Virtual Population for Obesity Prevention (VPOP): Computational, Multi-Scale Models for Obesity Solutions

Bruce Y. Lee, MD, MBA

Associate Professor of International Health

Associate Professor, Carey Business School

Executive Director, GOPC

Twitter: @bruce_y_lee

Grant: U01HD086861

9/27/15-7/31/20

JOHNS HOPKINS

GLOBAL OBESITY
PREVENTION CENTER

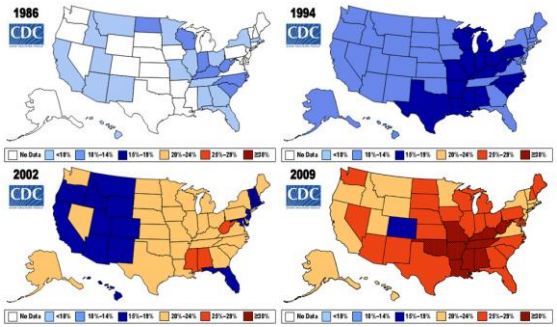
Validating VPOP Labs

- Face

  Working directly with decision makers

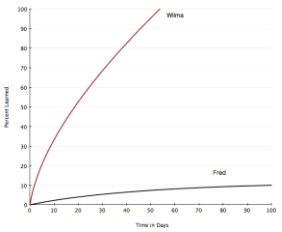
- Criterion

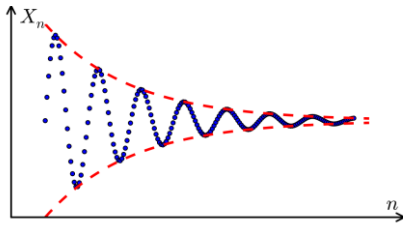
  Reproducing observed trends at multiple levels



- Convergence and Divergence

  Comparing with other models and calculations





Systems Modeling Guided Bone Regeneration

Xiaobo Zhou, Ph.D.

School of Biomedical Informatics,

The University of Texas Health Science Center at Houston, Houston, TX

Peter Yang, Ph.D.

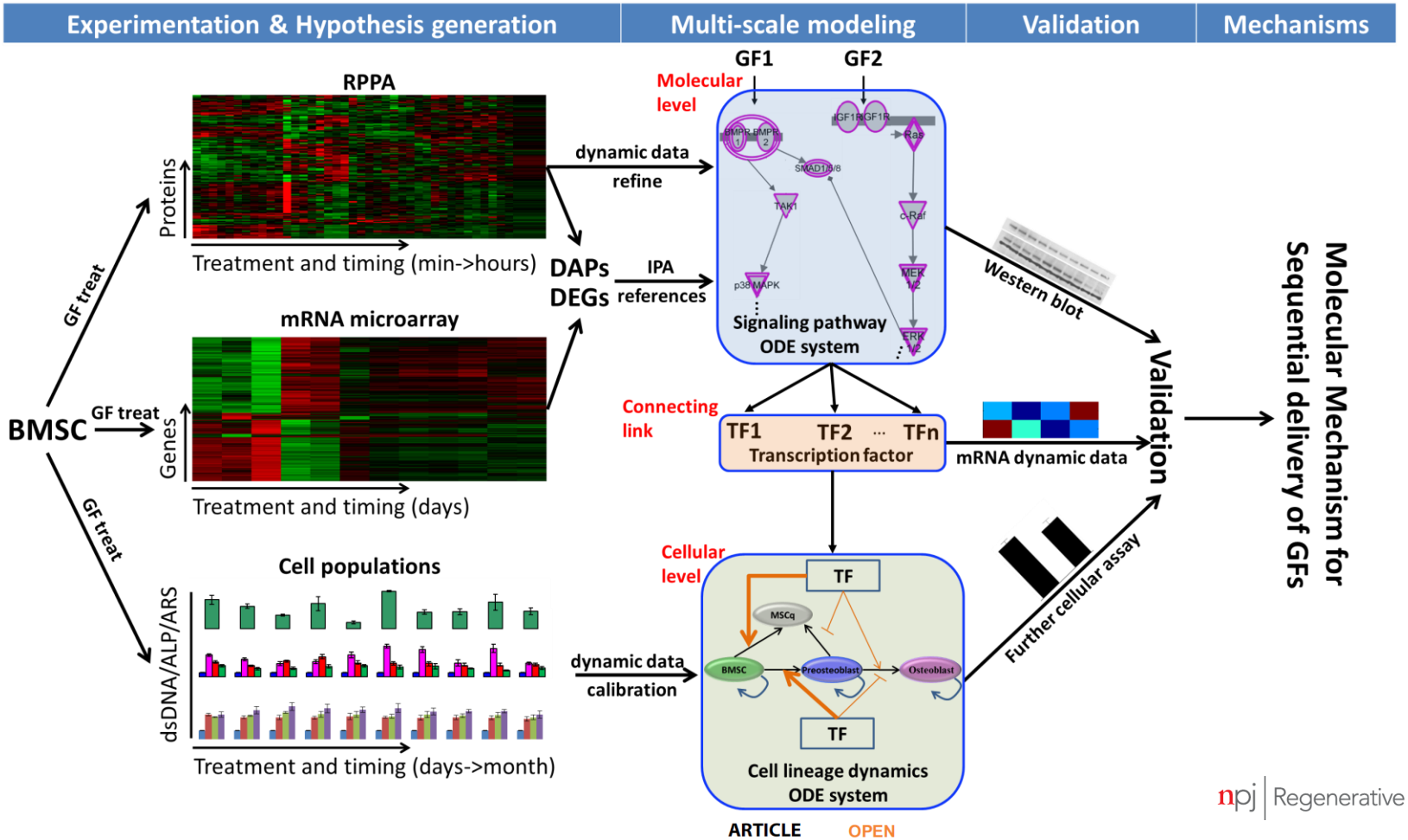
Department of Dental and Material Sciences

Stanford University, Winston-Salem, CA

NIH 1U01AR069395-01A1
9/2016-8/2022

Model Credibility

Systems biology approach to studying the molecular mechanisms for sequential delivery of growth factors has been completed



npj | Regenerative Medicine

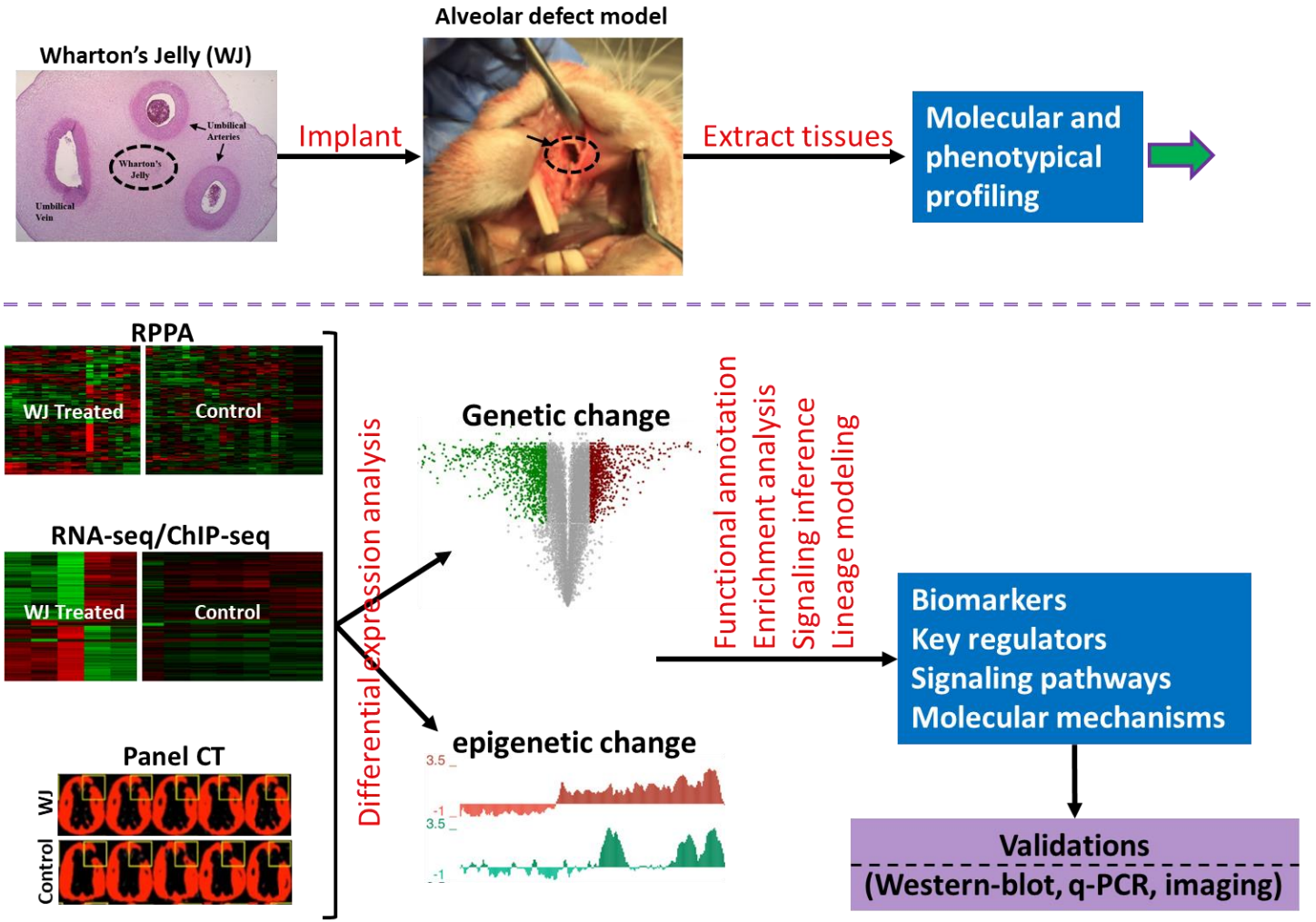
ARTICLE OPEN

A systems biology approach to studying the molecular mechanisms of osteoblastic differentiation under cytokine combination treatment

