missing in the model. We are in the process of incorporating the single cell analysis results into the model, to iteratively develop the next version of the cellular network model of liver regeneration.

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

You may insert images by copying and pasting below

Develop freely accessible and rigorous didactic/training resources on various MSM methods and illustrative applications

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

Please list as "Expertise – Name, email"

Systems Engineering – Rajanikanth Vadigepalli, Rajanikanth.Vadigepalli@jefferson.edu
Molecular Biology and Biochemistry – Jan Hoek, Jan.Hoek@jefferson.edu
Bioinformatics – Madhur Parihar, Madhur.Parihar@jefferson.edu
Molecular Biology and Immunology – Ankita Srivatsava, Ankita.Srivatsava@jefferson.edu
Biomedical Engineering – Aalap Verma, averma@udel.edu

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

Click here to email your form to the NIBIB IMAG mailbox

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: Thomas Yankeelov and Vito Quaranta
Institution(s): The University of Texas at Austin and Vanderbilt University
MSM U01 Grant Number: U01CA174706
Title of Grant: Image Driven Multi-Scale Modeling to Predict Treatment Response in Breast Cancer

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

2 -- Our models integrate the cellular and pathway scales to make predictions that are clinically meaureable at the tissue scale

4 -- We have combined partial differential equations, agent based models, and ordinary differential equations to account for different phenomena at different scales

6 -- Our models are initialized and calibrated with in vitro, pre-clinical and clinical data obtained at multiple scales

7 -- We use patient specific data to calibrate models and then test the effects of different therapeutic regimens (this is currently in a very preliminary state)

8 -- We make extensive use of the Texas Advanced Computing Center for parallelized computing,

10 -- We have developed a Bayesian methodology for model selection, calibration, validation, and uncertainty quantification

18 -- The overall goal of our project is to use patient-specific modeling to predict the response of breast cancers to neoadjuvant therapy.

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

You may insert images by copying and pasting below

No; our methods are mechanism-based systems of coupled ordinary and partial differential equations.

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

You may insert images by copying and pasting below

1. Developed mathematical formalisms for linking in vivo quantitative imaging with multi-scale models of tumor growth. 2. Developed a mechanics-coupled reaction-diffusion equation

for predicting the response of breast tumors to therapy. 3. Developed Bayesian methods to enable the selection of the most plausible models (for given data) and then determine if the model is a valid tool for predicting tumor growth and morphology. 4. Developed a coupled experimental/modeling approach to establish an *in vitro* pharmacokinetic/pharmacodynamic model to describe how the concentration and duration of combination therapies shapes subsequent cell population dynamics. 5. Developed methodologies and computational tools to overcome the biases associated with static end-point measurements by using an estimated rate of proliferation as the metric in anticancer drug dose–response studies. 6. Led a special section of Annals of Biomedical Engineering on Multi-scale modeling in Medicine. 7. Developed a unified mathematical formalism for relating changes in cell proliferation rates to synergistic drug activity using independent variables for efficacy and potency. 8. Developed a stochastic mechanistic model of cell cycle progression that reflects single-cell variability in checkpoint passage times.

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

You may insert images by copying and pasting below

While there is, generally speaking, much interest in machine learning and "big data" approaches to modeling complex systems, there is comparatively less emphasis on mechanism-based modeling. I would respectfully suggest that a future MSM challenge could be focused exclusively on the development, application, and uncertainty assessment of mechanism based, multi-scale models.

