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- NIH
  - NIBIB
  - CSR
  - NCI
  - NCRR
  - NHGRI
  - NIAID
  - NICHD
  - NIDA
  - NIDCD
  - NIEHS
  - NIGMS
  - NIMH
  - NINDS
  - NLM
- NSF
  - Eng
  - Bio
  - CISE
  - MPS
- NASA
  - HRP
- DOE
  - BER
  - ASCR
- DOD
  - Army
  - DARPA
  - TATRC
- USDA

Multiscale Modeling Grantees Meeting

February 6, 2006

IMAG

PI: Victor Barocas

Title: Multiscale Mechanics of Bioengineered Tissues

Institution: University of Minnesota

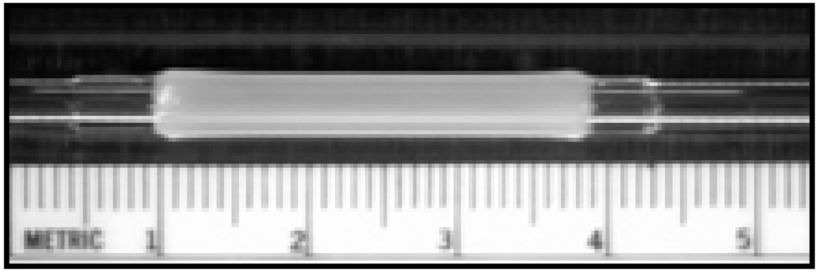
Funding Agency: NIH/NIBIB

Multiscale Mechanics of Bioengineered Tissues

- Victor Barocas, UMN
- Bob Tranquillo, UMN
- Mark Shepherd, RPI
- Jan Stegemann, RPI
- Joe Flaherty, RPI

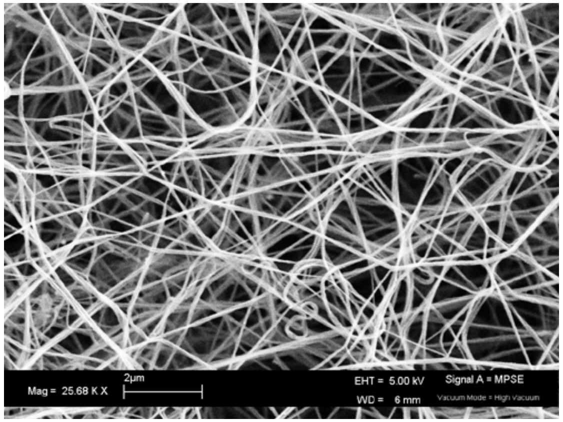
MISSION: To develop a modeling platform to describe the continuum-level mechanical behavior of an engineered tissue based on its microscopic-scale architecture

Matching Model to Scale

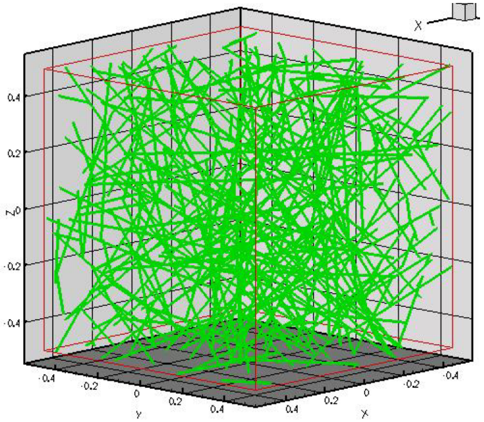


10^{-2} m

QuickTime™ and a
TIFF (LZW) decompressor
are needed to see this picture.

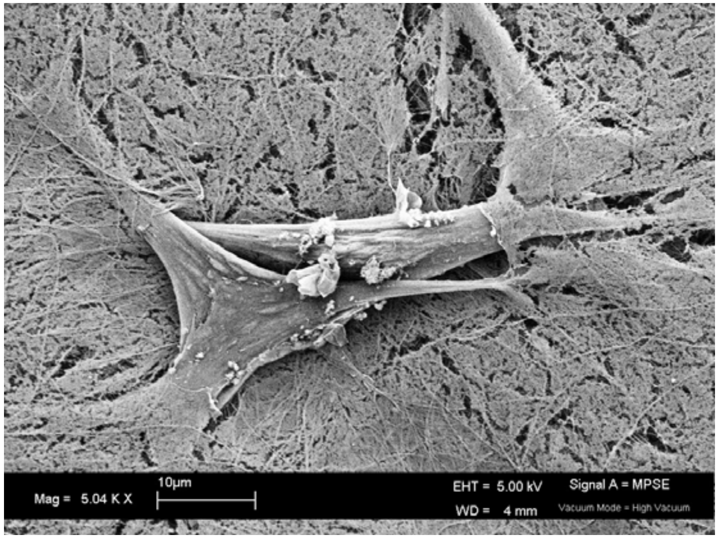


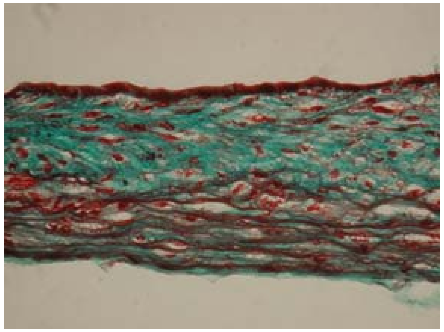
10^{-6} m



Current and Planned Work

- Incorporate multiscale model into adaptive framework
- Challenges for the upcoming year:
  - Better physical model
  - Multiple components
  - Cells
  - Spatial inhomogeneity





IMAG

PI: James Bassingthwaighte

Title: Adaptive Multi-Scale Model Simulation, Reduction and Integration for Cardiac Muscle Physiology

Institution: University of Washington

Funding Agency: NSF/BES

Adaptive Multi-Scale Model Simulation, Reduction and Integration for Cardiac Muscle Physiology

J. B. Bassingthwaighte, L. E. Atlas, H.J. Chizeck, H. Qian
University of Washington

Motivation: Multiscale modeling 'on the fly' (that is, in real time)

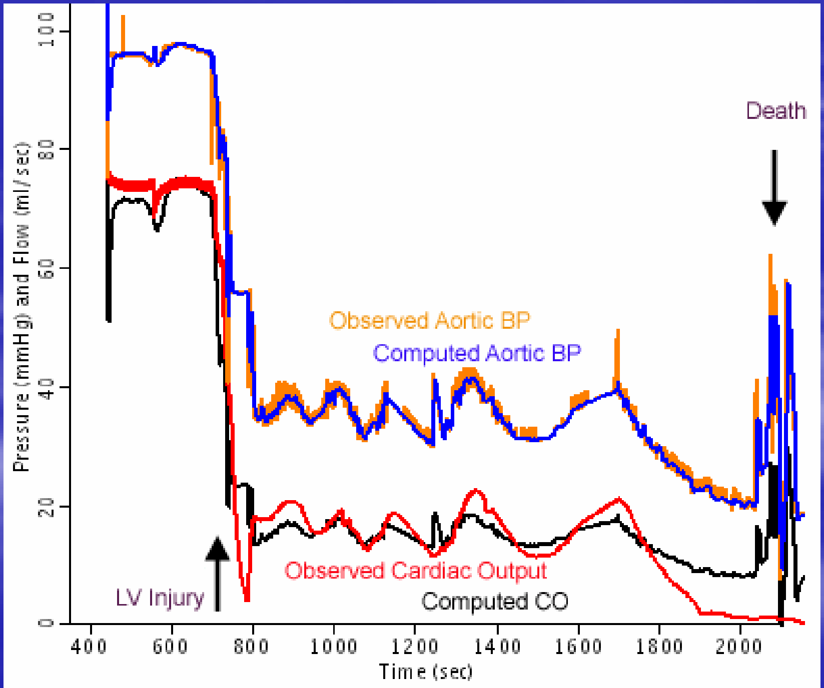
- Data-driven, real-time predictive model (for diagnosis, treatment, monitoring)
- **Potential applications:** in the operating room, the intensive care unit or (in the long term) for ambulatory use
- We need multiple levels of model reduction
- We want this process to be as fast as possible with specified accuracy and robustness.

Key elements of our approach:

1. Set of models (of different spatial and/or temporal scales) and software for simulating them
    - JSim modeling environment and extensions
2. Method of moving to a *more* complex model or submodel, during simulation
3. Method of moving to *less* complex model or submodel, during simulation
4. Detecting when an *increase* complexity is necessary (and for which submodels)
5. Detecting when a *decrease* in model or submodel complexity is acceptable

Planned Work and Outcomes

1. **Algorithms for Changing Model Complexity**
   - Approach involves use of constrained parameter identification
   - Constraints (equality and inequality), on relationships of variables and on allowable parameter values
2. **Algorithms for Detecting When to Change Model Complexity**
   - Approaches under investigation include SPRTs, and various machine intelligence methods
3. **Demonstration Examples**
   - Models, simulations, algorithms
   - Cardiovascular system
4. **Documented Software Package**
5. Dissemination



Model CO drives the model BP, to match the observed aortic BP. Validation of the model is shown by the match between model and observed CO.

IMAG

PI: Daniel Beard

Title: Multiscale Modeling of the Heart in Metabolic Syndrome and Cardiovascular Disease

Institution: Medical College of Wisconsin

Funding Agency: NIH/NIBIB

IMAG

PI: Marco Cabrera

Title: Time Course of Metabolic Adaptations during Loading and Unloading

Institution: Case Western Reserve University

Funding Agency: NASA

Introduction

- Chronic lack of a mechanical stimulus on “weight-bearing” muscles of astronauts during prolonged space travel leads to alterations in skeletal muscle structure, metabolism, and function.

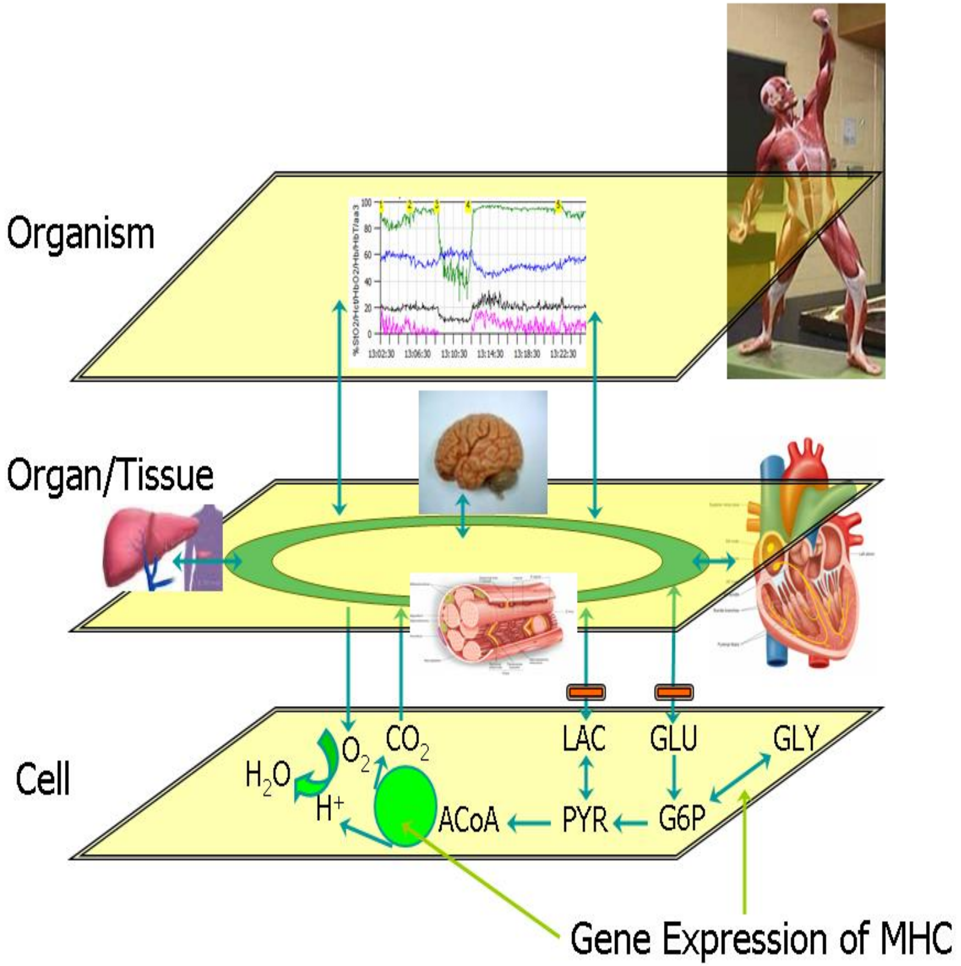
- Alterations span from
  - Cellular (expression MHC isoforms, I-IIa)
  - Skeletal Muscle Fibers (CSA, protein content)
  - Muscle (strength, endurance, insulin resistance)
  - Organism (work capacity)

Cabrera, Marco E. Time Course of Metabolic Adaptations during Loading and Unloading

Biomedical Significance

- The chain of events linking alterations at cellular, tissue, and organism level are not fully understood.
- Integrate multi-scale events represents
  - Challenge
  - Opportunity

for computational physiology



Specific Aims and Long-term Goal

- Develop multi-scale model of skeletal muscle metabolism
  - Cellular biochemical processes to muscle fibers
  - Muscle fibers (I, IIa, IIb, IIX) to whole muscle
  - Skeletal muscle + other organs metabolism to whole body function

- Predict integrated response of
  - muscle fibers
  - skeletal muscle
  - whole body

  at rest and during exercise, after periods of space travel.

- **Long-term Goal:** Develop an aspect of the *“Metabolome”* component of the *“Digital Astronaut”*

Cabrera, Marco E. Time Course of Metabolic Adaptations during Loading and Unloading

IMAG

PI: George Karniadakis

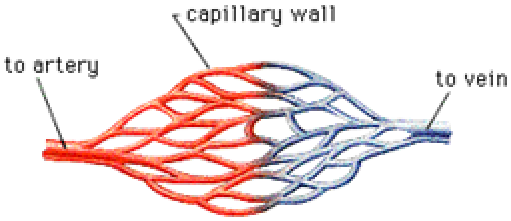
Title: A Stochastic Molecular Dynamics method for multiscale modeling of blood platelet phenomena

Institution: Brown University

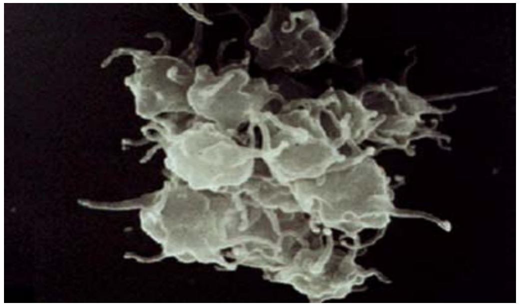
Funding Agency: NSF/DMS

A stochastic Molecular Dynamics method for multiscale modeling of blood platelet phenomena

- **PIs**: G.E. Karniadakis, P.D. Richardson, M.R. Maxey
- **Collaborators**: Harvard Medical School, Imperial College, Ben Gurion

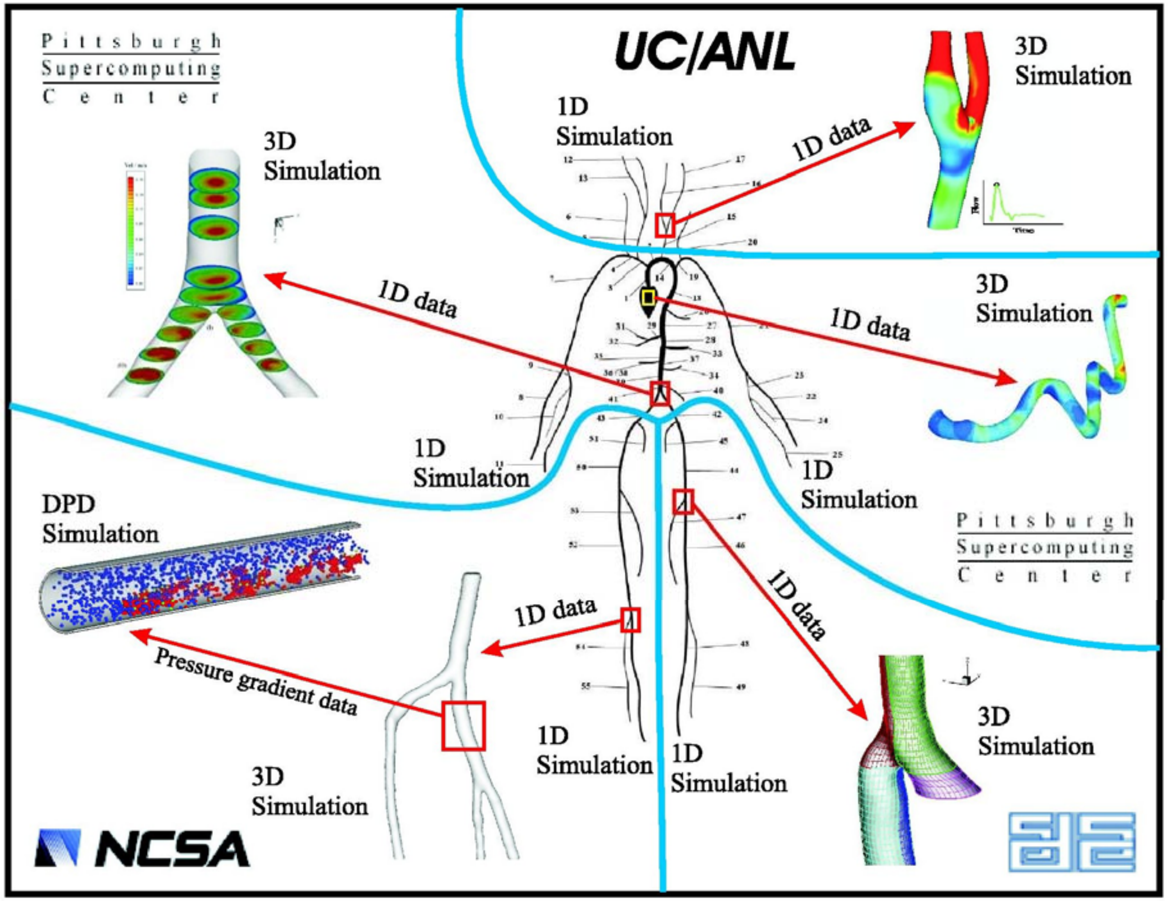


- Arterioles/venules 50 microns



activated platelets

- **Platelet diameter is 2-4 μm**
- **Normal platelet concentration in blood is 300,000/mm^3**
- **Functions: activation, adhesion to injured walls, and other platelets**