Hua Tan[1], Ruoying Chen[1], Wenyang Li[1,2], Weiling Zhao[1], Yuanyuan Zhang[3], Yunzhi Yang[4,5,6], Jing Su[1] and Xiaobo Zhou[1,7,8]

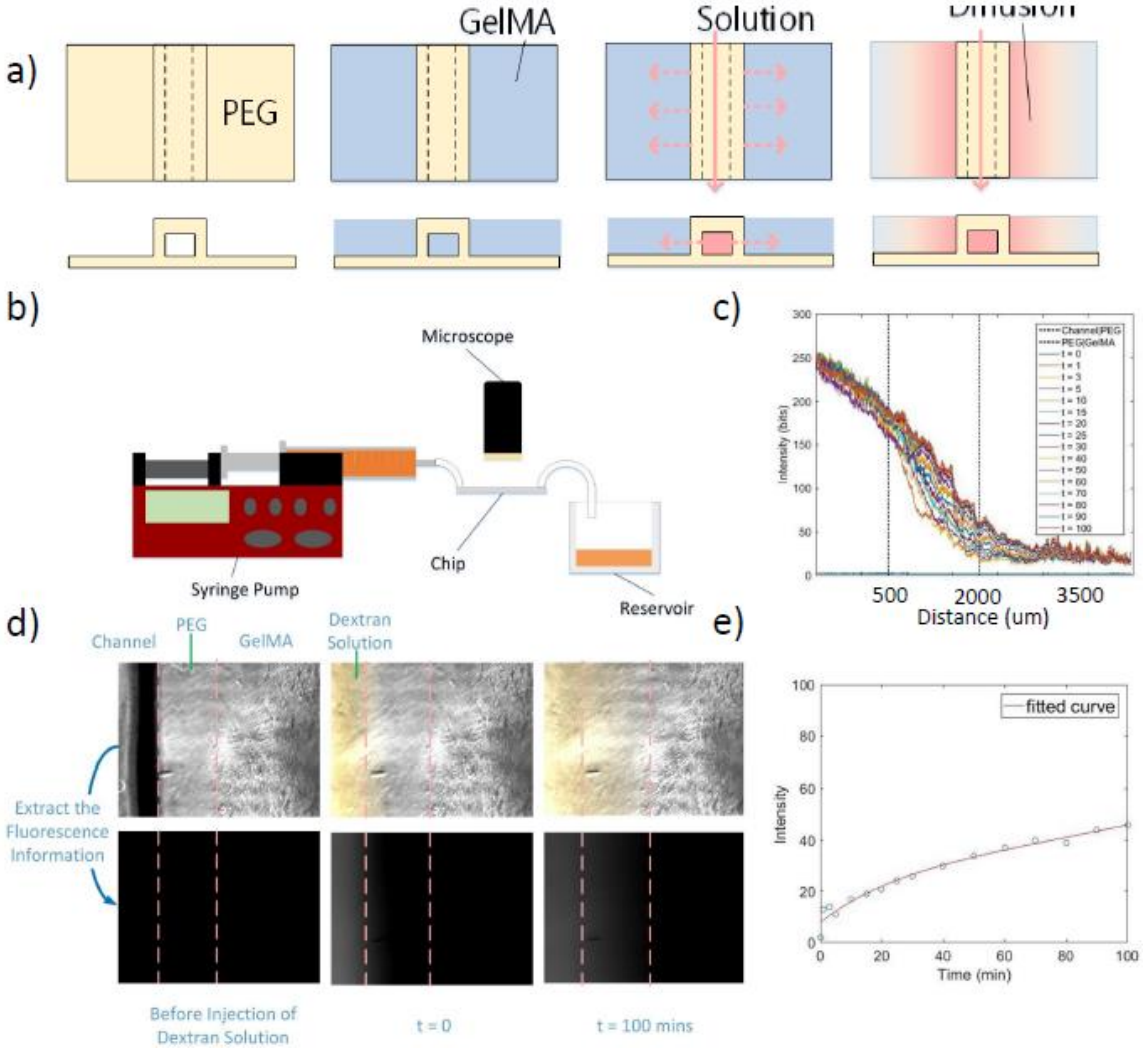
Project progress – part 1

Systems biology design on WJ-facilitated bone defect repair



Project progress – part 2

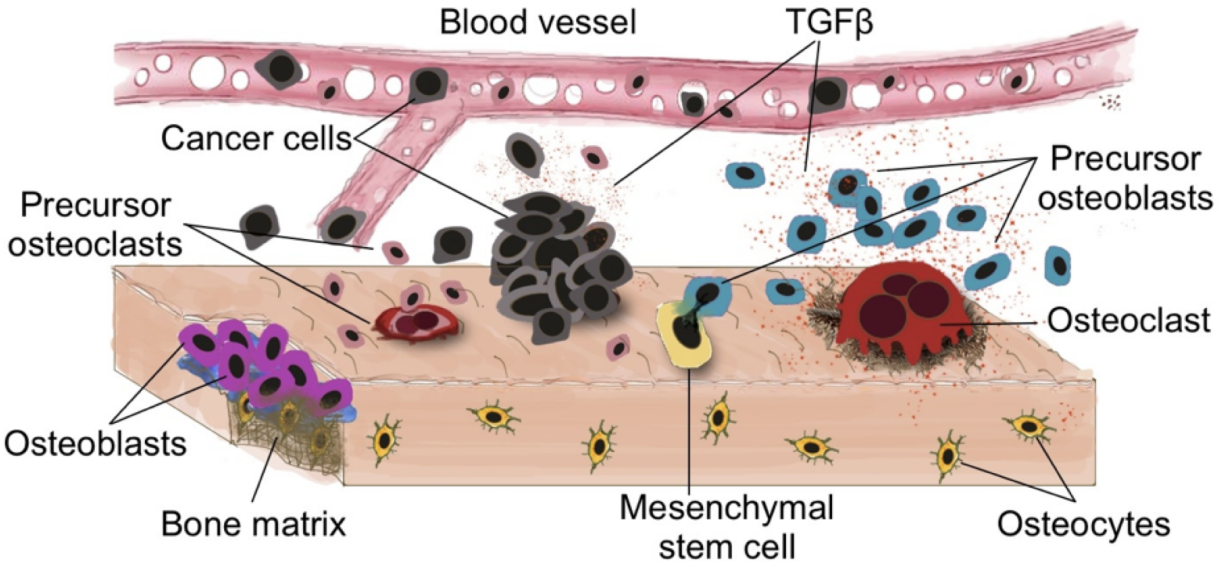
Device and experimental set up for cytokine diffusion test