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

Please list as "Expertise – Name, email"

Cancer Systems Biology -- Darren Tyson, darren.tyson@vanderbilt.edu;, Cancer Systems Biology -- Vito Quaranta, vito.quaranta@vanderbilt.edu;, Mechanical Engineering -- Michale Miga, Michael.i.miga@vanderbitl.edu;, Computational Science -- Danial Faghihi, danial@ices.utexas.edu; Biomathematics -- David Ekrut, davidekrut@utexas.edu; Computational Science -- Ernesto Lima, lima@ices.utexas.edu; Biomedical Engineering -- Anna Sorace, anna.sorace@austin.utexas.edu; Biomedical Engineering -- Thomas Yankeelov, thomas.yankeelov@utexas.edu

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

Click here to email your form to the NIBIB IMAG mailbox

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

Pre-Meeting Abstract Submission Form

PI(s) of MSM U01: Muhammad Zaman and Roger Kamm
Institution(s): Boston University and Massachusetts Institute of Technology
MSM U01 Grant Number: U01 CA177799
Title of Grant: Modeling Bi-Directional Signaling And Cytoskeletal Dynamics In 3D Cell Migrations

Abstract

Which MSM challenges are you addressing from the IMAG 2009 Report and how?

Our proposed research addresses challenges 1 and 9. To this end, we propose a multiscale modeling effort, integrating the fields of mathematics, mechanobiology, and cancer systems biology, and aided by concurrent experimental work, which addresses a significant gap in the current understanding of cancer biology: the effects of the mechanical tumor microenvironment on the pro- or anti-tumorigenic effects of the cytokine transforming growth factor-beta (TGF-β). TGF-β facilitates intercellular communication within tumors, exchanging information between cancer cells, immune cells, and other biological actors including stromal cells and the extracellular matrix. The effects of this cytokine on cancer progression range from tumor suppression to tumor promotion, and the mechanical properties of the tumor microenvironment have been identified as a driving factor in the selection between these outcomes. However, the exact mechanisms underlying this behavior remain unclear. The TGF-β pathway is known to interact with various mechanosensitive signaling actors including the Hippo-YAP/TAZ signaling axis and integrin αvβ6. We propose that these interactions, aided by various mechanical and biochemical feedback loops, facilitate this mechanosensitivity and in large part dictate the downstream effects of TGF-β signaling, which together result in tumor promotion or suppression, as shown in Figure 1. In order to demonstrate and probe this mechanosensitive relationship, we will construct a differential equation model of TGF-β signaling and its interactions with both mechanosensitive signaling pathways and other pathways affected by TGF-β that control processes including cell migration, tumor growth, extracellular matrix remodeling, and metabolism. Informing this model with concurrent experimental work, we will test the hypothesized interactions between these signaling pathways, determine the primary signaling species and network motifs responsible, and explore strategies by which TGF-β signaling may be forced toward a pro- or anti-tumorigenic state. Conducting these analyses in both single- and multi-cellular contexts, we intend to examine these processes both as they affect single cancer cells and as they result in distributed behaviors across the dynamic, heterogeneous, and intercommunicative tumor microenvironment.

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

In the course of this study, we will produce various parameter-rich models, which will require suitable parameter fitting methodologies. To achieve this, we intend to draw from established protocols from machine learning, including backpropagation.

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

The multiscale modeling environment we propose will combine elements of systems biology, physics, and molecular cancer biology. Our differential equation modeling framework will consider cell signaling dynamics, spatiotemporal variation in chemical and mechanical tumor contexts, and tumor-scale migratory and proliferative behavior.

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

We propose the following new MSM challenges: 1) the integration of immune science into modeling efforts, 2) the integration of biomechanics with cellular systems modeling, and 3) evidence based clinical data integrated into modeling.

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

Cell Mechanics and Migration – Muhammad Zaman, Ph.D., zaman@bu.edu
Cell Mechanobiology – Roger Kamm, Ph.D., rdkamm@mit.edu
Applied Mathematics – Fabian Spill, Ph.D., f.spill@bham.ac.uk
Cancer Biology – Ran Li, Ph.D., rli14@mgh.harvard.edu
Computational Modeling – R.J. Seager, rseager@bu.edu
Cancer Biology – Cynthia Hajal, chajal@mit.edu