- Multiscale Simulation of Arterial Tree on TeraGrid

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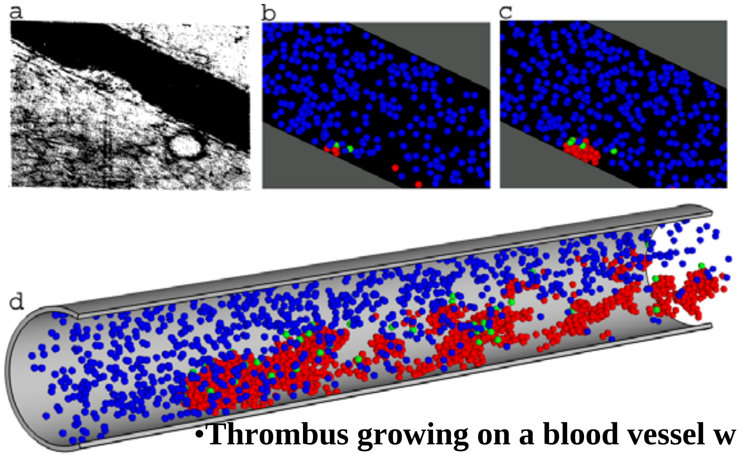
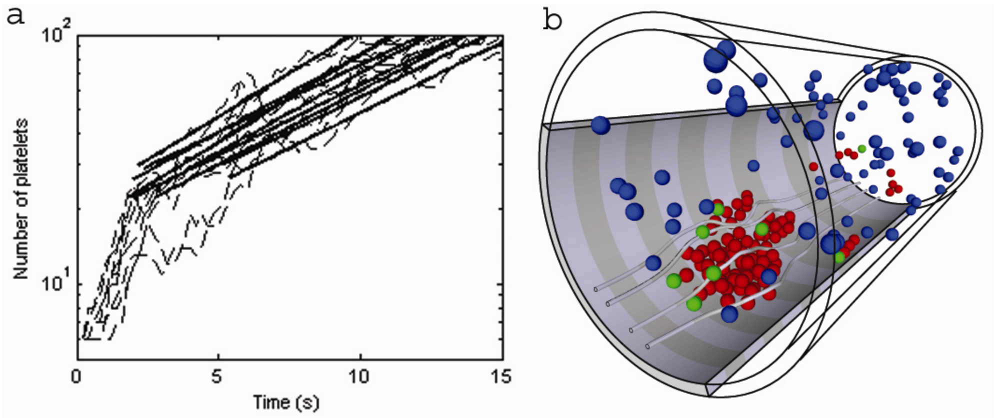
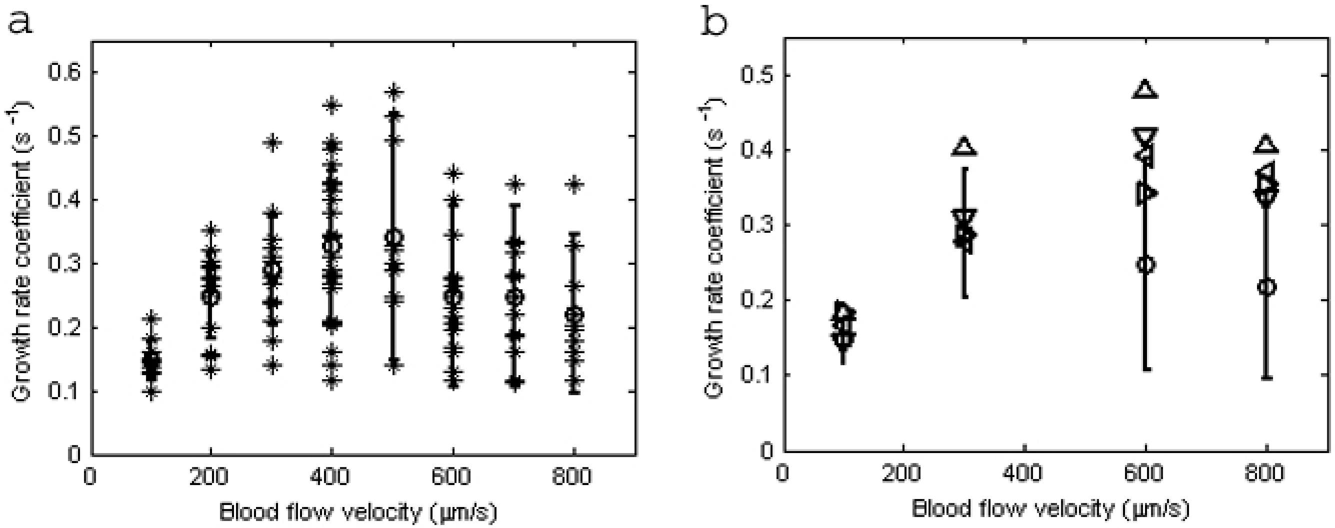
Stochastic Model - First Simulation of Begent & Born Experiment



- Thrombus growing on a blood vessel wall in vivo

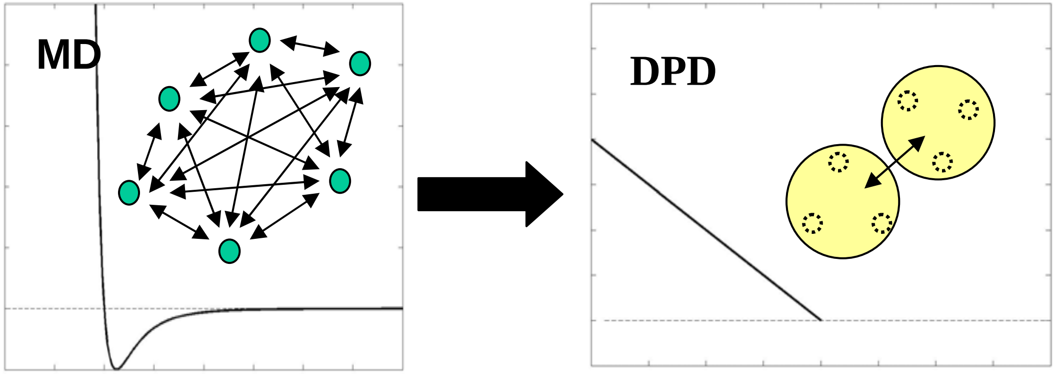


- Accumulation of platelets in a thrombus



- Exponential thrombus growth rate coefficients -- effects of pulsation (right)

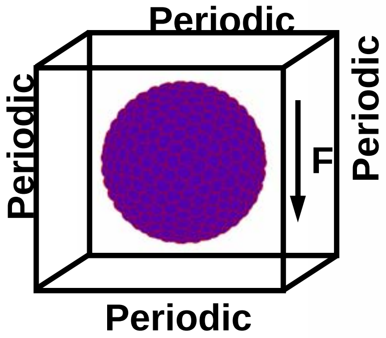
Dissipative Particle Dynamics (DPD) – Coarse-Grained MD

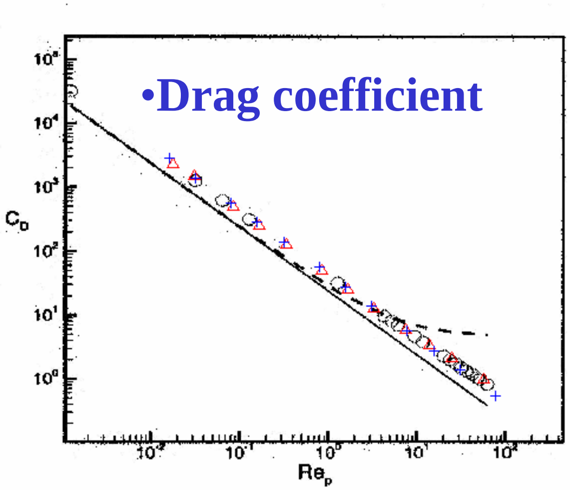


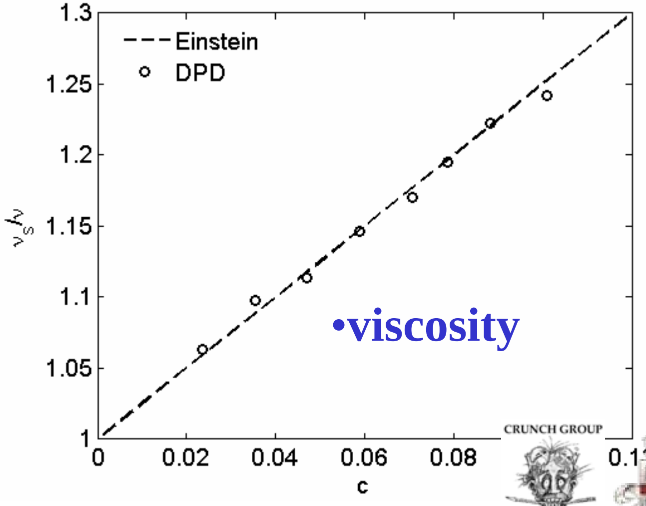
- **Momentum-conserving**
- **Galilean-invariant**
- **Off-lattice**
- **Soft-potentials**

- **Conservative** $\vec{F}_{ij}^{C} = F_{ij}^{(c)}(r_{ij})\vec{e}_{ij}$
- **Dissipative** $\vec{F}_{ij}^{D} = -\gamma\omega^{D}(r_{ij})(\vec{v}_{ij}\cdot\vec{e}_{ij})\vec{e}_{ij}$
- **Random** $\vec{F}_{ij}^{R} = \sigma\omega^{R}(r_{ij})\xi_{ij}\vec{e}_{ij}$

- **Speed-up w.r.t. MD (N mol/DPD)**
- 1000 x $N^{8/3}$; e.g. N=10: **500,000 times**







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References on Dissipative Particle Dynamics

- E. Keaveny, I. Pivkin, M.R. Maxey and G.E. Karniadakis, “A comparative study between dissipative particle dynamics and molecular dynamics for simple- and complex-geometry flows”, J. Chemical Physics, vol. 123, p. 104107, 2005.
- I. Pivkin and G.E. Karniadakis, “A new method to impose no-slip boundary conditions in dissipative particle dynamics”, J. Computational Phys., vol. 207, pp. 114-128, 2005.
- V. Symeonidis, G.E. Karniadakis and B. Caswell, “A seamless approach to multiscale complex fluid simulation”, Computing in Science & Engineering, pp. 39-46, May/June 2005.
- V. Symeonidis, G.E. Karniadakis and B. Caswell, “Dissipative particle dynamics simulations of polymer chains: Scaling laws and shearing response compared to DNA experiments”, Phys. Rev. Lett., vol 95, 076001, 2005.
- V. Symeonidis & G.E. Karniadakis, “A family of time-staggered schemes for integrating hybrid DPD models for polymers: Algorithms and applications”, J. Computational Phys., to appear.
- I. Pivkin and G.E. Karniadakis, “Coarse-graining limits in open and wall-bounded DPD systems”, J. Chemical Physics, submitted.
- I. Pivkin and G.E. Karniadakis, “ Controlling density fluctuations in wall-bounded DPD systems, Phys. Rev. Lett., submitted.

IMAG

PI: Andrew McCulloch

Title: Multi-scale modeling of the mouse heart: from genotype to phenotype

Institution: UCSD

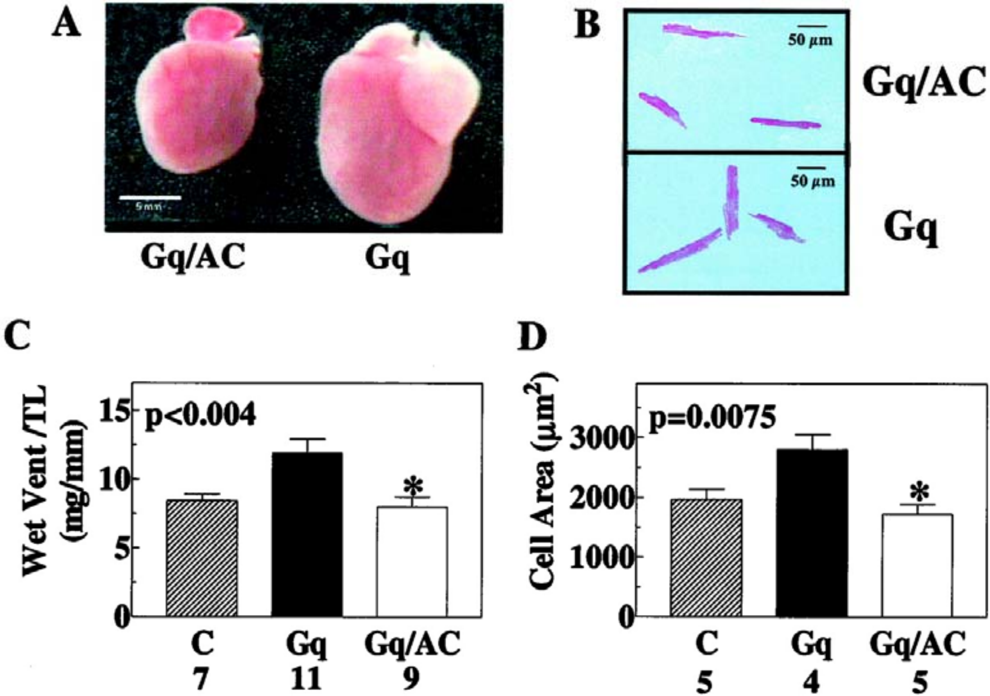
Funding Agency: NSF/BES

Cardiac Mechanics Research Group

UCSD Jacobs | Bioengineering & The Whitaker Institute

Multi-scale modeling of the mouse heart: From genotype to phenotype

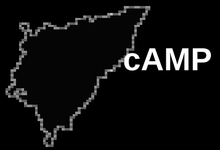
Andrew McCulloch, UCSD; H. Kirk Hammond, UCSD VAMC
Tom Borg, Bob Price, University of South Carolina

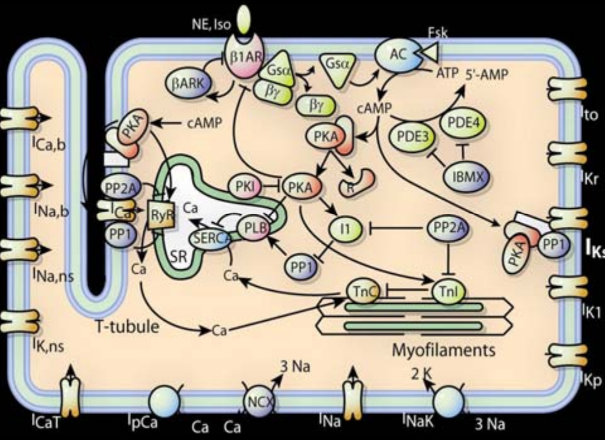


Roth, D. M. et al. Circulation 2002;105:1989-1994

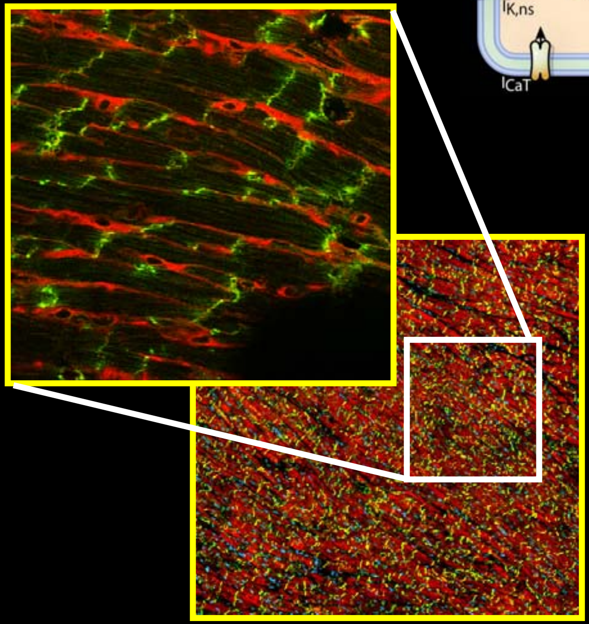
Interagency Modeling and Analysis Group
Multi-Scale Modeling Grantees Meeting
February 6th, 2005, NSF