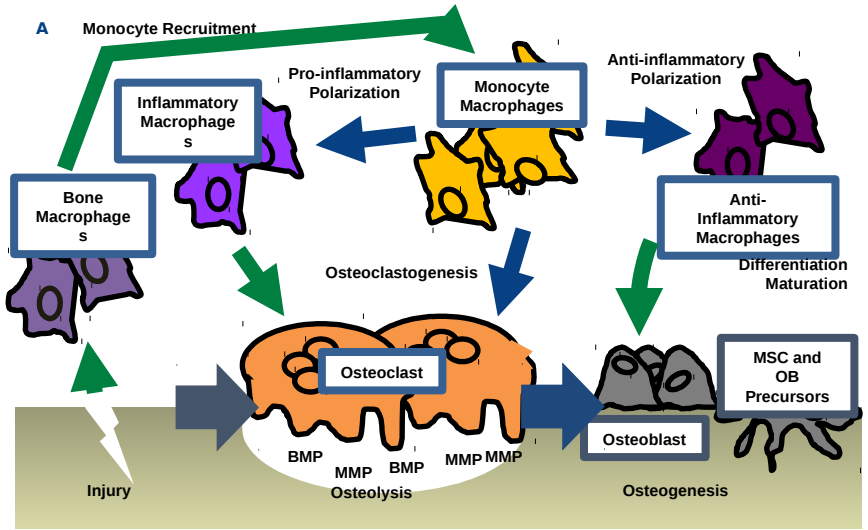


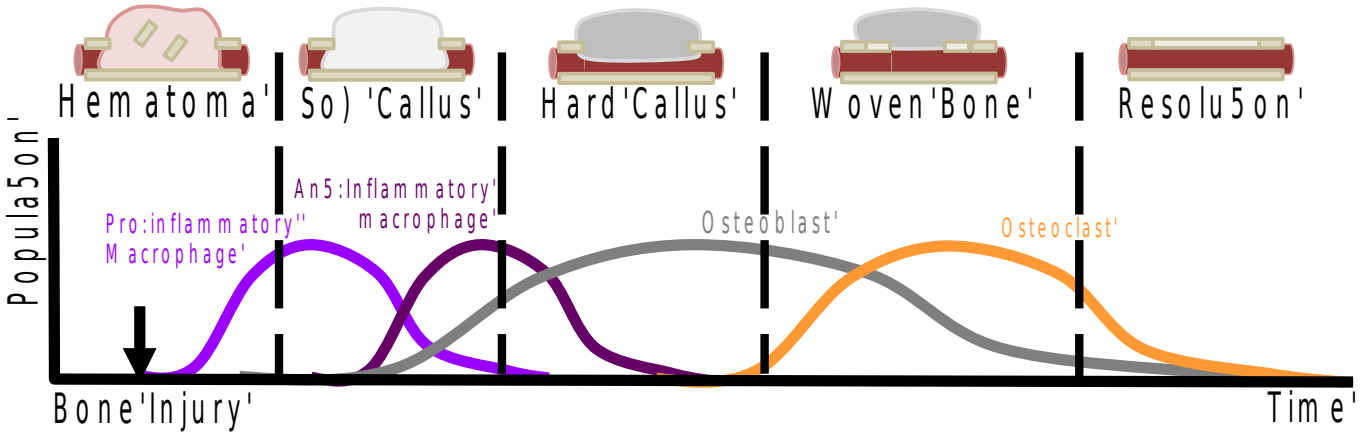
Credibility in multiscale modeling of bone environment response to metastatic cancer

David Basanta and Conor Lynch

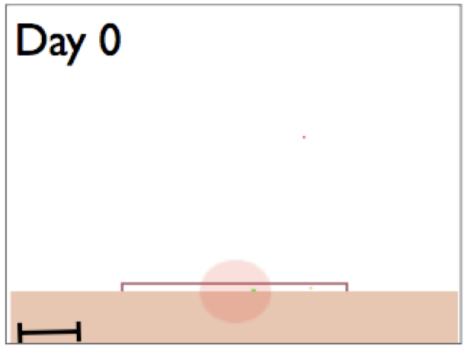
The problem

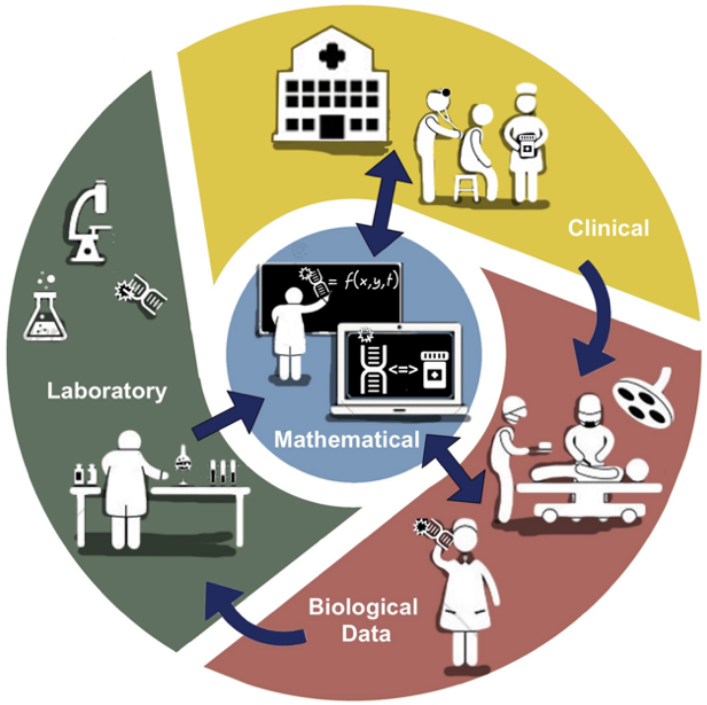

Blood vessel
TGFβ
Cancer cells
Precursor osteoblasts
Precursor osteoclasts
Osteoclast
Osteoblasts
Bone matrix
Mesenchymal stem cell
Osteocytes

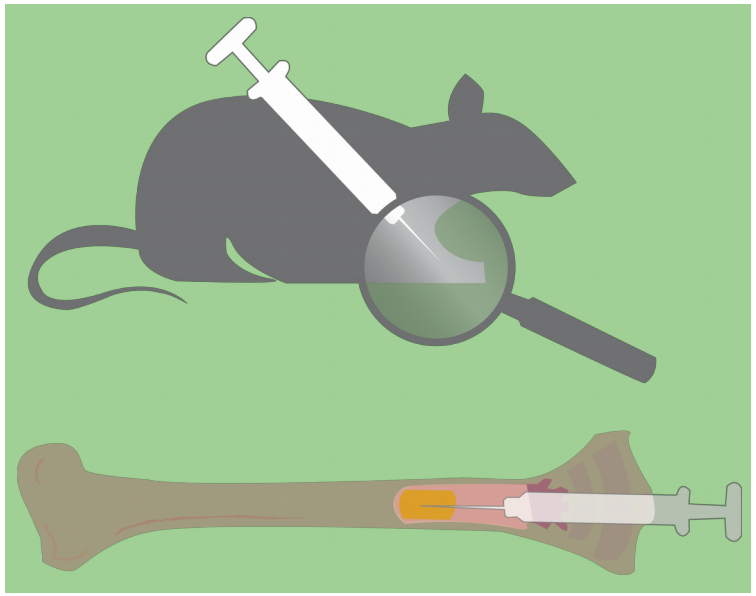

A
Monocyte Recruitment
Pro-inflammatory Polarization
Anti-inflammatory Polarization
Inflammatory Macrophages
Monocyte Macrophages
Bone Macrophages
Anti-Inflammatory Macrophages
Differentiation Maturation
Osteoclastogenesis
Osteoclast
MSC and OB Precursors
Osteoblast
BMP
MMP
BMP
MMP
MMP
Injury
Osteolysis
Osteogenesis

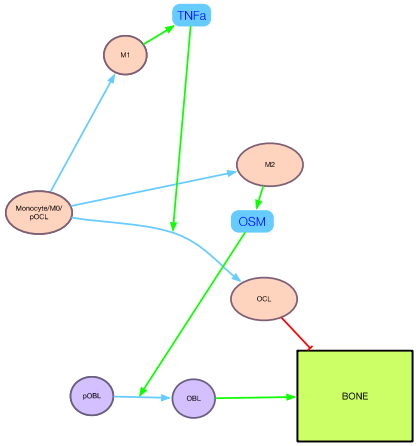

Hematoma
Soft Callus
Hard Callus
Woven Bone
Resolution
Population
Pro-inflammatory Macrophage
Anti-inflammatory macrophage
Osteoblast
Osteoclast
Bone Injury
Time

3 levels of credibility









$$\begin{pmatrix} & OB & OC & T & T_R \\ OB & & \alpha & \delta & \delta \\ OC & \beta & & & \\ T & & \gamma & \epsilon & \epsilon \\ T_R & & \gamma - r & \epsilon & \epsilon \end{pmatrix}$$

Multiscale Modeling of the Mammalian Circadian Clock: The Role of GABA Signaling, Michael Henson PI