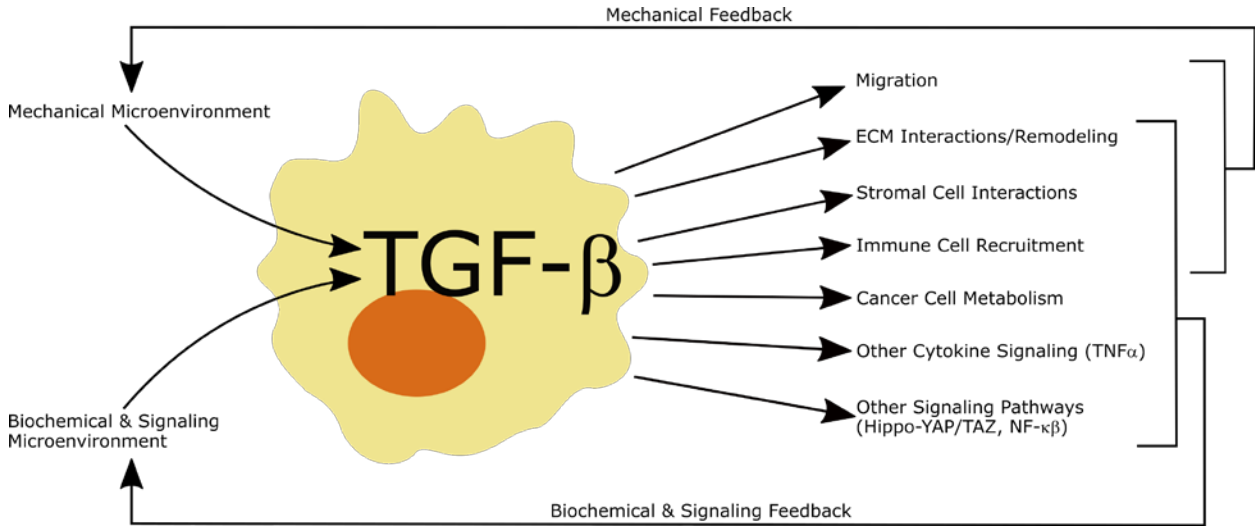


Figure 1. Mechanical regulation of the disparate effects of TGF-β signaling and resulting feedback. In response to TGF-β signaling, a variety of cancer cell behaviors including migration, ECM interactions, stromal and immune cell recruitment, metabolic changes, and interaction with other intracellular and extracellular signaling occur. All of these processes provide some form of feedback, whether mechanical or biochemical, that subsequently modulates TGF-β signaling, creating a feedback loop. Feedback loops are one network motif that enables TGF-β to act as such a powerful regulator, particularly in the multicellular, tumor context. Together, the downstream processes regulated by TGF-β result in either tumor promotion or suppression.

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: David C. Zawieja and James E. Moore Jr.
Institution(s): Texas A&M University and Imperial College London
MSM U01 Grant Number: HL-123420
Title of Grant: Transport Phenomena in the Lymphatic System

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. Integration of lymphatic biology and biomechanics to understand lymphatic function.

3. Development of lumped parameter models of lymphatic pumping; inferring currently unmeasurable system parameters from available experiments and modeling outcomes.

5. There are few models of any aspect of lymphatic function.

6. Modeling results have indicated which physiologic parameters are most important for function, which we have then pursued with experiments.

8. Modeling of immune cell communication in lymph nodes using agent-based modeling.

9. Modeling results have indicated which physiologic parameters are most important for function, which we have then pursued with experiments.

18. Our results have indicated a possible mechanism for enhancing lymphatic pumping which could be used to help treat lymphedema (currently and untreatable condition). We have developed a prototype and are testing it on healthy volunteers.

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

You may insert images by copying and pasting below

Not as such. We are challenged with parameter inference, like most modelers, but have not had to employ these methods yet.