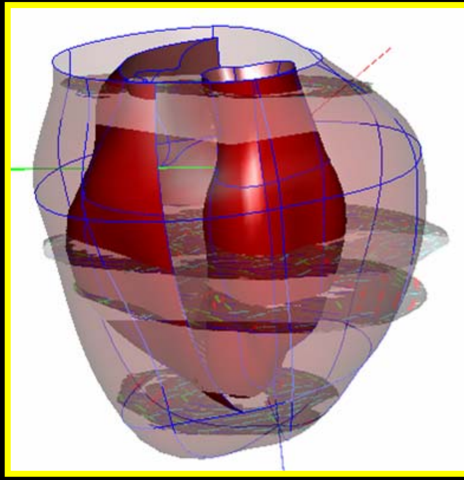
Structural and Functional Integration

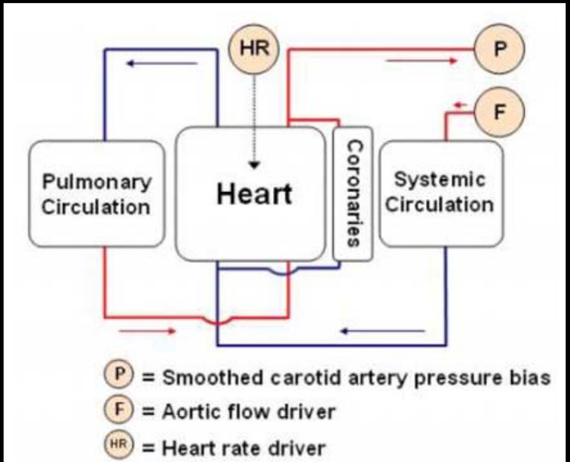




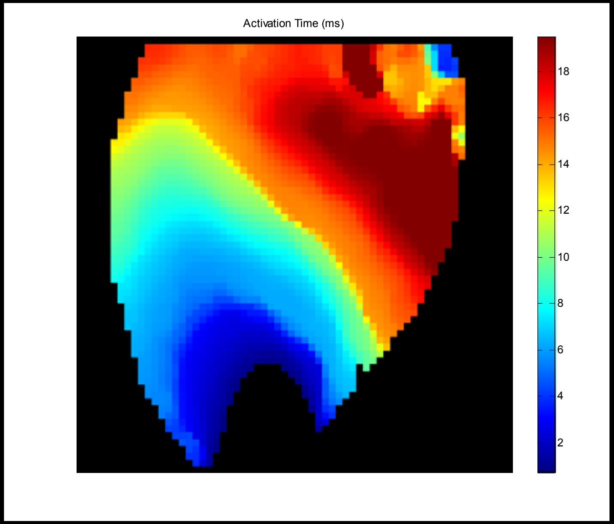
1. Mechanistic biochemical models of molecular regulatory networks
2. Biophysical common pool models of whole myocyte excitation-contraction coupling mechanisms
3. Microstructurally-based constitutive models of anisotropic tissue electrical and mechanical properties
4. Three-dimensional continuum models of left and right ventricular electromechanics that include 3D muscle fiber and sheet orientations
5. Systems models of circulatory hemodynamics



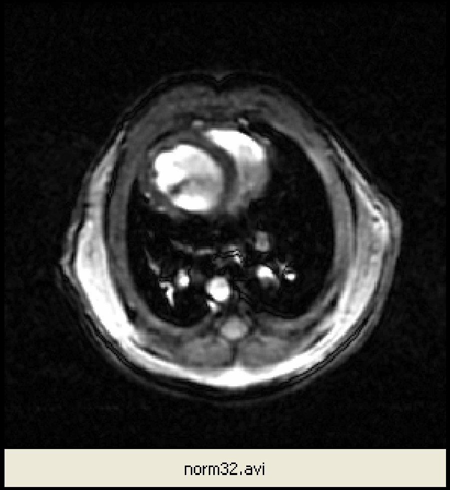




Experimental Validation



High-Speed Optical Mapping



High-Field MR Imaging

IMAG

PI: Robert Kunz

Title: Multiscale Human Respiratory System Simulations to Study the Health Effects of Aging, Disease and Inhaled Substances

Institution: Pennsylvania State University

Funding Agency: NIH/NIEHS

Multi-Scale Human Respiratory System Simulations to Study the Health Effects of Aging, Disease and Inhaled Substances

Robert F. Kunz[1], Daniel C. Haworth[1], Andres Kriete[2]

[1] Penn State University, USA, [2] Drexel University

MSM PI Meeting, Arlington, VA, 6 February 2006

Project goal: Develop, couple, apply, and validate medical imaging and physics modeling of resolvable and sub-resolvable scales in human respiration.

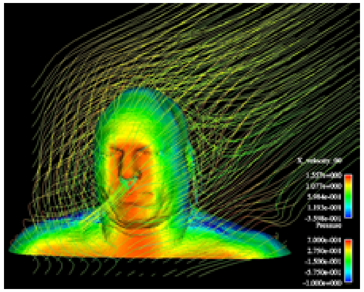
- High-resolution computed tomography (HRCT) will be used to characterize the “macroscale” convective range geometry of the lung.
- Microscopic computed tomography (µCT) and confocal microscopy (CLSM) will be used to characterize the “microscale” global and cellular architectures of the respiratory units.
- Multiphase computational fluid dynamics (CFD), and quasi-one-dimensional (Q1D) functional modeling will be used to simulate the multi-component fluid mechanics at these macro and micro scales, respectively.
- Software infrastructure and two-phase fluid mechanics models will be developed to address the coupling between the physics at these two scales. Model predictions will be validated against experimental and clinical data from the literature.

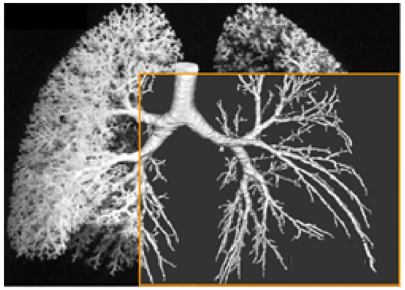
Elements of Program

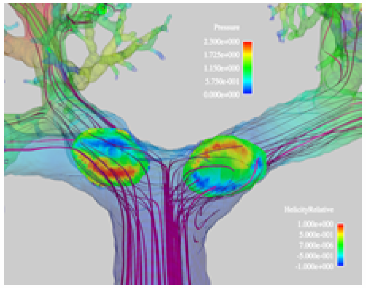
Upper Respiratory System:

Near-field, oro-nasal pharyngeal cavities, bronchi generations 0 to ~15

Time-dependent, 3D, multi-phase Navier-Stokes CFD modeling







Number, size distribution and spatial distribution of convective regime termial bronchi, inhalation constituent concentration and velocities rates to respratory units

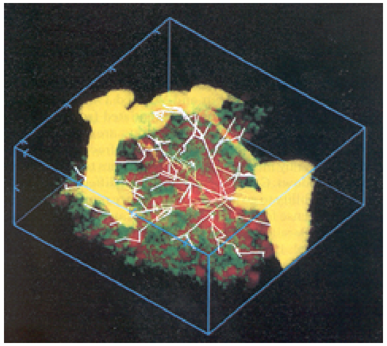
Inter-Scale Data Transfer

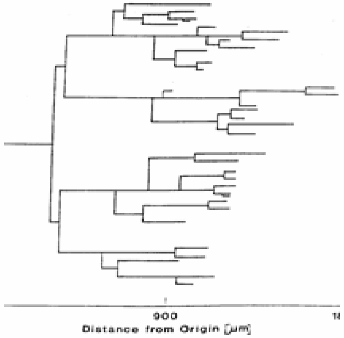
Pressures, effective volumes, exhalation constituent concentration and velocities to convective regime bronchi

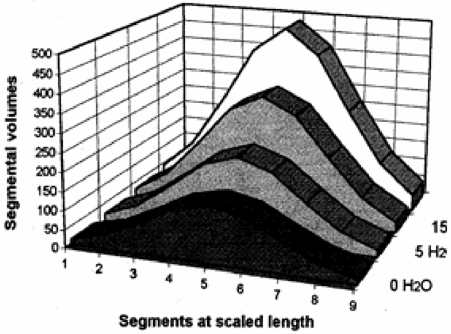
Respiratory Units:

Bronchi generations ~15 to ~24

Q1D functional sub-models







ARL
Penn State

Elements of Program

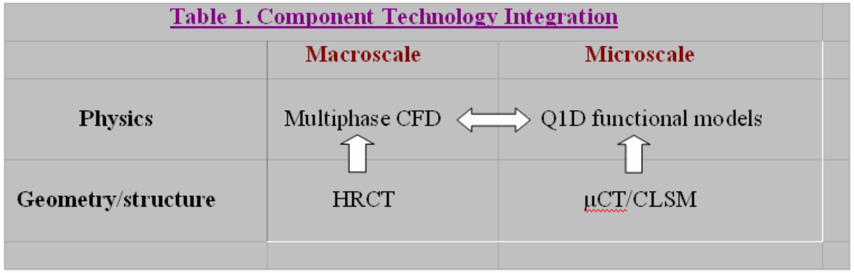
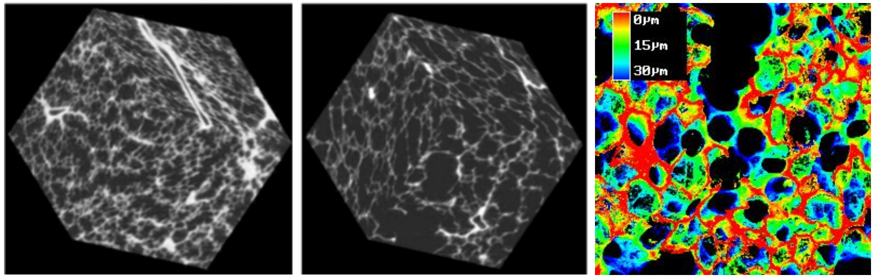
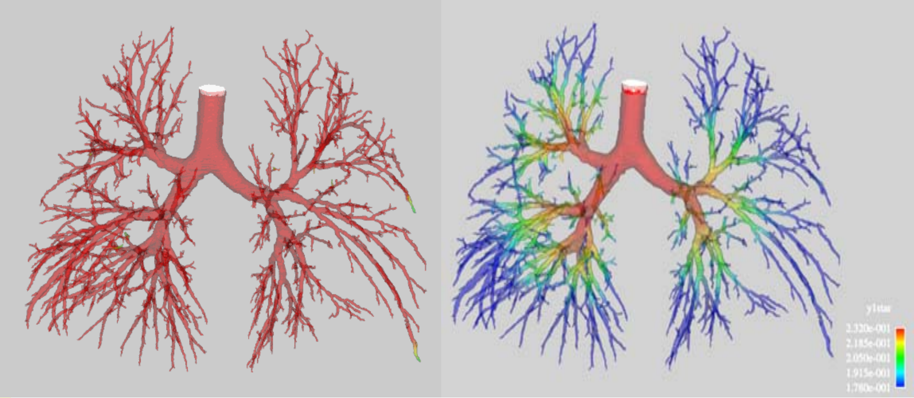


Table 1. Component Technology Integration

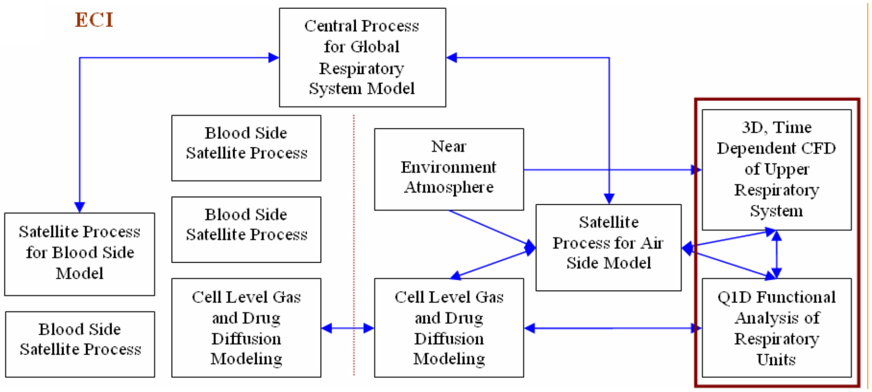
	Macroscale	Microscale
Physics	Multiphase CFD ⟺	Q1D functional models
	⇧	⇧
Geometry/structure	HRCT	µCT/CLSM



Micro-CT renditions of a 25-year-old control lung (left) and a76-year-old lung (middle). CLSM image stack of alveoli in lung color-coded for depth (right)

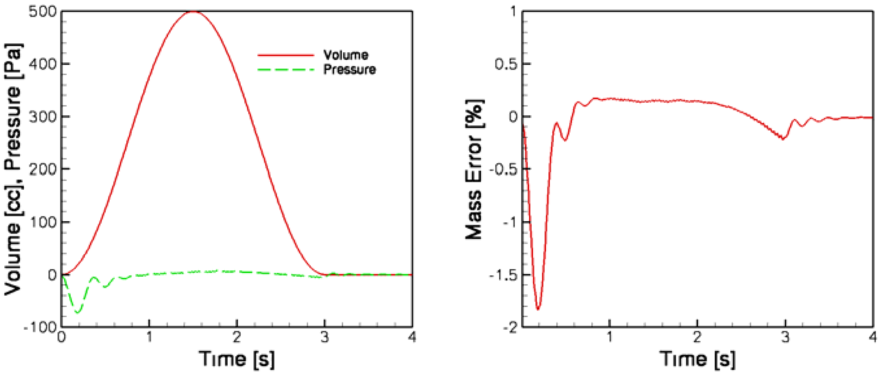


Unsteady oxygen uptake CFD simulations



Exterior Communications Interface (ECI) process connectivity for respiratory system analysis

Quasi-1D modeling of effective respiratory unit volume through one breathing cycle using a control feedback algorithm



IMAG

PI: Ching-Long Lin

Title: Multiscale simulation of gas flow distribution in the human lung

Institution: University of Iowa

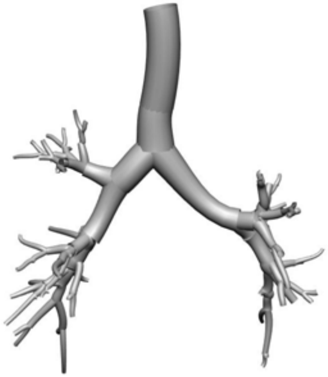
Funding Agency: NIH/NIBIB

NIH MSM Multiscale simulation of gas flow distribution in the human lung

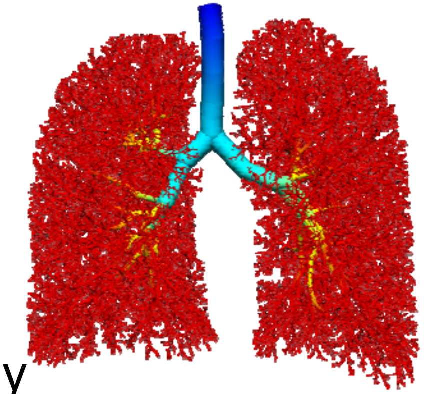
Specific Aims

- Establish efficient techniques for generating subject-specific computational meshes for CFD analysis, including mesh construction of conducting airways from CT images and synthesized airways beyond the limitation of CT resolution using a volume-filling algorithm;
- Integrate the custom developed 3D CFD model to the one-dimensional (1D) gas transport model by developing an efficient algorithm to facilitate 3D to 1D coupling (large to small airways) or 1D to 3D coupling (bronchioles to alveolar ducts) for multiscale simulation;
- Develop and experimentally validate a new predictive model of ventilation distribution by linking 3D CFD models to dynamic imaging of ventilation, via 1D flow models;
- Make available the coupling algorithms and databases to the research and clinical communities.