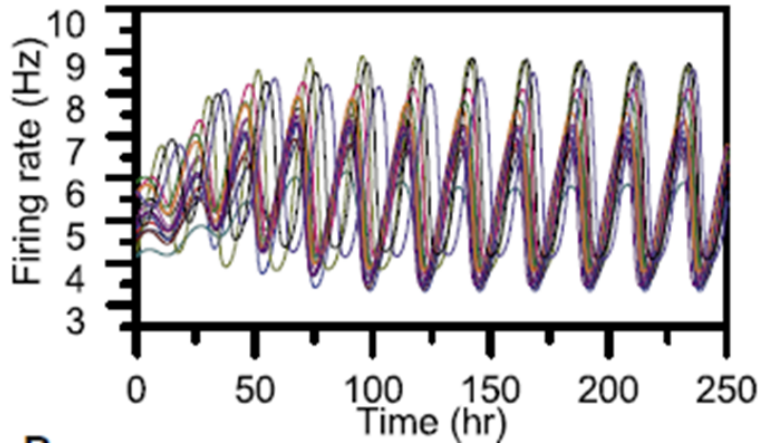
Plan Outline

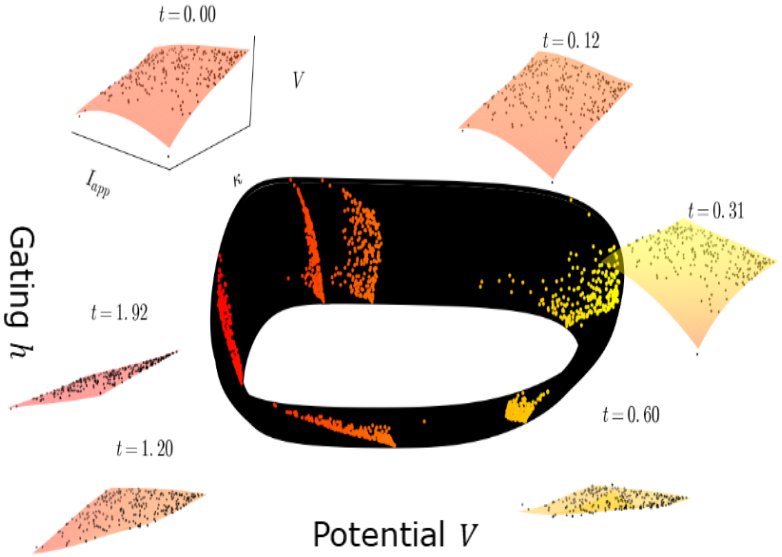
- MATLAB and C++ for initial development followed by conversion into SBML
- Model tool assessment metrics include synchronization & entrainment dynamics
- Simulation tool assessment metrics include flexibility, speed & integration with modeling codes

Changes & Uniqueness

- Modular code architecture
- Multiple PIs developing multiple codes using different languages
- Use of funded third-party evaluator outside the MSM consortium
- Questioning need for code conversion to SBML

Multiscale Modeling of the Mammalian Circadian Clock: The Role of GABA Signaling, Michael Henson PI





Challenges & Needs

- Translation of code between languages onerous
- An evaluator (Dr. Herbert Sauro) was identified for SBML code evaluation
- Need additional evaluators for MATLAB & C++ codes
- Partner with other funded circadian project

Building multi-level models of therapeutic response in the lungs

1 UO1 HL131046-01

Model Credibility Plan

Lightning Presentation

Tim Corcoran, Ph.D.

Pulmonary, Allergy, and Critical Care Medicine

Bob Parker, Ph.D.

Chemical and Petroleum Engineering

University of Pittsburgh

Study goal:

For Cystic Fibrosis, create in silico models to predict organ (lung) level therapeutic response based on response in nasal cell cultures.

Currently enrolling subjects to inform models:

Collecting cell level physiology/response data from nasal cells

Collecting organ level physiology/response from imaging studies, sweat chloride measurements, and pulmonary function tests.

First half of subjects informs model. Second half validates model.

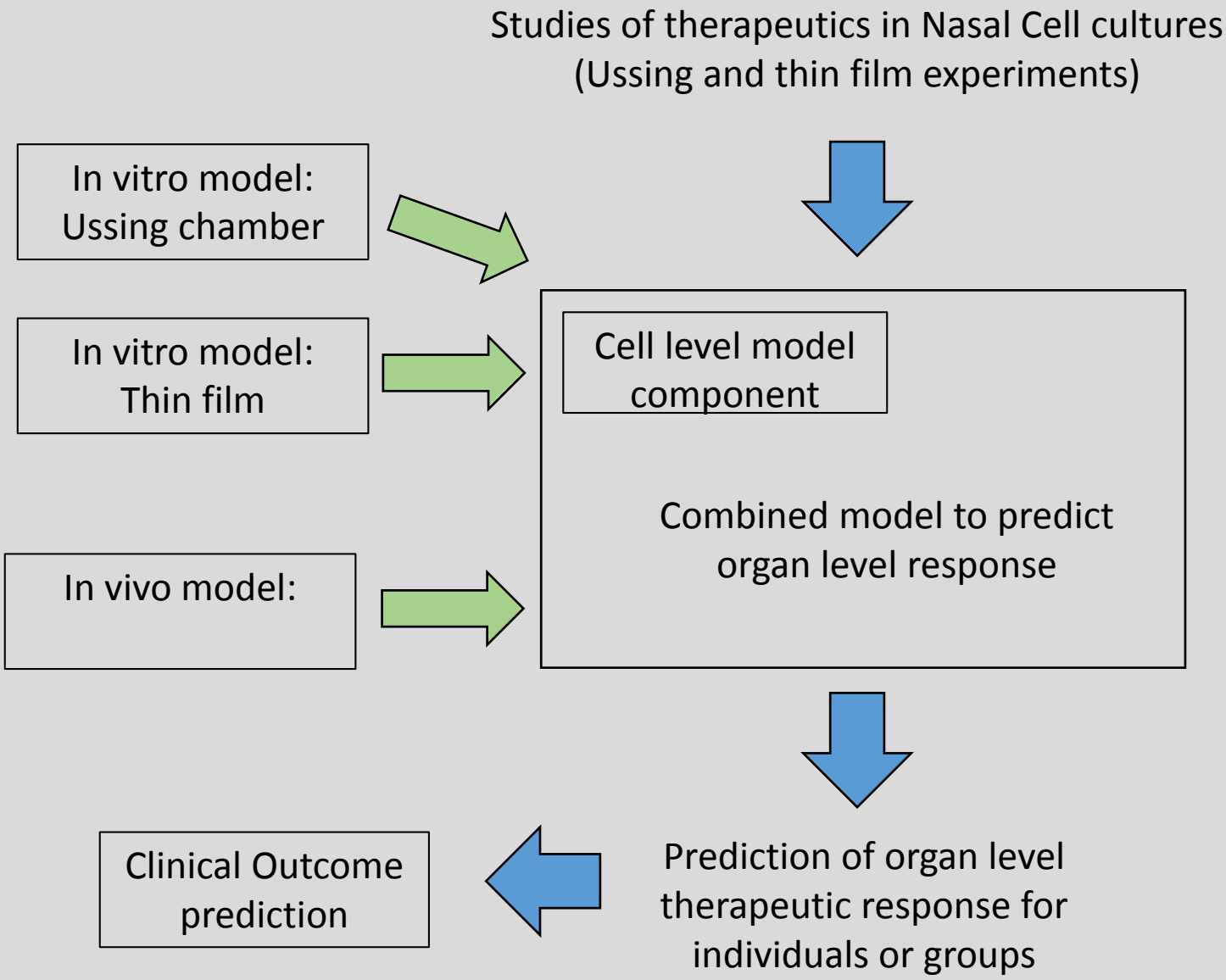
Enrollment:

group	Enrolled as of 3/2018	Planned total enrollment
CF patients	11	30
Single mutation carrier parents of CF patient	6	16
Healthy controls	12	16

Funding start 9/2016, First enrollment 1/23/17

Clinicaltrials.gov NCT02947126

Measurements and information flow for final model:



Model Credibility: Timeline and Milestones

- Existing, ready for review
  - organ-scale submodel (Markovetz *et al.*, PLoS One, 2014)
  - prospective validation will be conducted through our award

- In development (Lung 2017-18; nasal 2018-19)
  - cell-scale electrophysiologically-based submodel of human lung epithelia
  - extension to human nasal epithelia
  - extensibility of structure across populations (non-CF, carriers, CF patients)

- Planned (2019-2020)
  - integrated model, using nasal epithelial data to understand lung dynamics
  - development of model-based for treatment design

Model Credibility: Ideal Third-Party Evaluation Team

1. **systems engineering**, including experience constructing nonlinear dynamical models of physical systems using experimental data
2. **epithelial disease basic science**, ideally with cystic fibrosis and/or the lung, with a focus that may range from intracellular response to cell-scale regulation to systems-level (or organ-level) monitoring and disease progression
3. **clinical training**, with experience in pharmacologically-guided treatment of disease; it would be advantageous, but not necessary, to have lung disease/CF experience
4. **regulatory/industrial pharmacology/translational experience**, with a history of using mathematical models in concert with disease treatment

Cell-to-Macroscale, Clinical and Translational issues, Model and Data Sharing, and potentially the Theoretical and Computational Methods Working Groups

Python/Pyomo and C++ are our primary tools

Multiscale Modeling of Blood Flow and Platelet Mediated Thrombosis

PI: Danny Bluestein, **Co-PIs:** Marvin J. Slepian, Yuefan Deng

Credibility Plan: Validation of model parameters

- **Geometrical, rheological, and material properties** of coarse grained molecular dynamics (CGMD) platelet model validated using published **literature** and ***in vitro*** **experiments**
- In silico shear-mediated **platelet shape change** validated with **scanning electron microscopy** images of platelets exposed in **Hemodynamic Shearing Device (HSD)**
- Flow-mediated **platelet flipping, aggregation, and adhesion** models validated with high magnification **DIC microscopy** and **high framerate capture** of shear-mediated platelet behavior in **microchannels**
- **Antiplatelet agent-induced membrane fluidity** modeling validated using a **dielectrophoresis (DEP)** setup

Changes in Credibility Plan from Year 1

- **Platelet-platelet recruitment/aggregation** validated with flow-mediated platelet aggregation in microchannels
- **Machine learning** approaches to optimize **high performance computing (HPC)** and **aggregation prediction**.