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

You may insert images by copying and pasting below

First explanation of the origin of subatmospheric interstitial pressures. First model of lymph flow through lymph nodes. First model of mass transport of chemokines in lymph nodes. Modeling of the effects of modulating external pressure on lymphatic pumping has revealed a possible new treatment for lymphedema. First rigorous characterization of lymphatic valve behavior. Discovery that

calcium channels in lymphatic endothelial cells function very differently from those in blood endothelial cells. First measurements of the mechanical properties of human lymphatic vessels.

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

You may insert images by copying and pasting below

More extensive outreach to the medical and biological communities to demonstrate the value of modeling. It's an endless battle, I suppose.

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

Please list as "Expertise – Name, email"

Engineering, biomechanics – James Moore, james.moore.jr@imperial.ac.uk
Engineering, biomechanics – Christopher Bertram, c.bertram@sydney.edu.au
Mathematics – Charlie Macaskill, charlie.macaskill@sydney.edu.au
Lymphatic biology and physiology – David Zawieja, dcz@tamu.edu
Lymphatic biology and physiology – Michael Davis, davismj@health.missouri.edu
Lymphatic biology and physiology – Anatoliy Gashev, gashev@tamu.edu
Lymphatic biology and physiology – Wei Wang, weiwang@tamu.edu
Physics, image segmentation – Igor Sazonov, I.Sazonov@swansea.ac.uk
Engineering, computational modeling – Raoul van Loon, r.vanloon@swansea.ac.uk

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

Click here to email your form to the NIBIB IMAG mailbox

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: Xiaobo Zhou and Yunzhi Yang
Institution(s): UThealth at Houston & Stanford
MSM U01 Grant Number: 3U01AR069395-02
Title of Grant: Systems Modeling Guided Bone Regeneration

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)
(#5) We are starting to focusing on a big challenging that how to systemically modeling tumor evolution based on single-cell genomics. Various mutation events occurred in the process of tumor formation. Single-cell genomic data will guide us to develop patient-specific tumor model for revealing mechanisms and potential treatment strategies.

Are you using machine learning and or causal inference methods and how?
Yes, we are using machine learning to learn parameters in our models.
We are designing a binary linear programming (BLP) approach by combining Gibbs structural sampler with binary linear programming-based discrete modeling to infer signaling pathway network with time-series RNA-seq data.

Please briefly describe significant MSM achievements made (or expected).
1. We constructed a multiscale systems model to simulate the BMSC lineage commitment under cytokine treatments (BMP2, IGF1) at both molecular and cellular levels. The multiscale model integrated our experimental data of various scales to represent a coordinated system. We also evaluated the significance of involved parameters to model output through global sensitivity analysis. We validated our model with an independent set of experimental data, and consequently proposed a convincing mechanism to explain the outcomes of combined treatment with specific growth factors.

2. We established a 3D mechanistic hybrid multi-scale model (HMSM) for systematically understanding the immunity leading to castration-resistant prostate cancers (CRPC). In our HMSM model, we infer the cell-cell interaction and connected cytokines from our RNA-Seq data generated under various co-culture conditions. Based on the inferred cell-cell interaction networks, HMSM model simulated tumor growth, immune infiltration, and angiogenesis with in an integrated 3D space, which included tumor spaces and lymph node. After optimized with the dynamic cell population data quantified from our mice model, HMSMS is capable of predicting the optimal treatment strategies for CRPC.

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

How can systems modeling address drug resistance and recurrence in clinic studies? How to consider mutations in systems modeling to simulate clinical treatment? How to incorporate single cell sequencing and epigenetics regulation in systems modeling?

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

Please list as "Expertise – Name, email"

Engineering - Peter Yang (ypyang@stanford.edu); Math - Xiaobo Zhou(xiaobo.zhou@uth.tmc.edu) / Hua Tan (hua.tan@uth.tmc.edu); Computer Science - Zhiwei Ji (zhiwei.ji@uth.tmc.edu) / Guangming Zhang (guangming.zhang@uth.tmc.edu) ; Clinical - Weiling Zhang (weiling.zhao@uth.tmc.edu)

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

Click here to email your form to the NIBIB IMAG mailbox