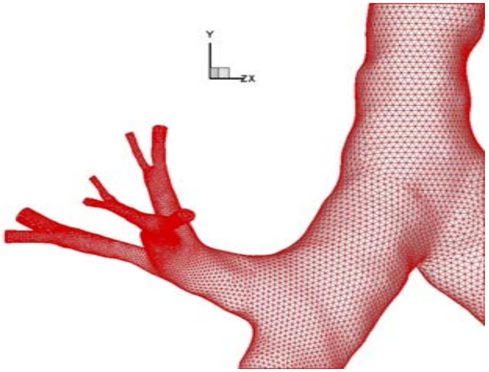
Multi-Scale Modeling for Ventilation



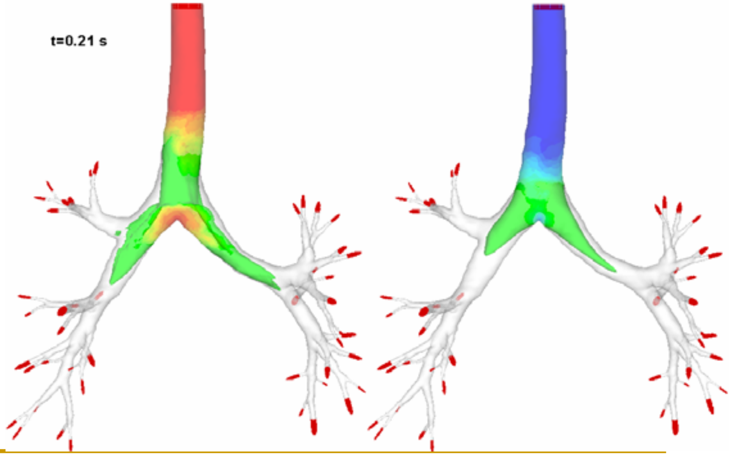
1D Poiseuelle



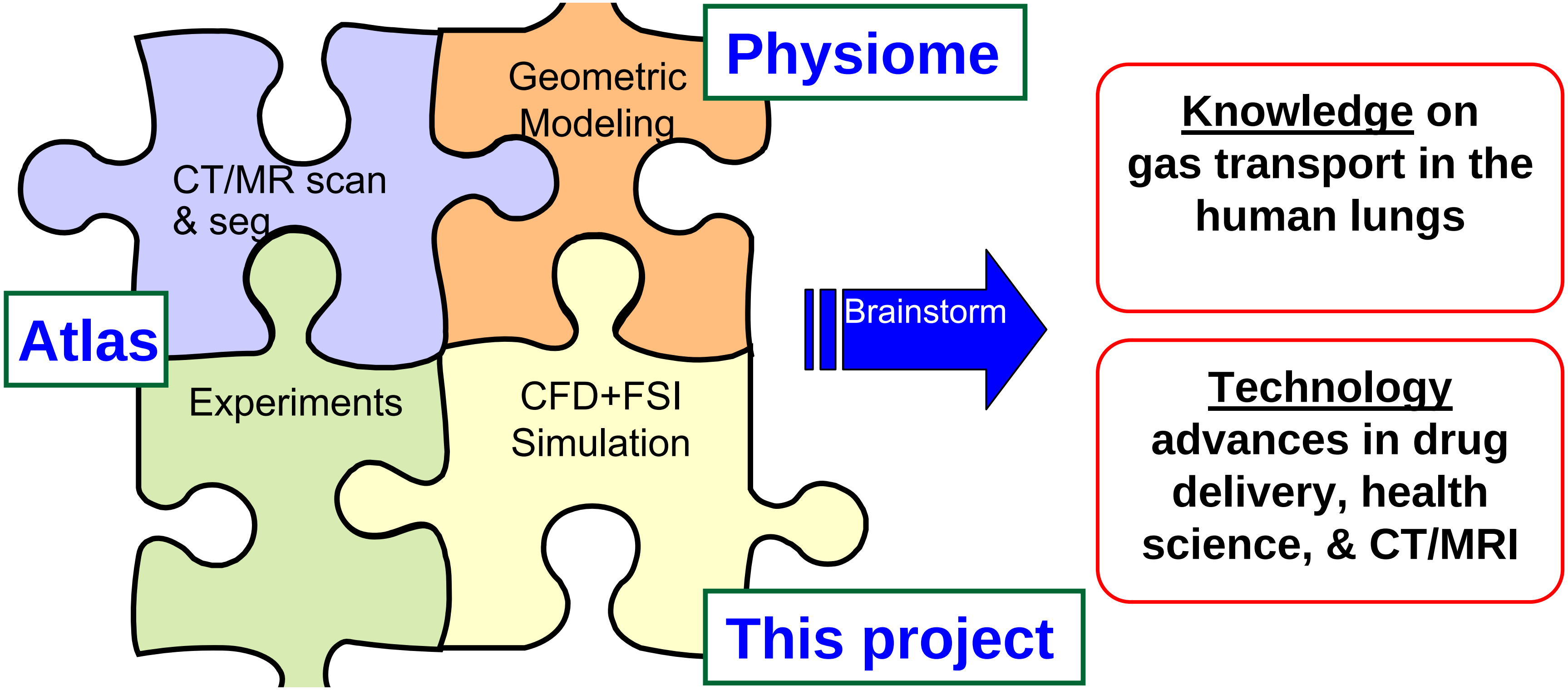
- **<u>1D model</u>**: entire conducting airway tree, but less accurate
- **<u>3D model</u>**: more accurate, but limited number of airways
- **<u>Coupled 1D + 3D model</u>**: benefits of each approach



3D Navier-Stokes



Multidisciplinary Research



Physiome

Geometric Modeling

CT/MR scan & seg

Atlas

Experiments

CFD+FSI Simulation

This project

Brainstorm

<u>Knowledge</u> on gas transport in the human lungs

<u>Technology</u> advances in drug delivery, health science, & CT/MRI

Lung Atlas (Dr. Hoffman, co-PI): document airway geometry over four decades of age in healthy and diseased adult humans.

Lung Physiome (Dr. Tawhai, co-I): develop integrative computational models at all levels of biological organization.

Clinical Application (Dr. McLennan, co-I): relate results to clinical application.

IMAG

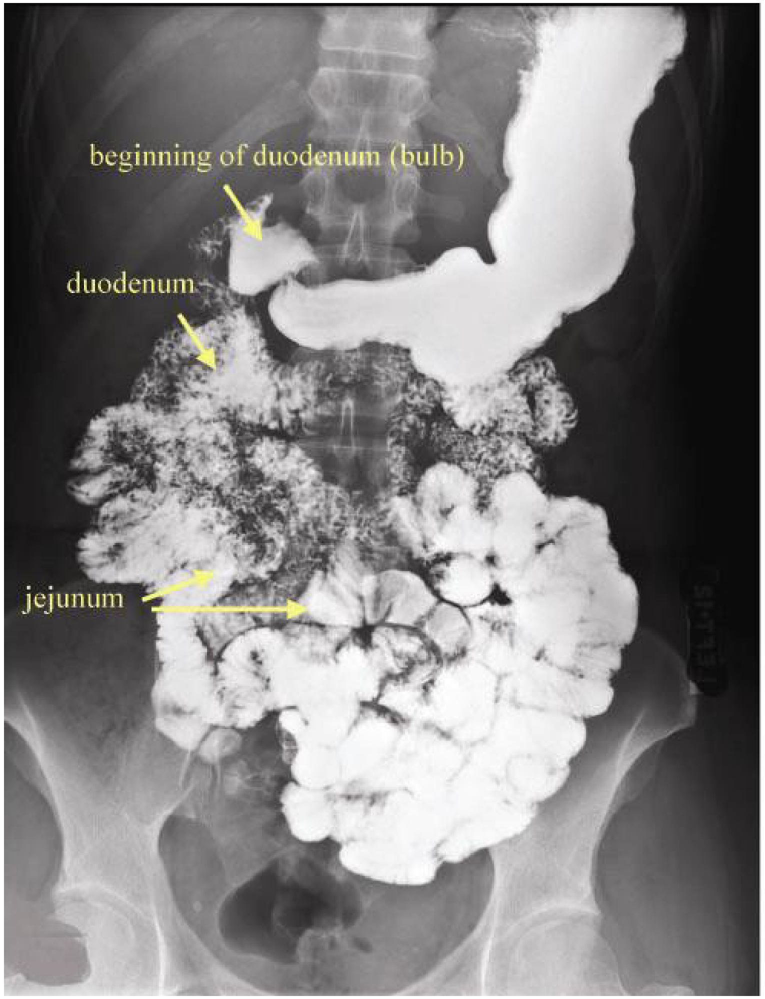
PI: James Brasseur

Title: Micro-scale Transport as a Critical Link between Molecular-scale Absorption and Macro-scale Mixing in Gut Physiology and Function

Institution: The Pennsylvania State University

Funding Agency: NIH/NIBIB

Micro-scale Transport as a Critical Link between Molecular-scale Absorption and Macro-scale Mixing in Gut Physiology and Function (NSF)



Principle Investigators

- Jim Brasseur - modeling/simulation
- Andrew Webb - MRI, imaging
- Nadine Smith - animal experiment

Students

- Amit Ailiani - MRI, image analysis
- Gino Banco - modeling, image analysis

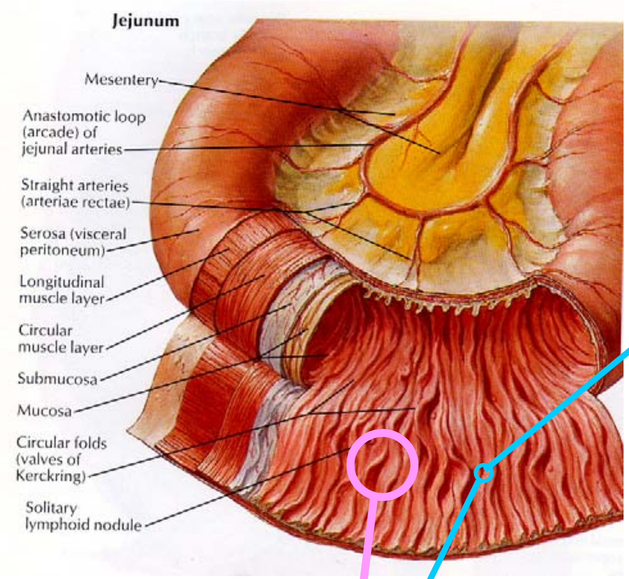
Consultants

- Jack Wood, Ohio State, GI neurophysiology
- Shiyi Chen, Johns Hopkins, LBM
- others informally (J Murray at Mayo,…)

Unfunded temporary help

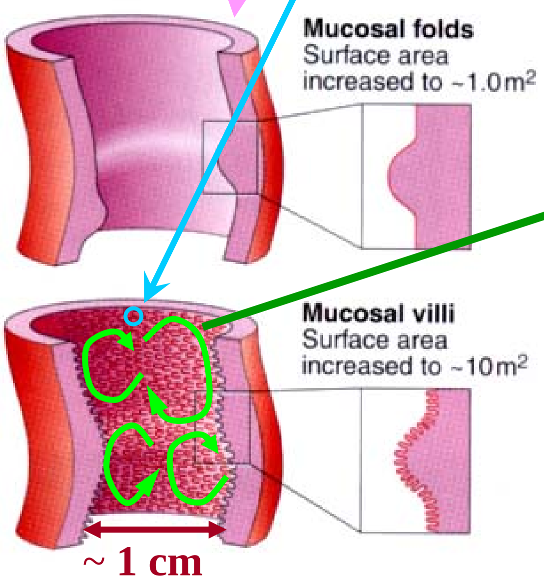
- Anupam Pal - postdoc, gastric modeling
- Thomas Neuberger - MRI researcher

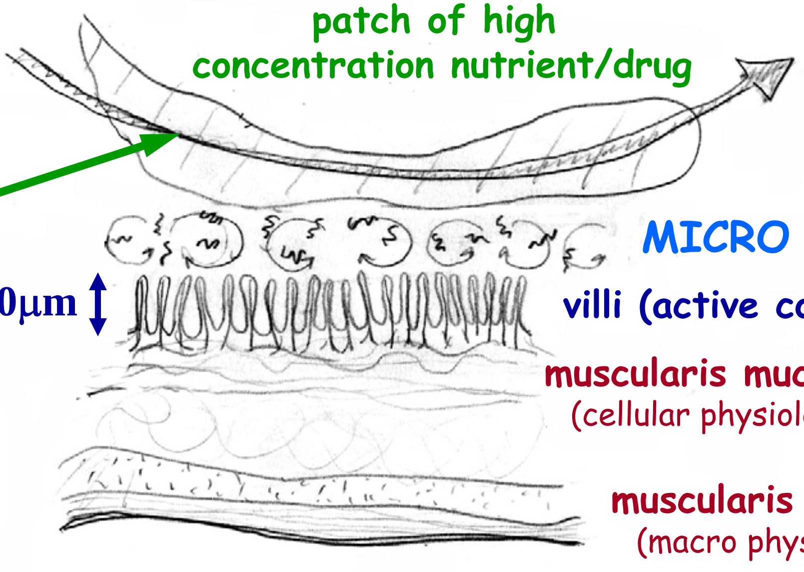
The Importance of Macro-Micro Couplings



mucosal villi

~ 100μm





MACRO MIXING;
patch of high
concentration nutrient/drug

MICRO MIXING

~ 100μm

villi (active control)

muscularis mucosae
(cellular physiology)

muscularis propria
(macro physiology)

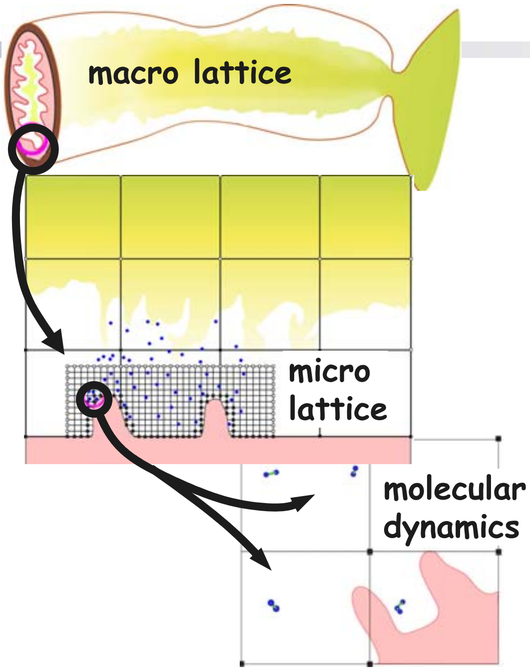
Objectives and Methods

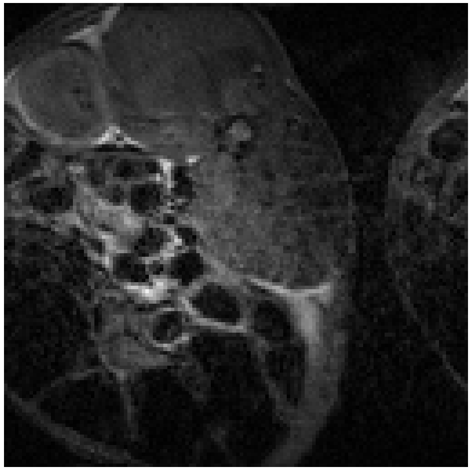
- Models and algorithms to couple macro to micro to molecular transport using Lattice-Boltzmann coupled with Molecular Dynamics methods.

- MR micro-coil technology to image gut villi *in vivo.*

- Advanced space-time image analysis systems MRI quantification.

- Integrate image data with numerical simulation to advance understanding of micro-macro-cellular physiology and function of the gut.





rabbit gut

IMAG

PI: David Cai

Title: Collaborative Research: Cortical Processing across Multiple Time and Space Scales

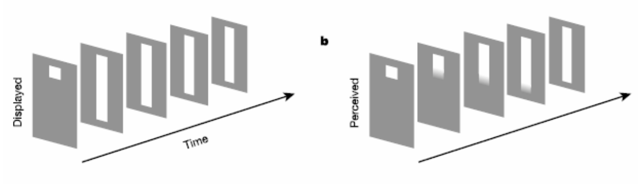
Institution: Courant Institute

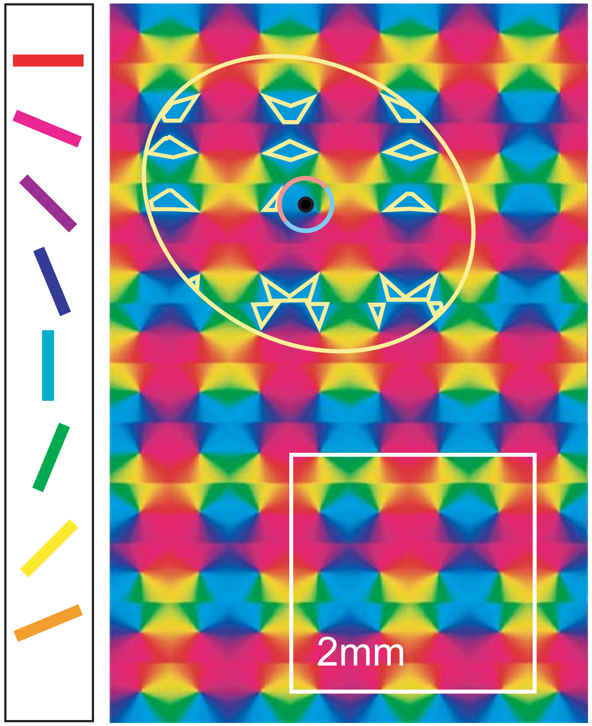
Funding Agency: NSF/DMS

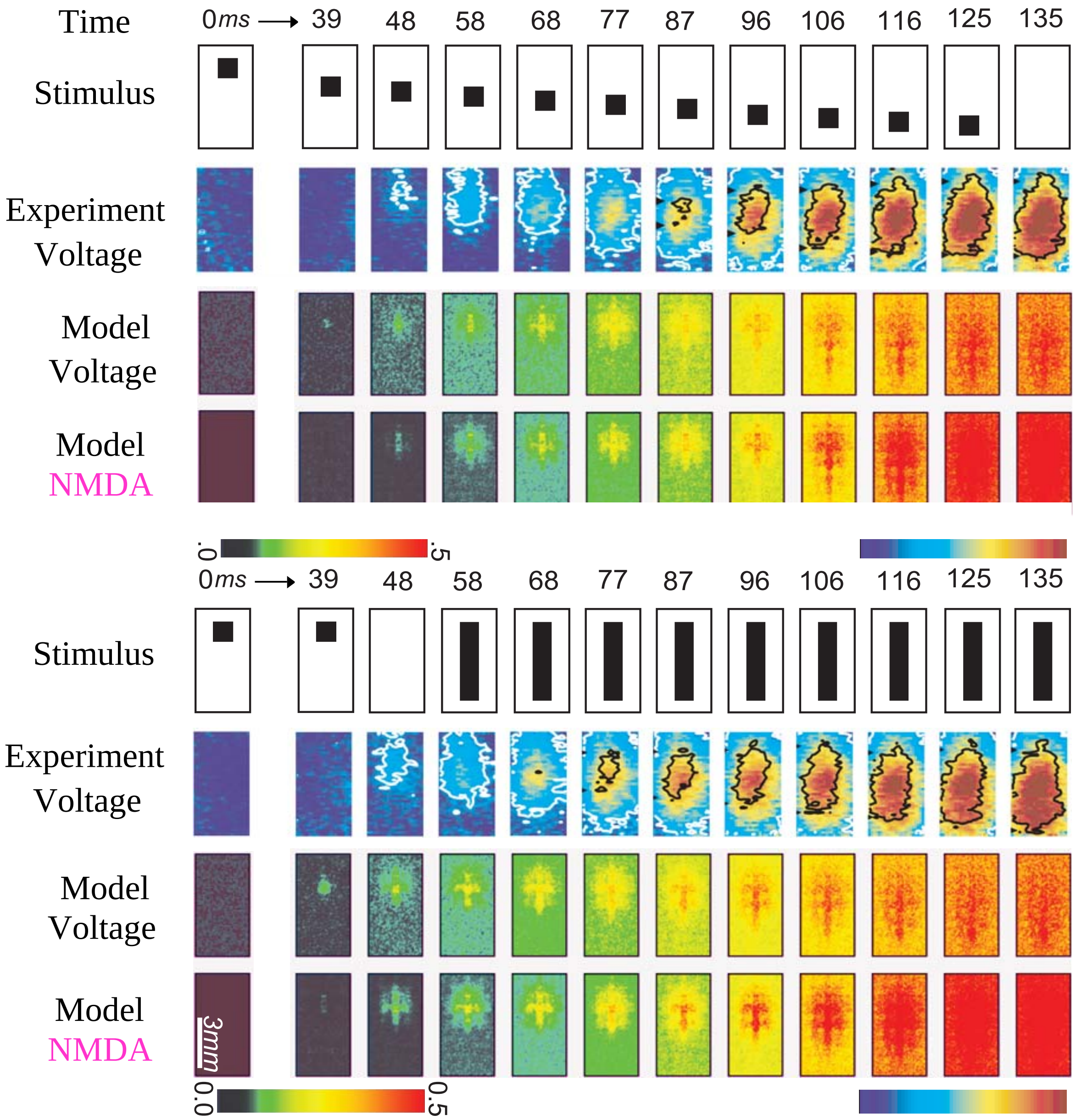
Large-Scale Modeling of Primary Visual Cortex