Unique aspects of the credibility plan

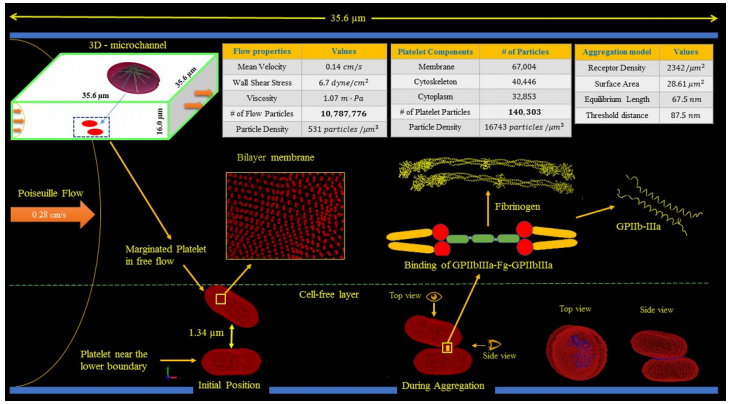
- Utilizes **in-house equipment** (HSD, DEP, DIC microscopy, and microchannel setup) for validation
- **Identifies and quantifies** the dominant sources of uncertainties, while **minimizing global uncertainties** arising from model and computational parameters
- Model parameters interfaced with ***in vitro*** observations via a **database**

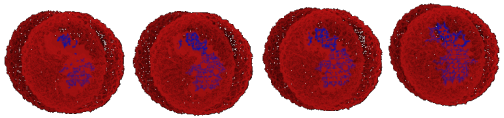
Determination of model parameters by correlating with *in vitro* results

Key Experimental Parameters	Key Independent Model Parameters	Adjustable Model Parameters
Properties: μ of plasma: 1.1~1.3 mPa·s at 37°C[229]. Diameter of platelet: 2~5 μm. Aspect ratio: ¼.	γ and r_{cut} in DPD correspond to resultant μ of plasma[230]. Current μ of plasma: 1.12 mPa·s. Diameter: 4 μm. Aspect ratio: ¼.	Increase γ to increase μ of plasma and r_{cut} needs to change accordingly. μ: viscosity.
Shape change (HSD and microchannel + microscopy/SEM): flow rate=> τ: 1~70 dyne/cm^2; exposure time: 0~480 sec; pseudopod length: 0.24~2.74 μm; number of pseudopods: 0~5; major axis: 2 ~3 μm; circularity: 0.9~1.0.	Couette flow shear stress: up to 400 dyne/cm^2. ts_{max} controls growth duration, α controls filopodia growth rate in response to shear stress-exposure time combinations[193], k_b - aspect ratio (range: 0.2~0.4), circularity (range: 0.8~1.0). r(ts,fb) and σ(ts, fb) controls pseudopod L-length and T-thickness.	Couette flow BCs adjusted for τ: shear stress; $\dot{\gamma}$: shear rate increase/decrease, k_b- change aspect ratio and circularity. r_0 – change pseudopod length L_{max} & T_{max}- converted to model parameter space=> >50 pesudopodia patterns- adjusted to expt. (***multiple parameters dependent on key parameters and change accordingly***).
Flipping experiments in microchannels - real time DIC microscopy (Jeffery's orbit $\phi(\dot{\gamma}t)$): shear stress: 0.2~100 (dyne/cm^2); flow rate: up to 17 cm/s.	γ in DPD and ε, σ in LJ potential controls the fluid-platelet interaction[230]. σ – key parameter controlling flipping platelets and their trajectory $\phi(\dot{\gamma}t)$. Flow rate: up to 15 cm/s.	Parameters are adjusted according to results from Jeffery's orbit. σ mainly controls the trajectory of flipping platelets. Other sub parameters change correspondingly[230]. $\phi(\dot{\gamma}t)$ is changed accordingly
Platelet stiffness with DEP: E = 1.93~6.88 KPa; ΔL/L: 0~0.2; Poisson's ratio: 0.25~0.35[231].	Bi-layered membrane: k_b=0.023 N/m, r_0 = 33 nm. Model values: E: from 1.14 KPa to total rigidity; ΔL/L: 0~0.5; Poisson's ratio: 0.37.	k_b adjusted by matching E of experiments. E: Young's modulus, L: axial diameter-deformability of platelet change correspondingly.
Micropipette aspiration[207]: γ=(2.9±1.4)×10^{-2} dyne/cm.	Stiffness of membrane controlled by spring force constant k_b. Model value γ from (3.3±0.9)×10^{-2} dyne/cm to total rigidity.	k_b adjusted to match the modulated elasticity of membrane in experiments. γ: shear elastic modulus.
μ of cytoplasm[232]: 4.1~23.9 mPa·s.	Morse potential[233]: control parameters include ε, α and R.	ε mainly controls μ. α takes empirical value (α=7). R- particles average distance.
Modulating membrane fluidity with antiplatelet agents (e.g., DMSO)-DEP+fluorescence measurements: E, γ change accordingly.	k_b of membrane changed (range 10^{-2} ~ ∞ N/m). Friction factor γ in membrane controls strength of adhesion forces between interacting particles.	Increase k_b to reflect membrane stiffness. Other parameters adjust accordingly. Platelets deformability adjusted, γ -adhesion properties are adjusted to corroborate experimental values for membrane.
Adhesion: microscopy of observed adhesion patterns (vasc. wall-cultured HUVEC + vWF + Fg +fibronectin. Device surface + Fg).	GPIIb/IIIa-vWF binding potential, GPIbα-vWF-GPIbα, f^A- adhesion force magnitude coefficient (time dependent), r_{ij}- inter-receptor distance, n_a- # of receptors, d_c- relaxation distance, vWF multimer, GPIIb/IIIa-Fg binding potential.	Up to 50,000 GPIIb/IIIa and 25,000 GPIB receptors, n_a controls receptor # - model patterns (plt-plt. and/or surface binding and number- r_{ij} adjusted to expt. $r_{ij} < d_c$; r_{ij} –distance between 2 receptors when 2 plts come in contact.).

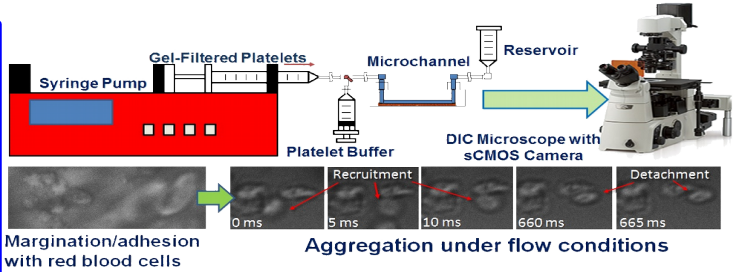
- Models interface with database of parameters recorded from platelet experiments
- Experimental results and model algorithms available on Harvard Dataverse (From Year 3)
- Considering storage/computation on Google Cloud Platform

Shear-Mediated Platelet Aggregation





Deformable platelet (contact area: 2.00 μm²)



Challenges and Review

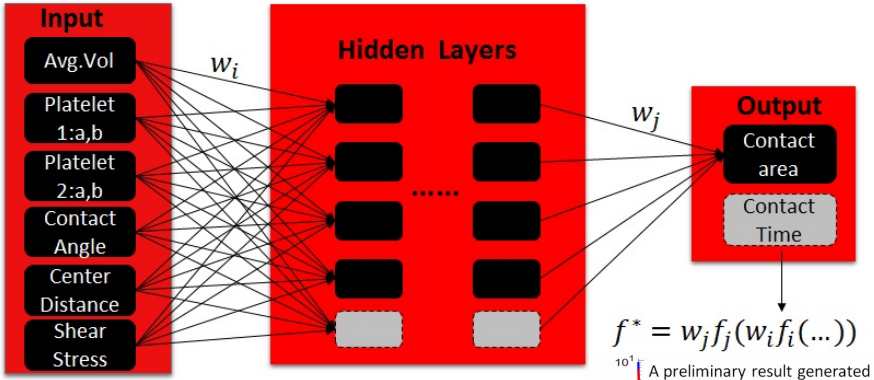
Challenges and Known Issues

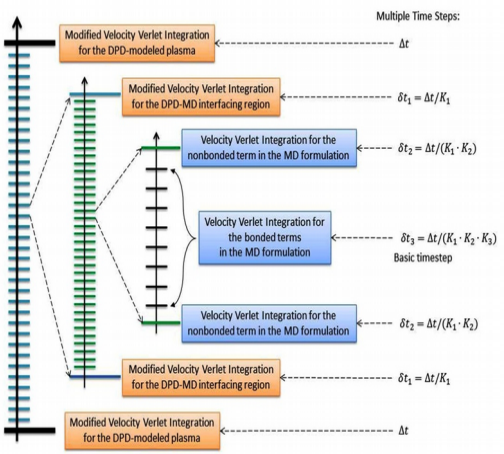
- Lack of techniques to observe platelet deformation, activation, aggregation, adhesion under flow conditions
- Large number of unknown parameters in the modeling and simulations
- Adapting discrete particle-based methods (DPD-CGMD) to describe continuum multiscale phenomena
- More Efficient Algorithms on HPC Resources: MTS (Multiple Time Stepping) + ATS (Adaptive Time Stepping)