- Networks of 10^6 Neurons
- Physiologically constrained

Line-motion Illusion







David Cai (Courant Institute), Cortical Processing across Multiple Time and Space Scales

Coarse-Graining Approach

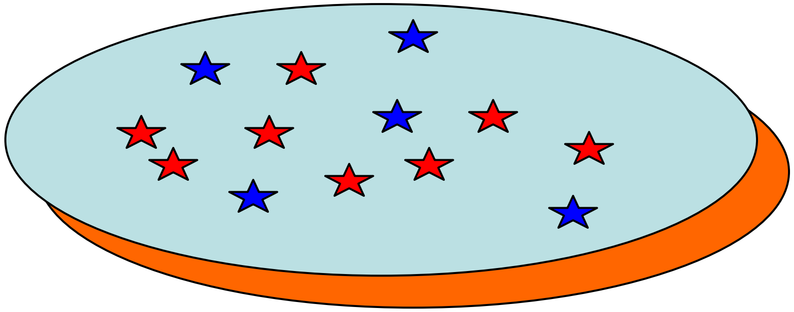
- From ‘Microscopic’ Equations of Neurodynamics
  to derive equations governing large-scale coarse-grained dynamics

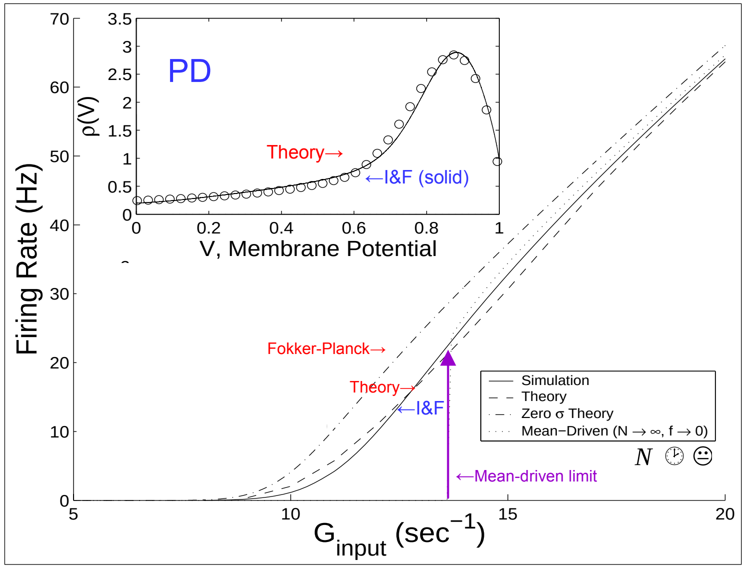
(1+1)-D Kinetic Equations:

$$\frac{\partial}{\partial t}\rho(v)=\frac{\partial}{\partial v}\left\{\left[\left(\frac{v-\varepsilon_r}{\tau}\right)+\mu_1(v)\left(\frac{v-\varepsilon_E}{\tau}\right)\right]\rho(v)\right\}$$

$$\frac{\partial}{\partial t}\mu_1(v)=\left[\left(\frac{v-\varepsilon_r}{\tau}\right)+\mu_1(v)\left(\frac{v-\varepsilon_E}{\tau}\right)\right]\frac{\partial}{\partial v}\mu_1(v)-\frac{1}{\sigma}\left[\mu_1(v)-\bar{g}(t)\right]+\frac{\sigma_g^{\,2}(t)}{\rho(v)}\frac{\partial}{\partial v}\left[\left(\frac{v-\varepsilon_E}{\tau}\right)\rho(v)\right]$$

- Embedded Network Approach



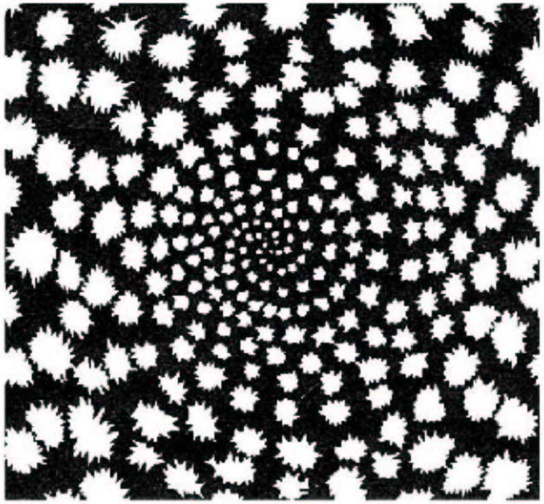


David Cai (Courant Institute), Cortical Processing across Multiple Time and Space Scales

Application of Spatially Coupled Coarse-Grained Equations

● LSD

Siegel, Sci. Am. (1977)



- Symmetries

Bressloff, Cowan, Golubitsky, Thomas and Wiener
Phil.Trans. R. Soc. Lond. B (2001)

- Dynamics?

Activity Patterns on Visual Cortex:

(32x32 Orientation Hypercolumns in our simulation)

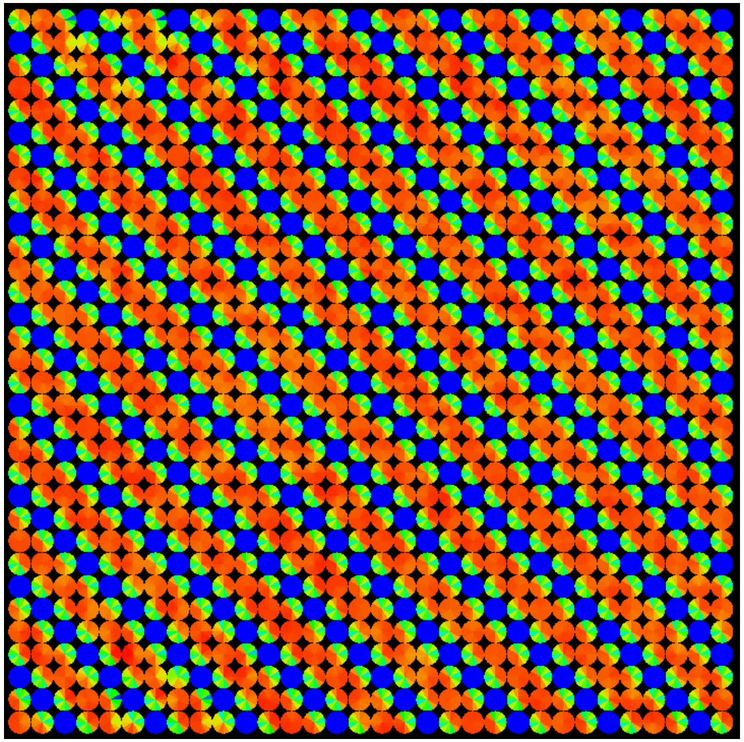
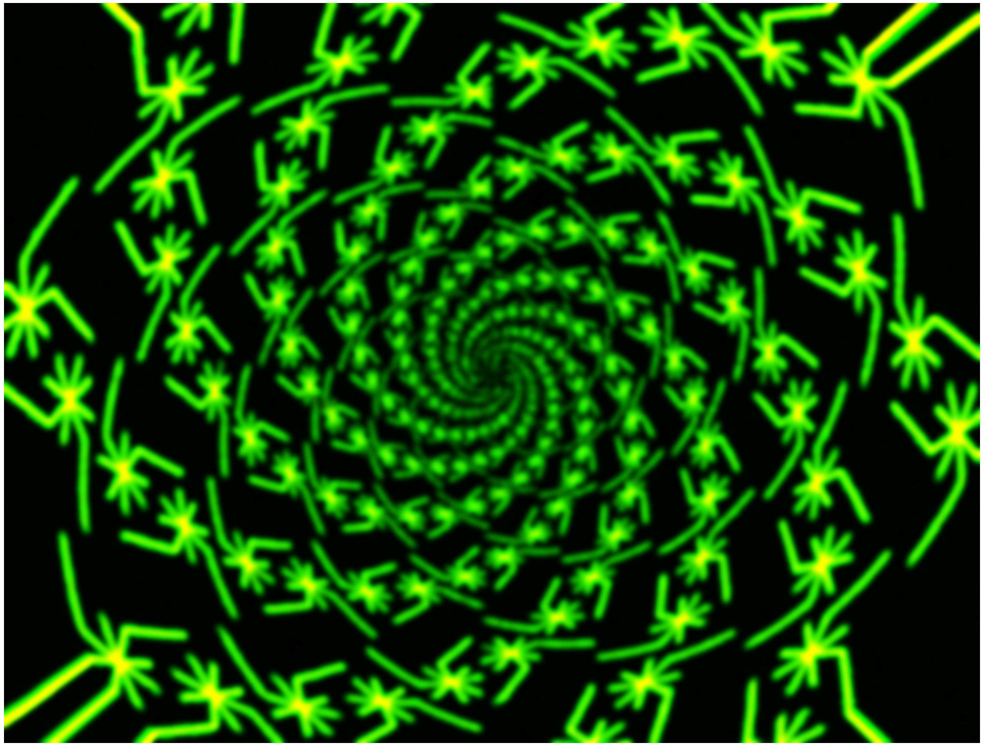


Image on Visual Field:

after inverse retinocortical map



IMAG

PI: Yoonsuck Choe

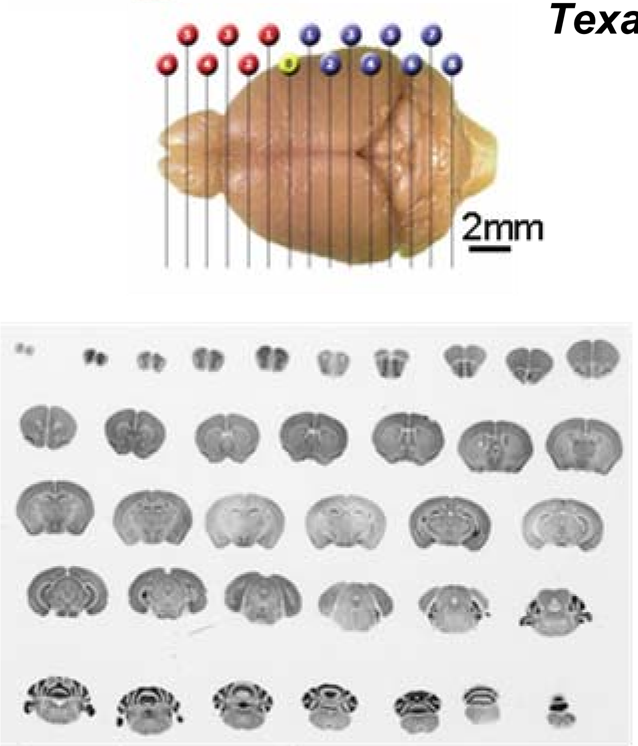
Title: Multiscale Imaging, Analysis, and Integration of Brain Networks

Institution: Texas Engineering Experiment Station

Funding Agency: NIH/NINDS

Multi-scale Imaging, Analysis, and Integration of Brain Networks

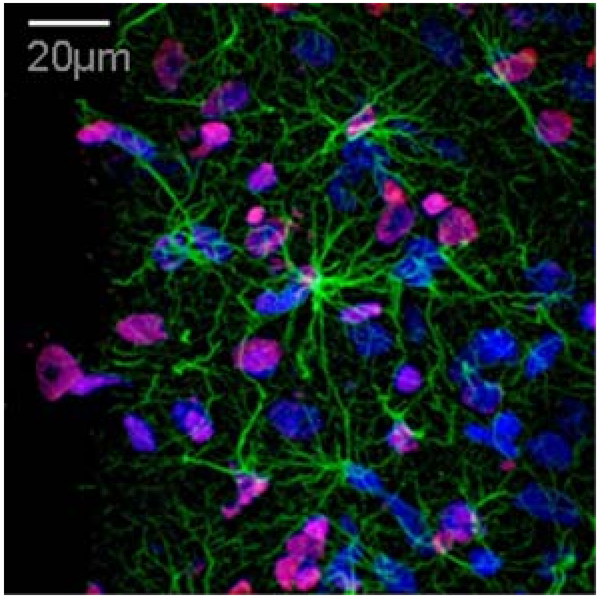
Texas A&M University • Stanford University



Macro-scale

C57BL/6J mouse brain and its coronal slides

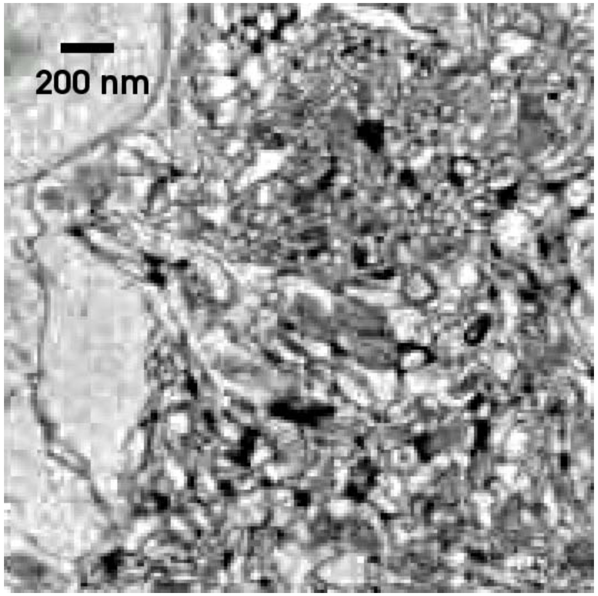
http://www.mbl.org/atlas170/atlas170_start.html



Micro-scale

Neurons in hippocampus

http://www.uhnresearch.ca/facilities/wcif/gallery.html

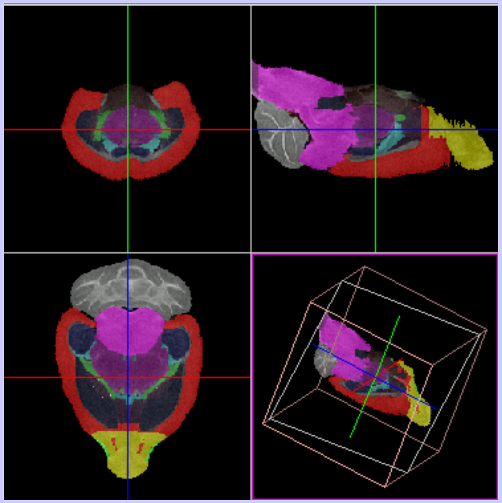


Nano-scale

Dense fibers in Zebrafish tectum

12nm x 12nm x 50nm voxels

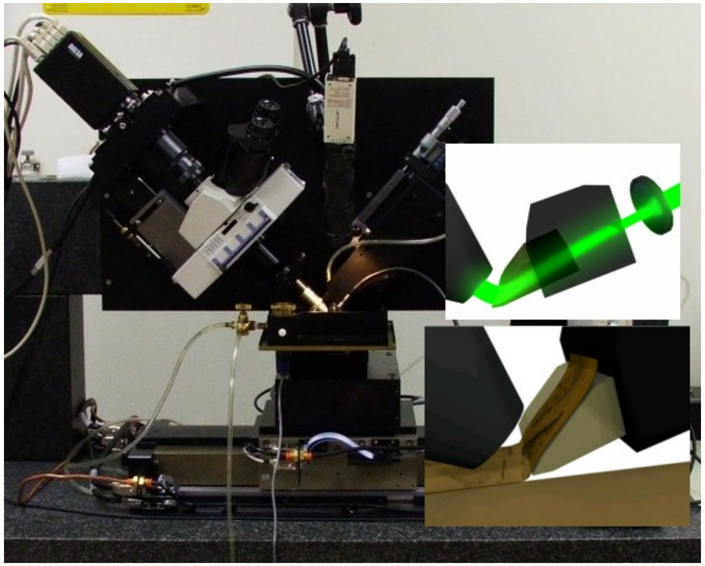
Multi-scale Brain-Network Data Acquisition