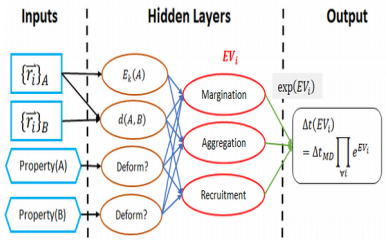
Requirements for Third Party Reviews

- Knowledge of LAMMPS molecular dynamics software
- Familiarity with both MD and DPD theory
- Familiarity with basics of platelet activation, aggregation, and adhesion
- HPC resources for large multiscale simulations

Machine Learning-Powered Solutions







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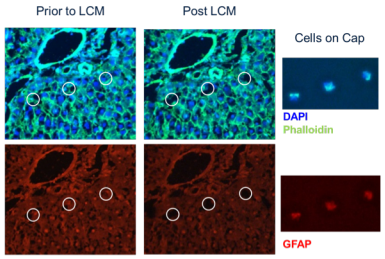
Philadelphia University +
Thomas Jefferson University

Modeling Multiscale Control of Liver Regeneration

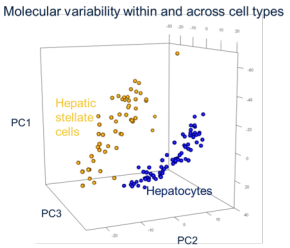
Jan B. Hoek and Rajanikanth Vadigepalli

Daniel Baugh Institute for Functional Genomics and Computational Biology
Department of Pathology, Anatomy, and Cell Biology
Thomas Jefferson University, Philadelphia, Pennsylvania

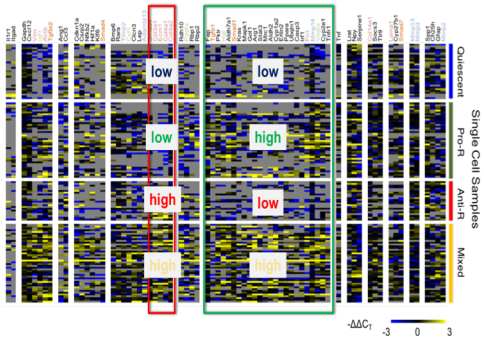
Laser Capture Microdissection



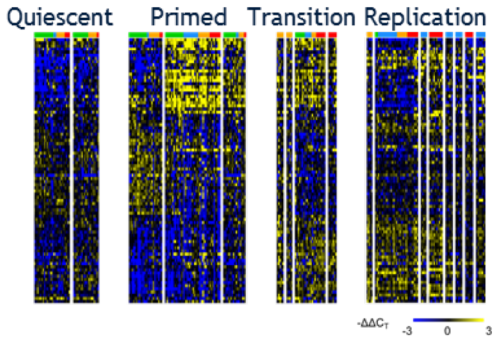
Cell Type Resolution



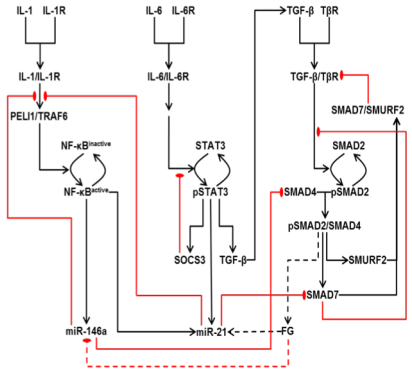
Hepatic stellate cell Single Cell Transcriptomics



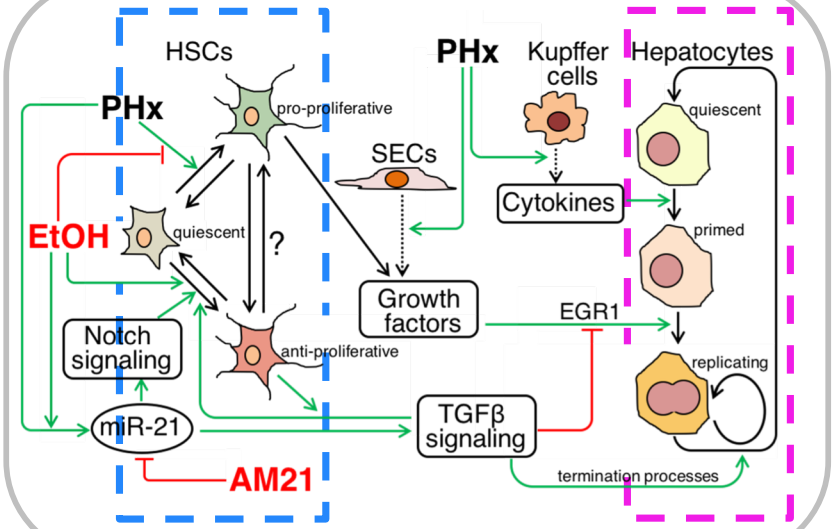
Hepatocyte Single Cell Transcriptomics



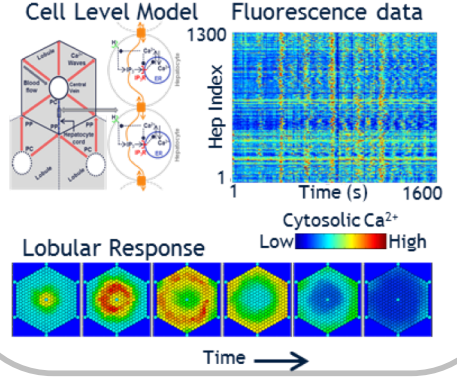
Cell-level Network Modeling of Cell Activation



Modeling Multiscale Control of Liver Regeneration



Spatial modeling of Lobular Scale Function



Credibility Plan – organized along Ten Simple Rules*

1	Define Context	Modeling molecular and cellular interaction network controlling liver regeneration response to injury. Specific details in the manuscripts.
2	Appropriate data	Single cell gene expression from multiple liver cell types; Spatial data from intravital imaging; Noninvasive measures of liver growth and function
3	Evaluate within context	Evaluate computational model for match to physiological data from liver resection in normal and alcoholic liver disease models
4	List Limitations	Assumptions and expected applicability are detailed in the manuscripts

* Committee on Credible Practice of Modeling and Simulation in Healthcare

Credibility Plan – organized along Ten Simple Rules*

5	Version Control	Manual and Limited; Need to systematize
6	Documentation	Manual and developer-dependent; Need to systematize
7	Dissemination	Model code and documentation available via manuscript supplement; Need to share through a generalized resource (BioModels?)
8	Independent Review	Members of lab not involved with project conduct independent review; Need to establish a systematic workflow for independent external review
9	Test Implementations	So far: Matlab, CompuCell3D, and SBML
10	Conform to Standards	Conform to the best practice standards of SBML and BioModels

* Committee on Credible Practice of Modeling and Simulation in Healthcare

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Multiscale Model of the Vagal Outflow to the Heart

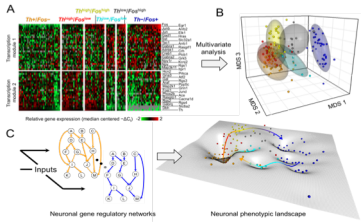
James S. Schwaber and Rajanikanth Vadigepalli

Daniel Baugh Institute for Functional Genomics and Computational Biology
Department of Pathology, Anatomy, and Cell Biology
Thomas Jefferson University, Philadelphia, Pennsylvania

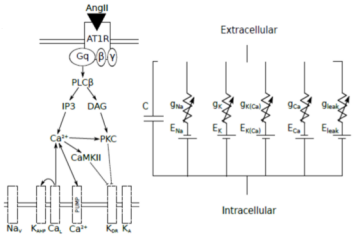
Modeling the Cardiac Vagal Control Loop
from Neuronal Gene Expression to Cardiac Physiology

Gene Network Dynamics → **Ion Channel Modulation** → **Neuron Response Phenotype** → **Model Integration** → **Cardiac Physiology**