Macro-scale

Mouse Brain Atlas (MAP): **UCLA**

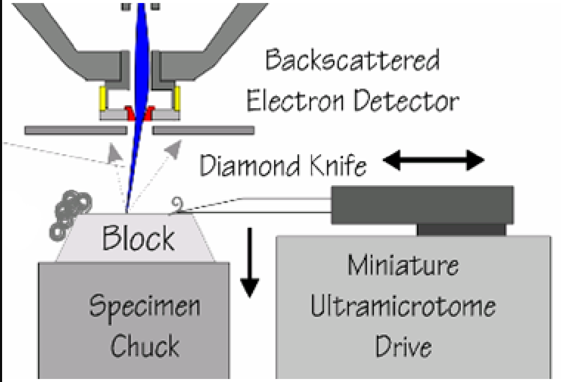
Data provided by Arthur Toga



Micro-scale

Knife-Edge Scanning Microscope (KESM): **Texas A&M University**

Bruce H. McCormick



Nano-scale

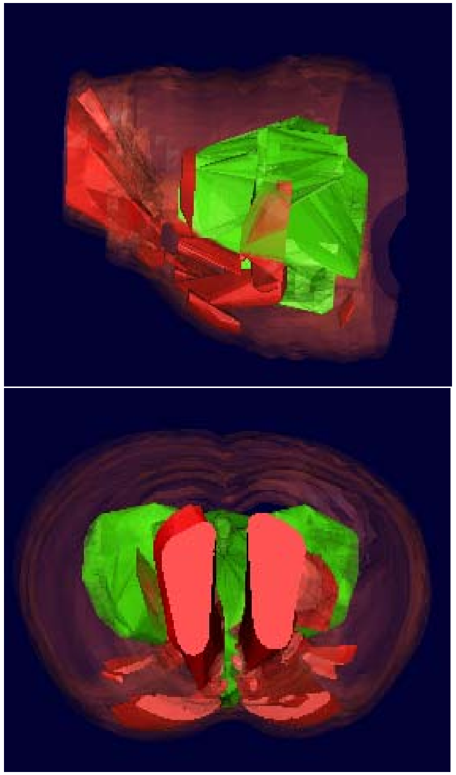
Serial Block-Face Scanning Electron Microscope (SBF-SEM):

Max Planck Inst. :

Winfried Denk

Stanford: *Stephen J. Smith*

Multi-scale Reconstruction and Integration



Macro-scale

Volumetric Atlas (Paxinos data)

Wonryull Koh (Texas A&M)

Navigation

Density Scaling

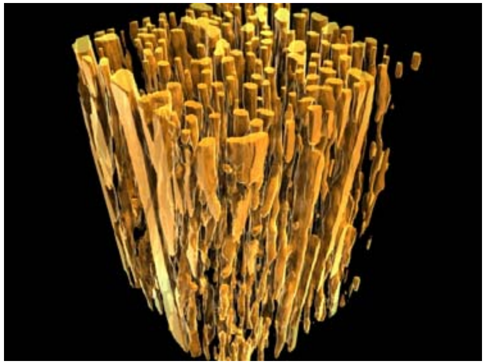
Micro-scale

Proximity Labelling (KESM)

David Mayerich (Texas A&M)

Conn. Inference

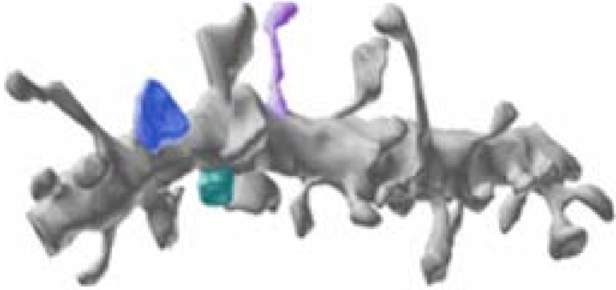
Synaptic Scaling



Nano-scale

SBF-SEM reconstruction

Brad Busse (Texas A&M)



Nano-scale (goal)

Spine Morphology

K. Harris (Med. Col. of GA)

Automatic reconstruction and inferring scaling properties

Acknowledgment: NIH/NINDS #1R01-NS54252

IMAG

PI: Trent Guess

Title: Dynamic Simulation of Joints Using Multi-Scale Modeling

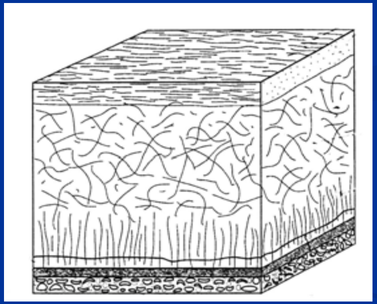
Institution: University of Missouri – Kansas City

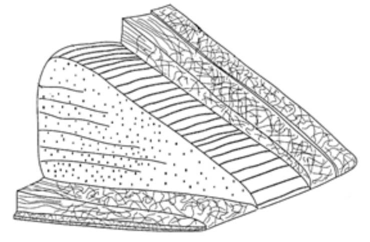
Funding Agency: NSF/CMS

Dynamic Simulation of Joints Using Multi-Scale Modeling

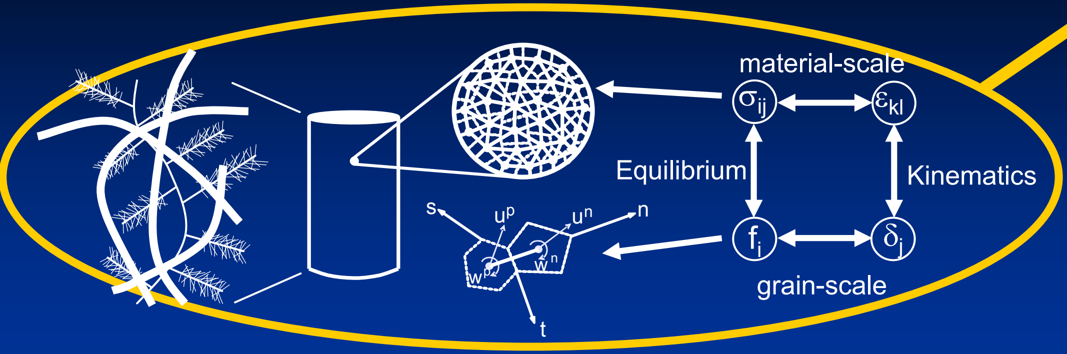
- Research Team
  - Trent Guess University of Missouri – Kansas City (UMKC) Musculoskeletal Biomechanics
  - Anil Misra UMKC Nano-Micro Scale Biomaterial Modeling
  - Ganesh Thiagarajan UMKC Finite Element Modeling
  - Reza Derakhshani UMKC Artificial Neural Networks
  - Lorin Maletsky University of Kansas Experimental Biomechanics
  - Terrence McIff University of Kansas Medical Center Clinical Biomechanics

- Objectives
  - Capture dynamic properties of joint tissues
    - Nonlinear, nonhomogenous, viscoelastic
  - For use in musculoskeletal models (rigid body)
    - Neuromuscular contributions
    - Tissue interdependencies
      - Joint injury and disease


(Aufderheide and Athanasiou 2004)


(Aufderheide and Athanasiou 2004)

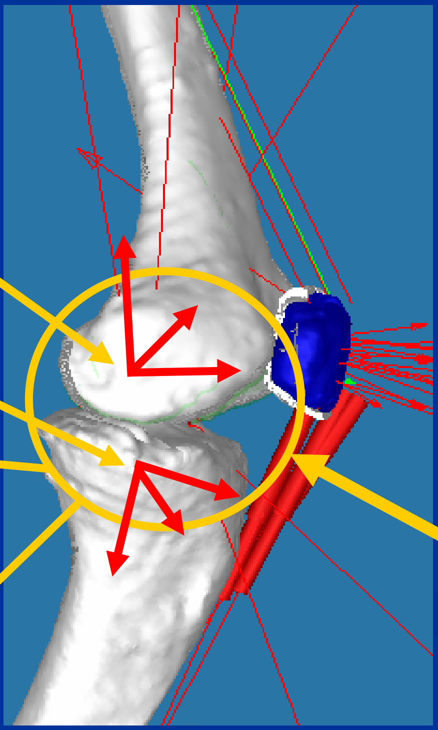
- Representation of tissue as nano-scale grains interacting through psuedo bonds



- Bi-Phasic Constitutive Equations
  - Articular Cartilage
  - Lateral Meniscus
  - Medial Meniscus

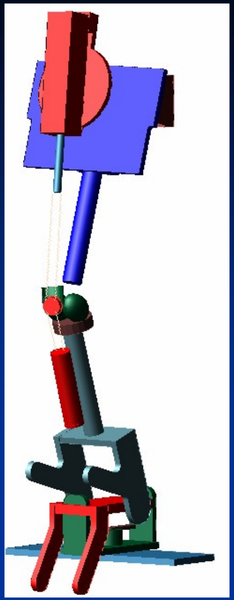
- Dynamic Finite Element (FE) Model
  - Tibia, Femur
  - Cartilage
  - Menisci

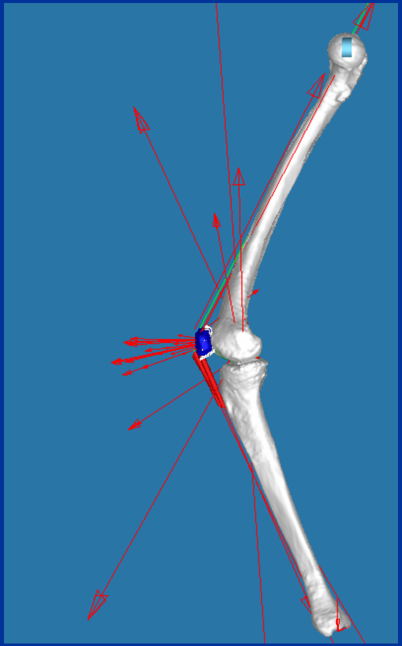
- ANN Model placed within Musculoskeletal Knee Model
  - ANN Model Inputs
    - Motion of Femur and Tibia
  - ANN Model Outputs
    - Reaction forces
      - 3-D forces and moments
    - Contact pressures



- Artificial Neural Network (ANN)
  - "Learns" dynamic response of articulations from computationally intensive FE simulations

- Model Validation
  - Dynamic Knee Simulator
  - 7 Cadaver knees
    - Kinematics
    - Ligament strain
  - Clinical Gait Lab (Human Subjects)
    - EMG
    - Kinematics
    - Ground reaction forces





- Project Contributions
  - Validated ANN Models
    - Capture the dynamic response of tibio-femoral-menisci articulations
    - Method could be used to capture other tissues such as ligaments
  - Tissue Interdependencies
    - Menisci properties
    - Tibio-femoral contact
    - Ligament strain

IMAG

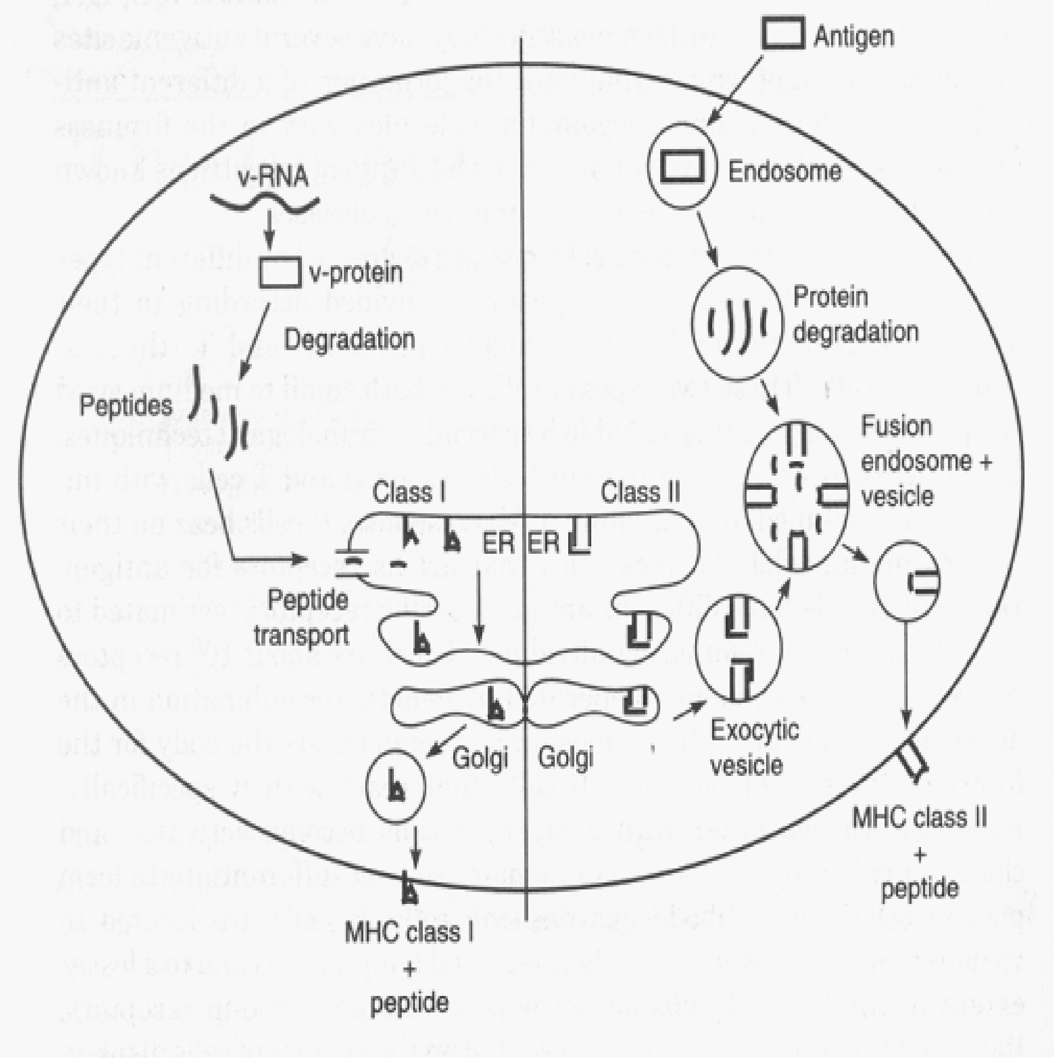
PI: Denise Kirschner

Title: A multi-scale approach for understanding antigen presentation in immunity

Institution: University of Michigan Medical School

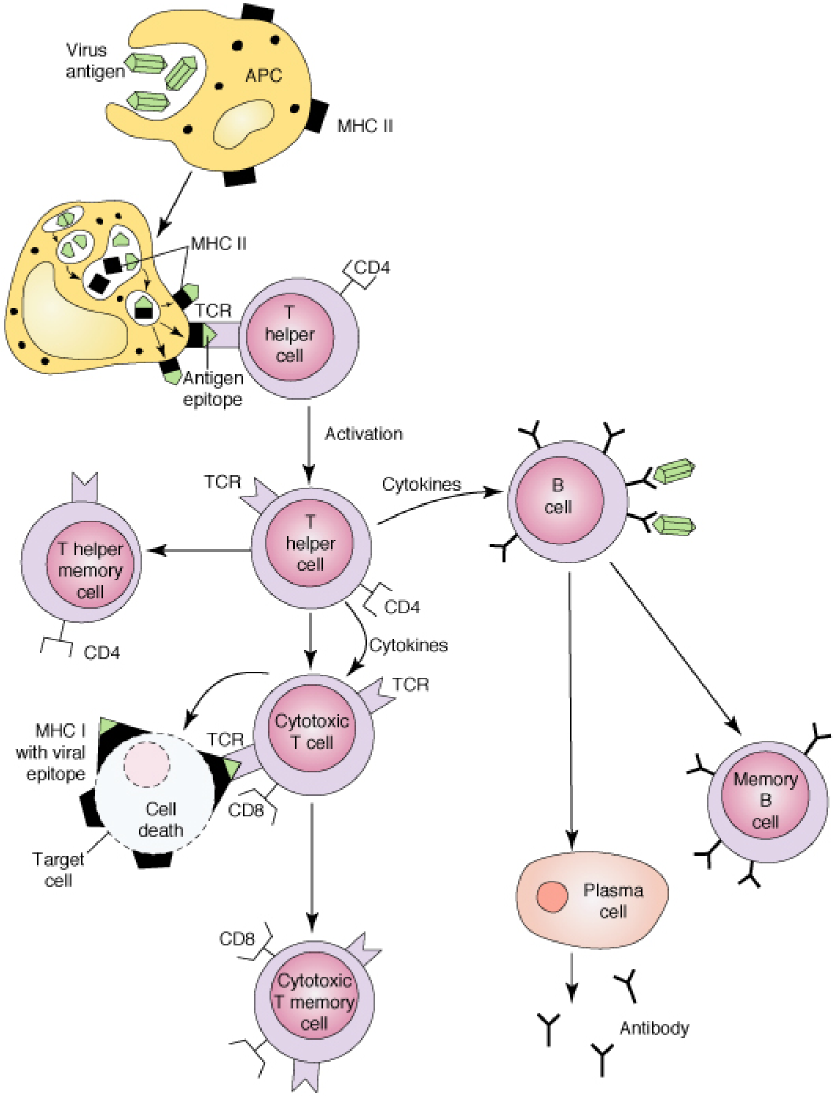
Funding Agency: NIH/NLM and NIAID

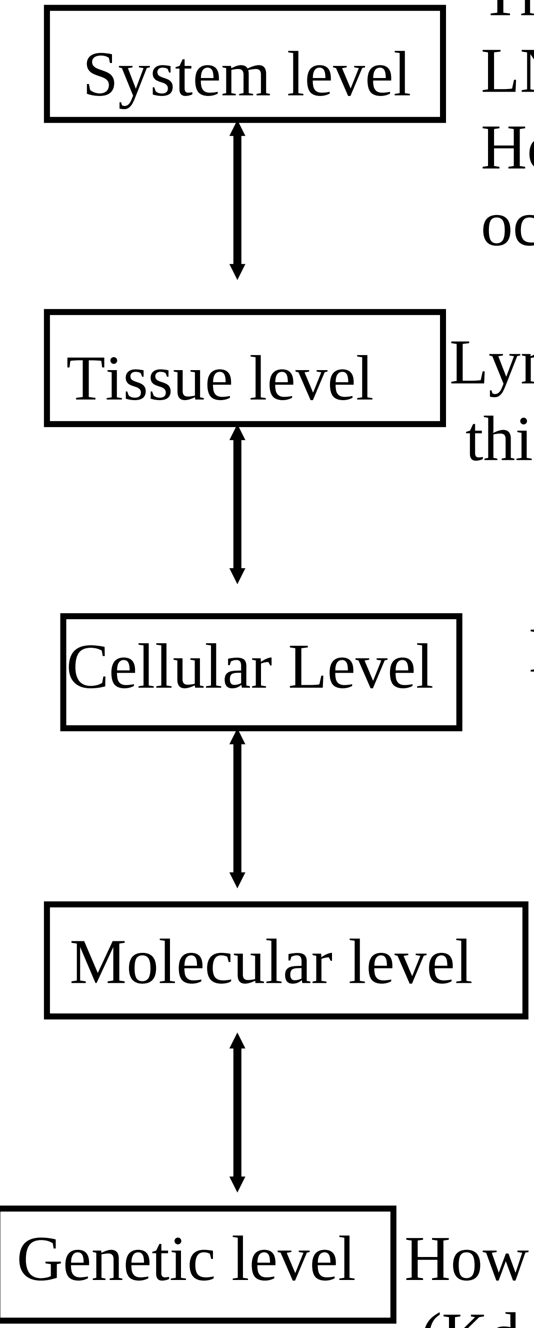
Antigen presentation



AP cell: macrophage or DC

Antigen presentation: Initiating and signaling the immune response





System level

The blood supplies LNs with non-activated cells, and LNs supply armed effector cells to the site of infection. How does trafficking of cells between compartments occur and how can it influence infection outcome?

Tissue level

Lymph nodes are the site of immune initiation-how does this environment augment the APC-T cell interaction?

Cellular Level

How do these genetic and molecular events relate to T cells recognition and function?

Molecular level

How do events occurring during antigen uptake, processing and loading affect peptide-MHCII levels on the surface of the APC?

Genetic level

How does the peptide sequence affect binding to MHCII (Kd, IC_{50} etc)?

What we hope to accomplish

- Develop new computational/mathematical and statistical tools to study complex biological systems at multiple scales
- Utilize data from mouse and non-human primate models to inform model development
- Uncover basic science of hypotheses of AP that can be tested
- Many pathogens interrupt one or more stages of antigen presentation
- *Mycobacterium tuberculosis* is the number one cause of death due to infectious disease in the world today (2 billion people infected)
- *M. tuberculosis* is known to interfere with a number of stages of AP
- Our goal is to elaborate understanding and generate hypotheses regarding this host-pathogen interaction and AP events
- Vaccines train the immune system to recognize pathogens via antigen presentation
- Information gained from our studies may be immediately applied to vaccine design for *M. tuberculosis* as well as other pathogens.

IMAG

PI: Ernst Georg Luebeck

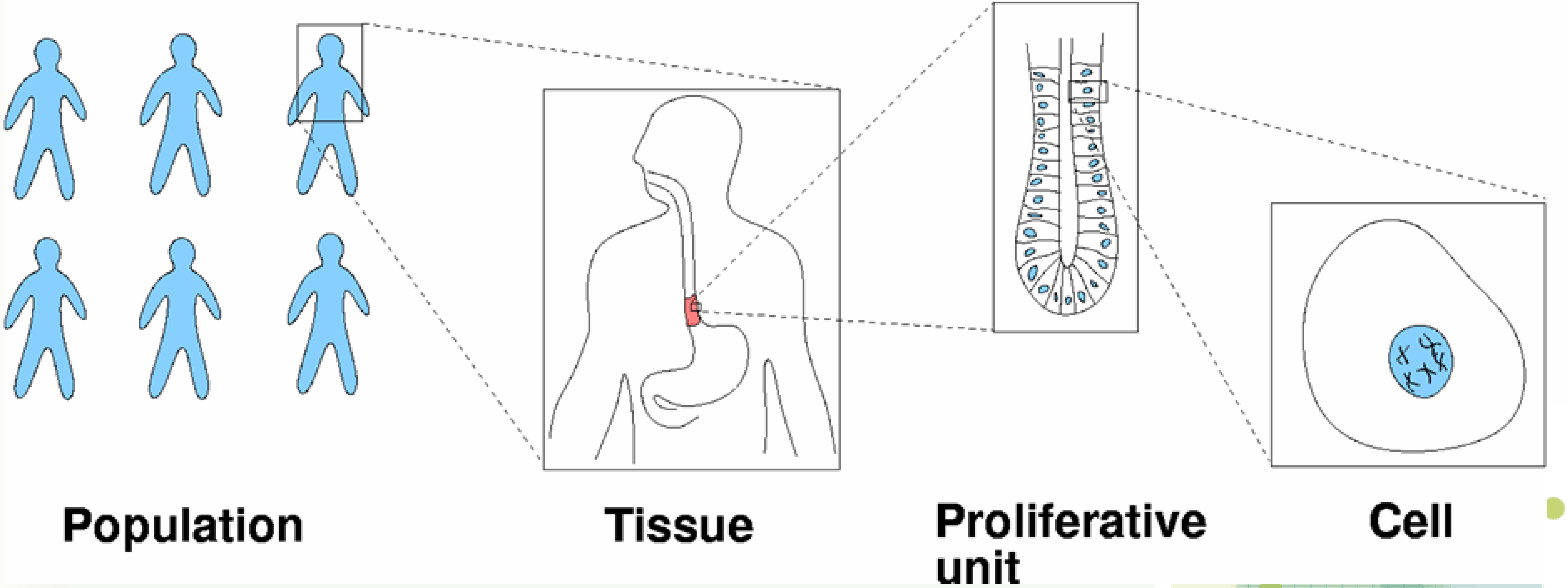
Title: Scales of carcinogenesis: cells, crypts and cancer

Institution: Fred Hutchinson Cancer Research Center

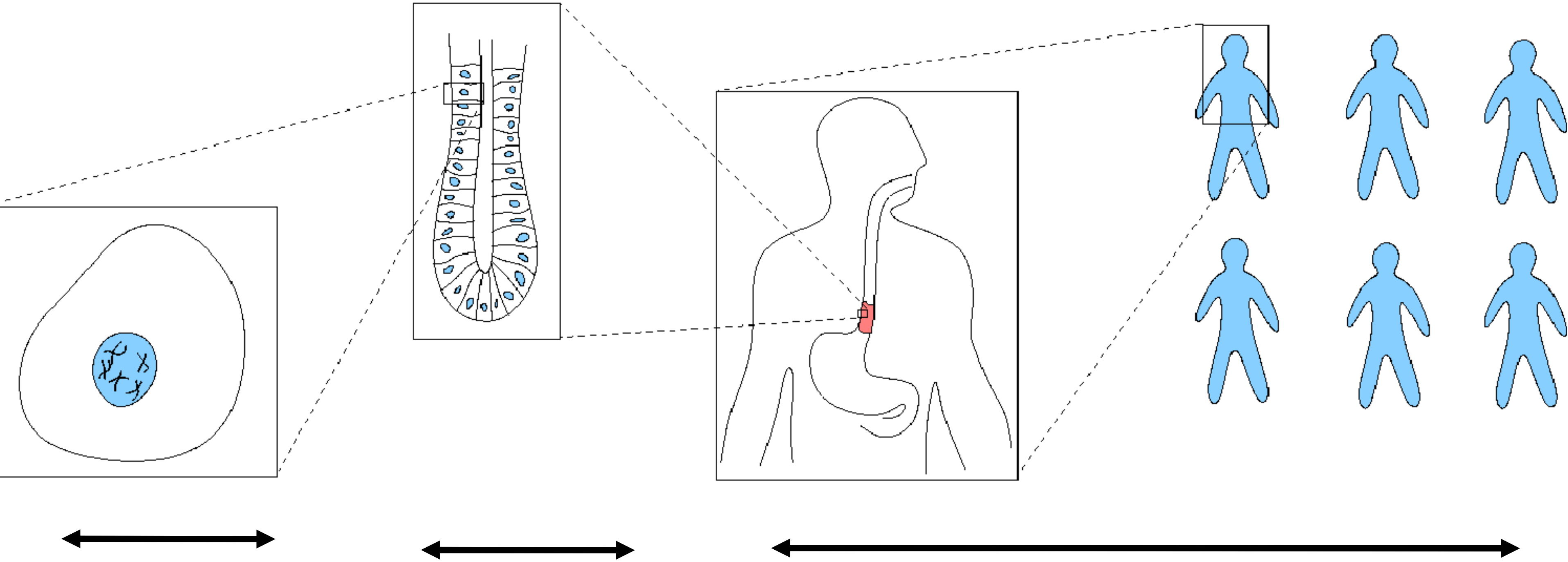
Funding Agency: NIH/NCI

Scales of carcinogenesis: cells, crypts and cancer

organ of interest: GI tract (colon, gastric and Barrett's esophagus)



Cells, crypts and cancer (Luebeck/Maley)



acquisition of mutations
(Armitage&Doll/Nordling)
DNA repair models
DNA and cell replication
differentiation?

niche models:
Moran-type models (Nowak et al)
conveyor-belt models:
computer models (Shibata et al,
Potten&Loeffler, Roeder&Loefler)

molecular and clinical epidemiology:
natural history models
survival & risk analysis

Multistage & Multiscale Carcinogenesis

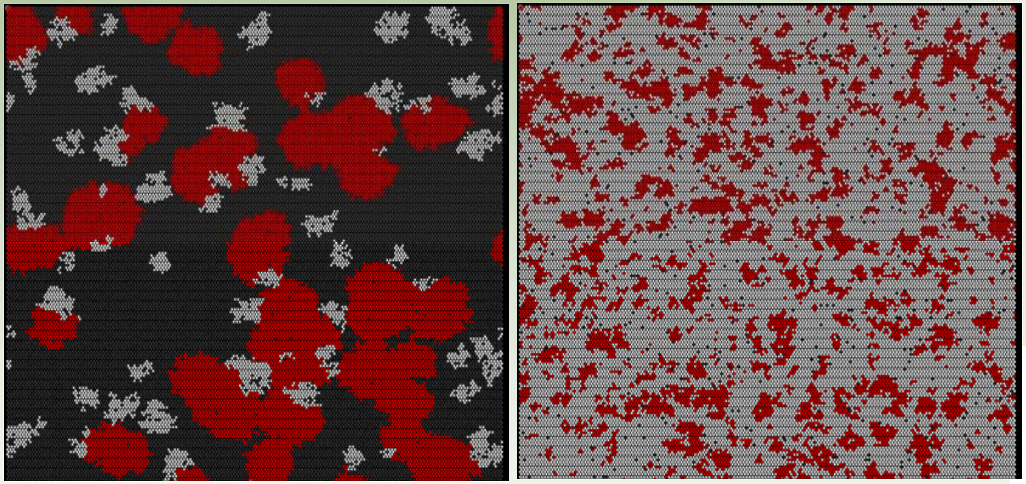
modular design to 'connect' scale-specific processes across scales

module 1: from a cell to a proliferative unit

account for cell cycle stages, cell division, DNA repair, sporadic and induced cell death, and accumulation of mutations

module 2: from a proliferative unit to a tissue unit (organ)

disruption of tissue architecture (e.g. wound-inflicted) and normal unit turnover, model clone evolution and expansion across tissue



module 3: from a tissue unit to cancer in populations

first-passage-times for the induction of clonal expansions,
clonal expansion parameters,
first-passage-time distributions of malignant transformations

Cells, crypts and cancer (Luebeck/Maley)

IMAG

PI: Bridget Wilson

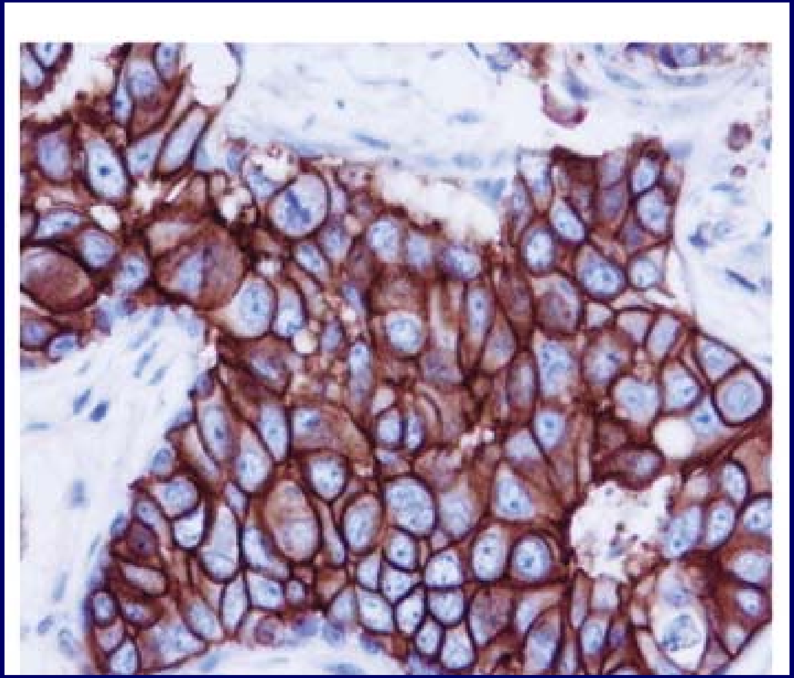
Title: Mapping and Modeling ErbB Receptor Membrane Topography

Institution: University of New Mexico Health Sciences Center

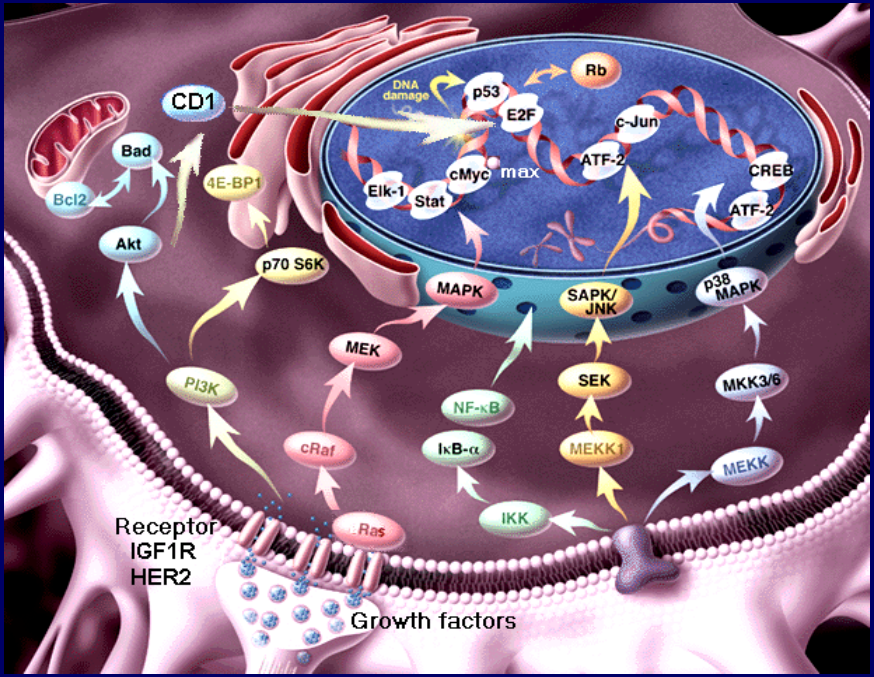
Funding Agency: NIH/NCI

MSM: Mapping and Modeling ErbB Receptor Membrane Topography

Bridget Wilson, PI (Univ. of New Mexico)
with J. Edwards, J. Oliver, S. Steinberg, K. Leslie, J. Zhang,
G. Hsieh, M. Raymond-Stintz