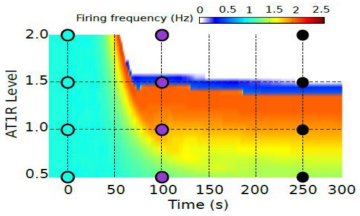
Co-expression networks



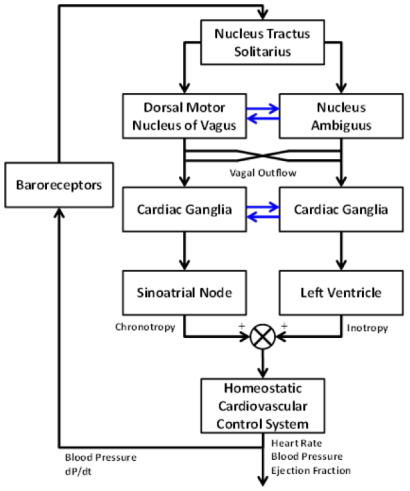
Signaling Pathways



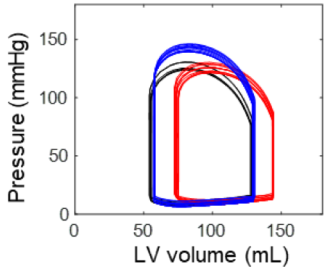
Single Gene Separatrix



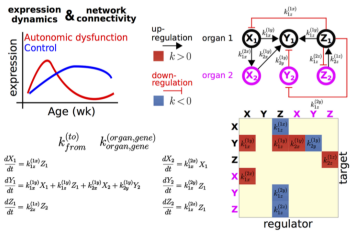
Conceptual Framework



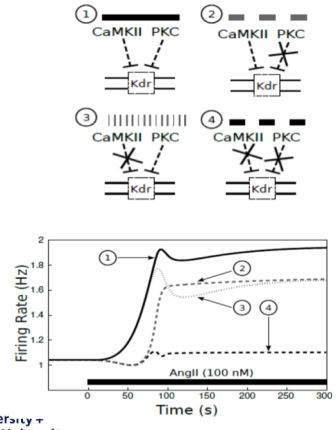
Cardiac Performance



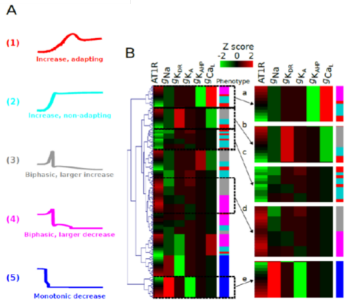
Expression Dynamics



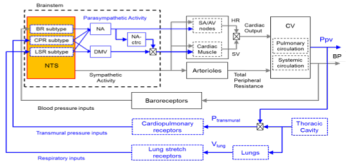
Modeling Influence



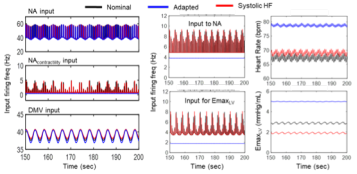
Gene Network Influences Firing Phenotype



Actual Implementation



Underlying Neuronal Firing Behavior



Credibility Plan – organized along Ten Simple Rules*

1	Define Context	Vagal control of cardiac function by neuronal populations that constitute the multilevel closed loop control circuit. Specific details in the manuscripts.
2	Appropriate data	Single neuron gene expression; Connectivity from tract tracing; Physiological data on cardiac functional parameters
3	Evaluate within context	Evaluate computational model for match to physiological data from essential hypertension and heart failure animal models.
4	List Limitations	Assumptions and expected applicability are detailed in the manuscripts

* Committee on Credible Practice of Modeling and Simulation in Healthcare

Credibility Plan – organized along Ten Simple Rules*

5	Version Control	Manual and Limited; Need to systematize
6	Documentation	Manual and developer-dependent; Need to systematize
7	Dissemination	Model code and documentation will be made available via ModelDB during and after peer review, as well as manuscript supplement
8	Independent Review	New members of the lab routinely review prior models as part of their initial training; Need to establish a systematic workflow for independent external review
9	Test Implementations	NEURON versus custom software in C++ from Drexel University
10	Conform to Standards	Conform to the best practice standards for ModelDB submission

* Committee on Credible Practice of Modeling and Simulation in Healthcare

Multiscale modeling to map cardiac electrophysiology between species

U01 HL136297

Eric Sobie, David Christini

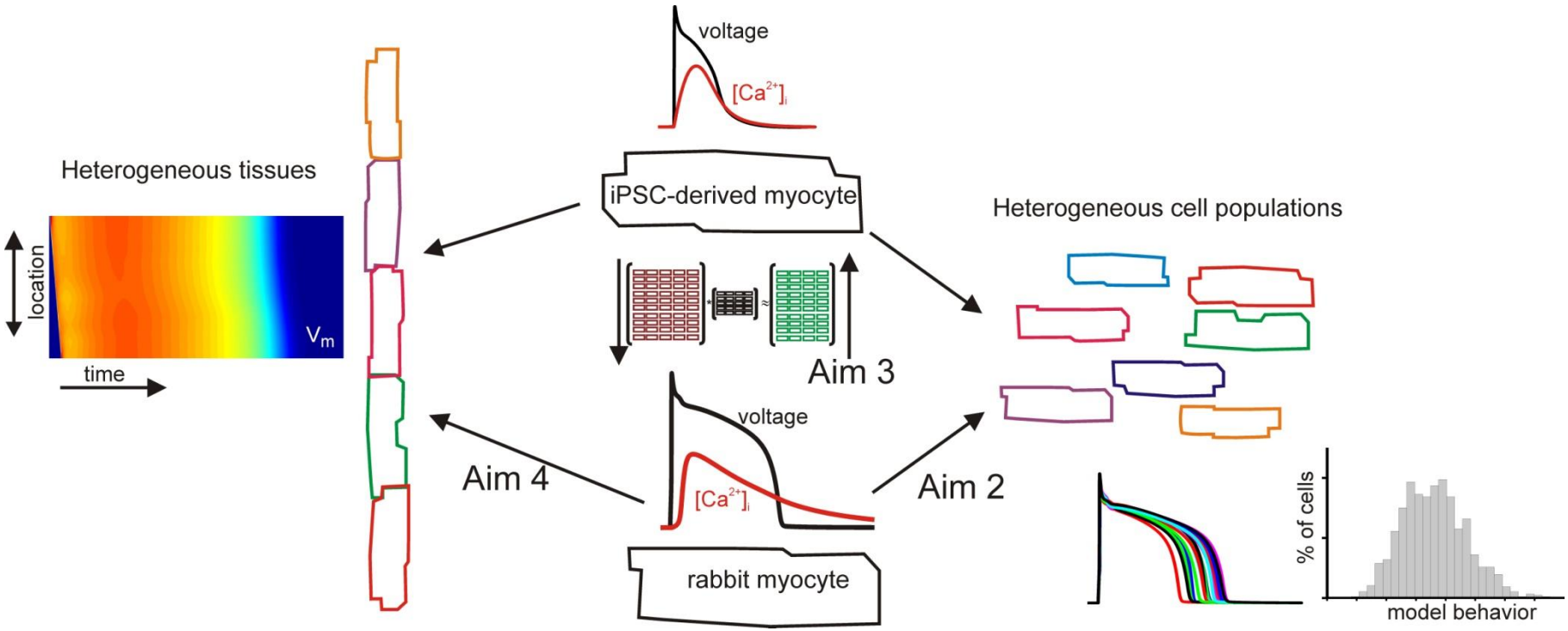
Model Credibility Lightning talk

Icahn School of Medicine at Mount Sinai

Weill Cornell Medical College

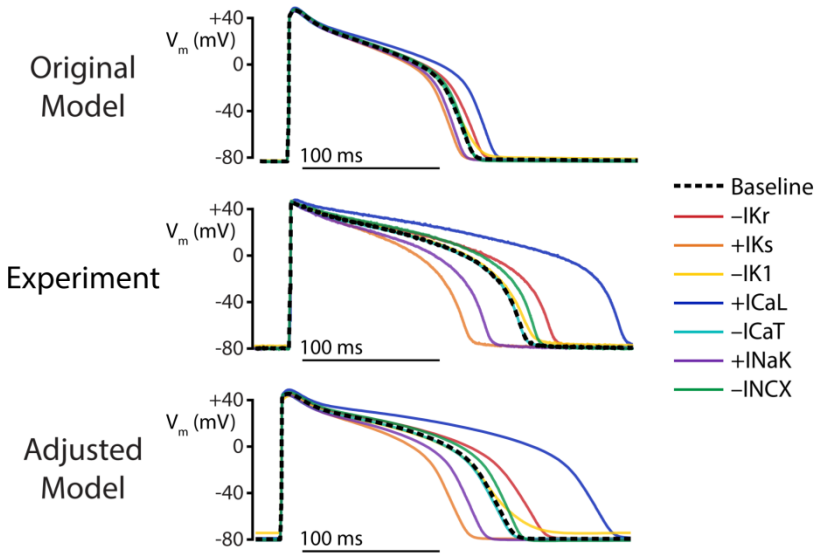
Project overview

Aim 1: Improve cellular models
Aim 2: Calibrate cell populations
Aim 3: Map behavior between species
Aim 4: Predict tissue-level consequences



Model credibility

Test 1: Perturb ionic currents to improve models



Test 2: Calibrate population behaviors

Test 3: Share code to enable 3rd party validation

npj | Systems Biology and Applications

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ARTICLE OPEN

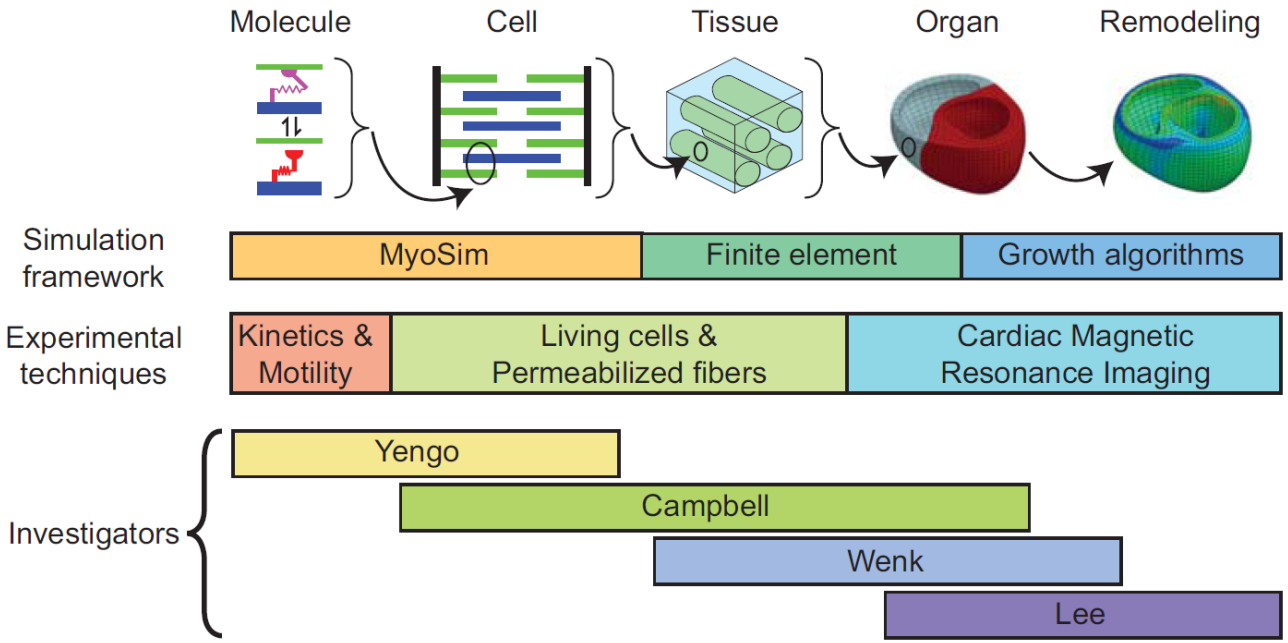
Population-based mechanistic modeling allows for quantitative predictions of drug responses across cell types

Jingqi Q. X. Gong[1] and Eric A. Sobie[1]

Multiscale Modeling of Inherited Cardiomyopathies and Therapeutic Interventions

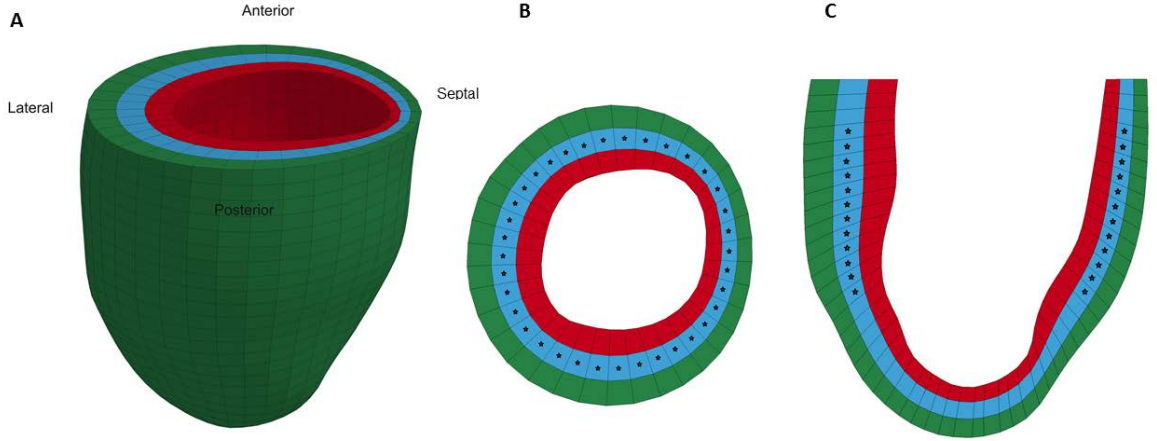
U01 HL133359 (Year 1)
Kenneth S. Campbell and Jonathan F. Wenk (University of Kentucky)

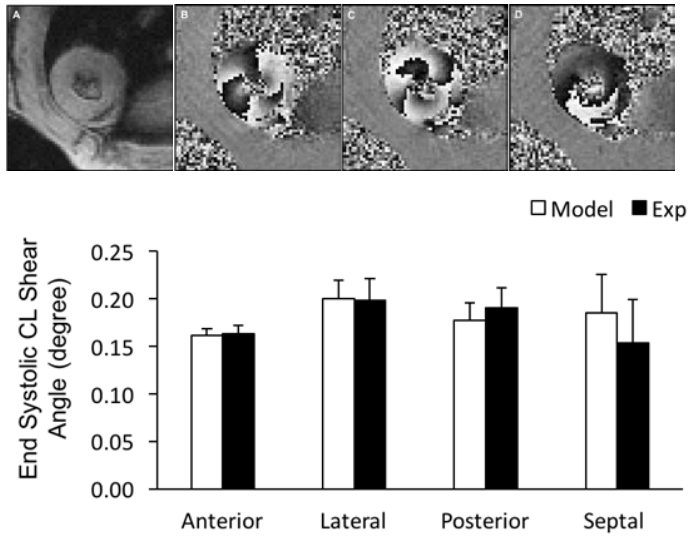
- Outline



- Unique aspects
  - Model the effects of two pharmaceutical treatments in clinical trial.
  - Model the effects of genetic mutation that causes HCM.

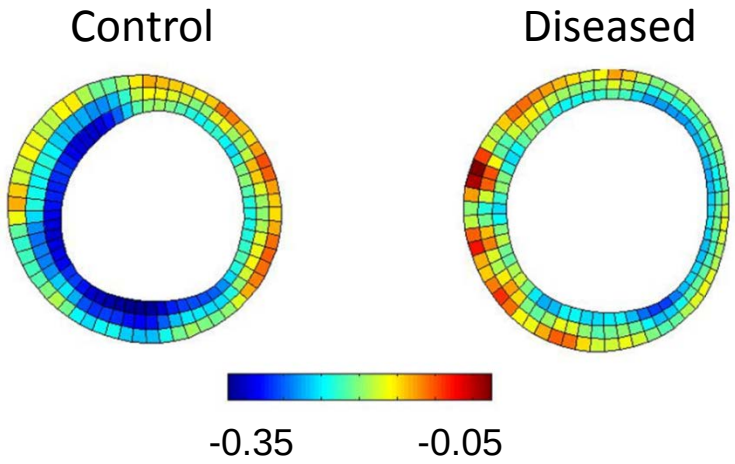
- Example Model Output and Comparative Metric
  - Organ level functional comparison between Model and MRI results





  - Compare the functional effects of genetic mutation or treatment to control

Circumferential Strain distribution



Multiscale modeling of cerebral blood flow and oxygen transport

PI: Timothy W. Secomb

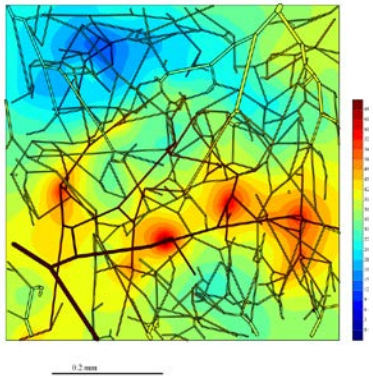
Aspects of model validity / credibility

Technical validity: are assumptions underlying the model accurately represented by the mathematical or computational method?

Biological credibility: does the model faithfully represent relevant aspects of the biological system behavior?

Technical validity

- Write-up of model developed in parallel with code
- Code tested against other methods and analytic solutions for special cases
- Extensive graphical outputs generated online



Biological credibility

- Close collaboration with experimentalists
- Parameterized for control state, predictions made for reduced blood pressure or blood oxygen levels
- Sensitivity analyses test model robustness
- Models as hypothesis tests: “failures” guide model development