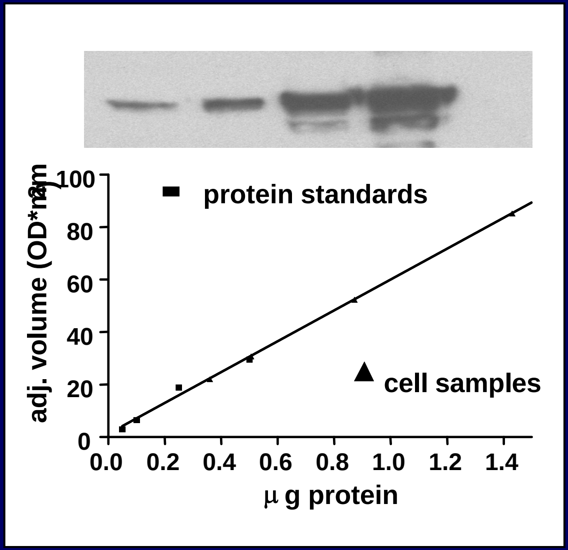


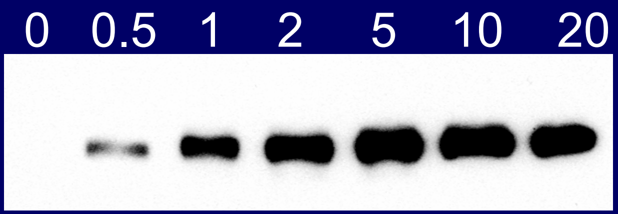
Endometrial Cancer Model



Complex Signaling Pathway

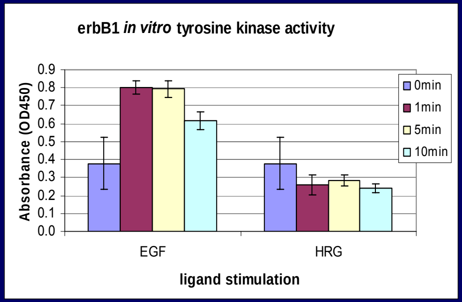
UNM Biology Team: Quantitative Measurements, Biochemistry, High Resolution Microscopy of Signaling Pathway

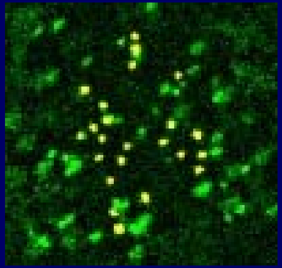




Phosphorylation kinetics

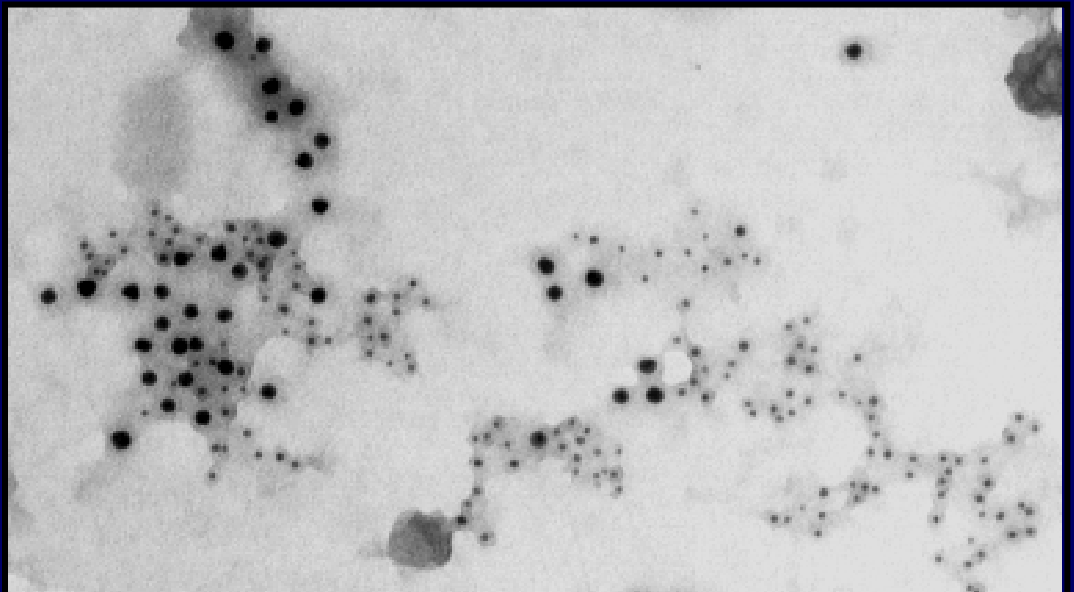
Cancer Drugs





Single Particle Tracking (Diffusion)

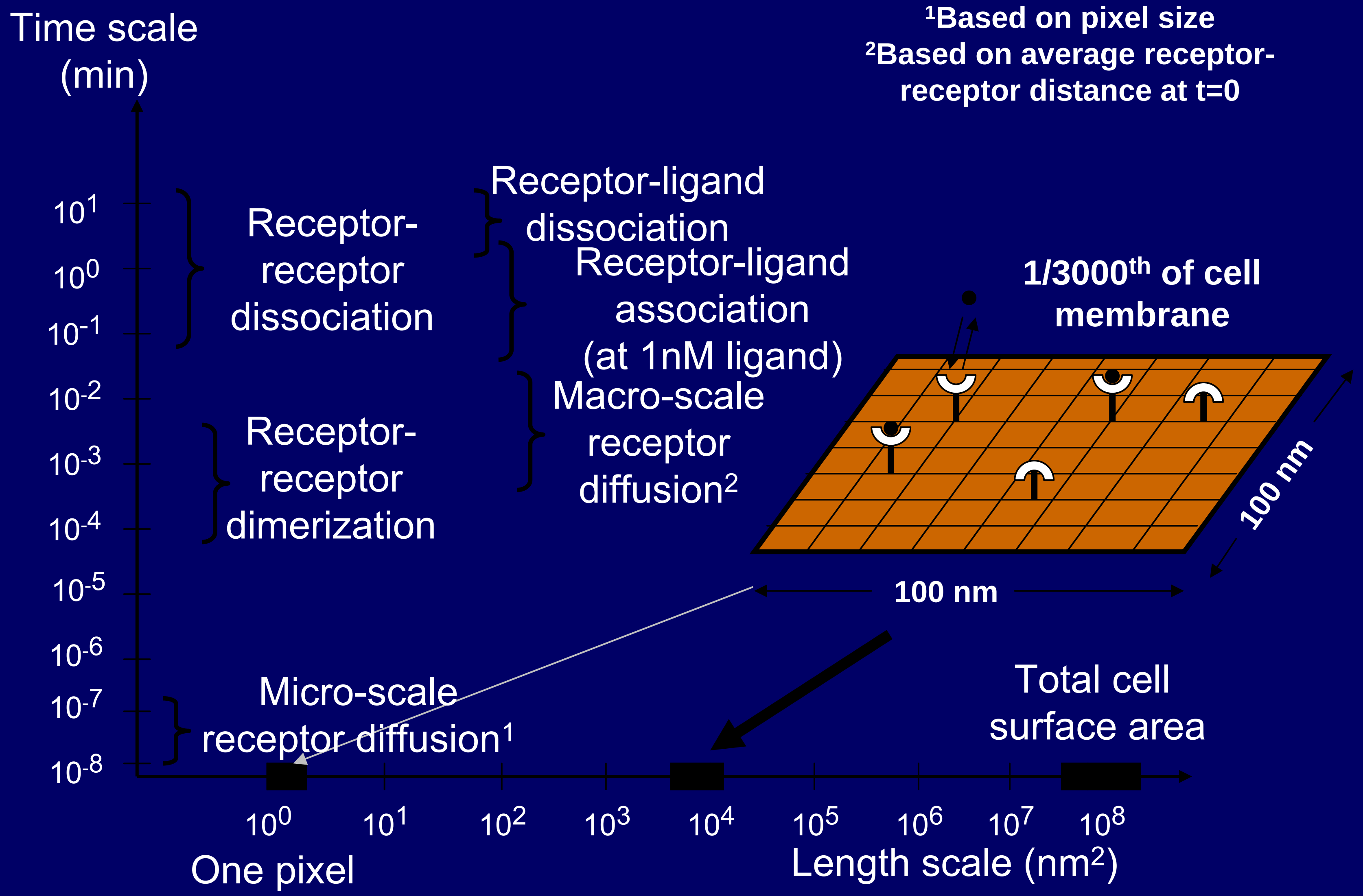
Mapping of Signaling Proteins in Native Membranes (EM)



UNM Computational Team: Simulations of Signal Transduction

MultiScale in Time and Space

[1]Based on pixel size
[2]Based on average receptor-receptor distance at t=0



Time scale (min)

Receptor-receptor dissociation

Receptor-receptor dimerization

Receptor-ligand dissociation

Receptor-ligand association (at 1nM ligand)

Macro-scale receptor diffusion[2]

Micro-scale receptor diffusion[1]

1/3000th of cell membrane

Total cell surface area

One pixel

Length scale (nm^2)

IMAG

PI: James Glazier

Title: Multiscale Studies of Segmentation in Vertebrate Embryos

Institution: Indiana University

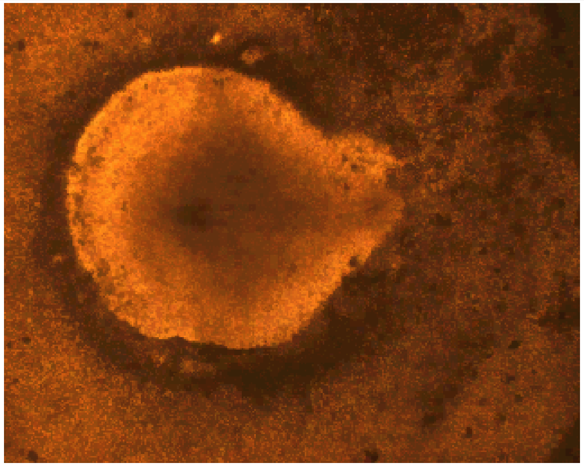
Funding Agency: NIH/NIGMS

Multiscale Models and Experiments on Somitogenesis

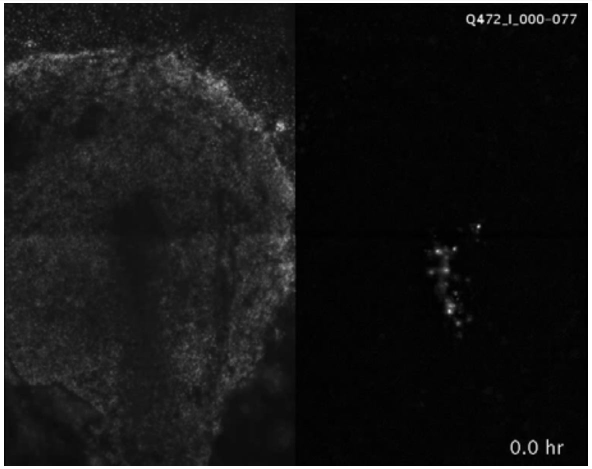
James A. Glazier, Santiago Schnell – Indiana University, Bloomington
Charles Little – Kansas University Medical Center
Mark S. Alber – University of Notre Dame

the biocomplexity institute

During the Gastrulation Stage of Early Embryonic Development , the Primitive Streak and the Three Germ Layers Form. Subsequently, Somitogenesis Lays Down the Initial Body Plan, in Particular, the Periodic Structures which Give Rise to Anterior-Posterior Patterning.

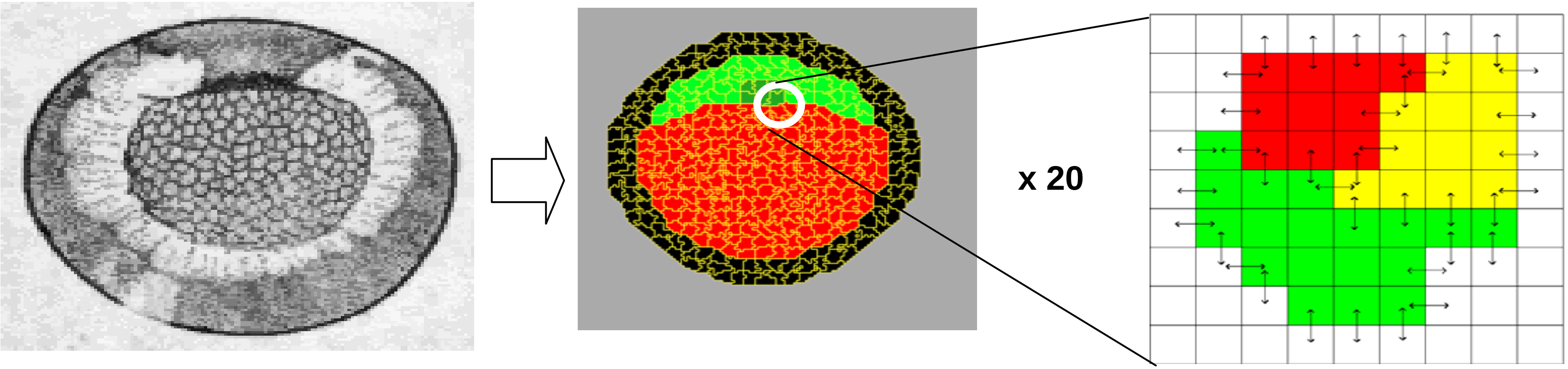


Somitogenesis in Chick EC Culture.
Courtesy: Susan Chapman. University College, London



Cell Movement during Gastrulation in Chick EC Culture.
Courtesy: Cheng Cui, KUMC, Kansas City

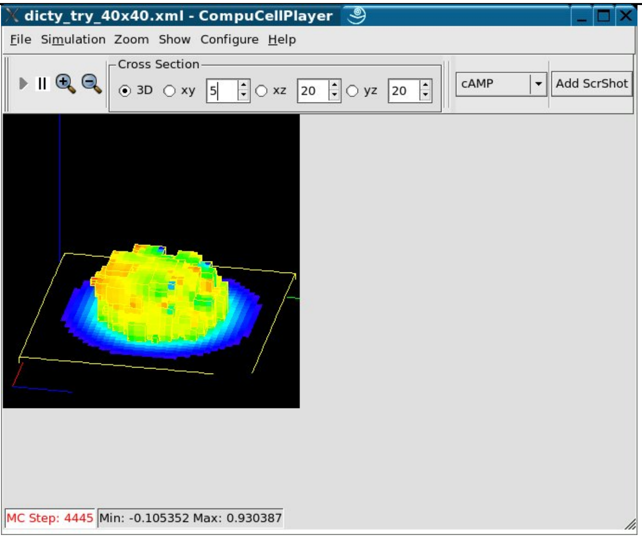
The Glazier-Graner Cellular Potts Model and CompuCell



- *Metropolis algorithm: probability of configuration change*

$$\begin{aligned} P(\Delta E) &= 1,\ \Delta E \leq 0 \\ P(\Delta E) &= e^{-\Delta E/kT},\ \Delta E > 0 \end{aligned}$$

$$\mathbf{E} = \sum_{\mathbf{x},\mathbf{x}'} \mathbf{J}_{\tau(\sigma(\mathbf{x})),\tau(\sigma(\mathbf{x}'))}(1-\delta_{\tau(\sigma(\mathbf{x})),\tau(\sigma(\mathbf{x}'))}) + \lambda_{\mathbf{v}}(\mathbf{v}_{\sigma} - \mathbf{V}_{\sigma})^2 + \ldots$$


dicty_try_40x40.xml - CompuCellPlayer

Cross Section: ● 3D ○ xy 5 ○ xz 20 ○ yz 20

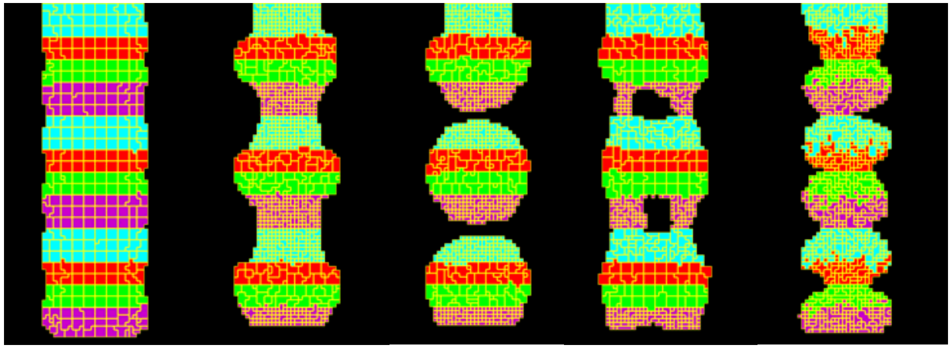
cAMP

MC Step: 4445 Min: -0.105352 Max: 0.930387

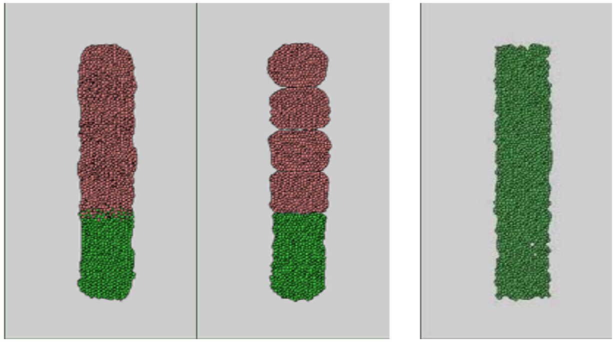
Compucell is an Open Source Monte-Carlo Cellular-Automaton Modeling Framework. It Allows Researchers to Implement Their Models Without the Need for Low-Level Programming. It Comes with a Full Featured Intuitive GUI And Visualization Tools.

Compucell is an Example of a Model Sharing Environment That is Easy to Extend and Intuitive To Use.

Current Somitogenesis Modeling



Effect of Changes in Cell Adhesion on Somite Segmentation and Morphology, Ying Zhang, IUB



Somite Segmentation Resulting from a Simple Molecular Clock, Nan Chen, ND

Development Plans

CompuCell: *Full Support for Scripting Languages, Graphical Tools for Configuring Simulations, Further Improvements in the Graphical Front-End, Real-Time Simulation Steering, Parameter Sweep Options, Parallel Grid-Oriented Version, Integration with Other Sharing Frameworks, E.g. Physiome and BioSpice*.

Somitogenesis Modeling: *Full Integration of Somitogenesis Models – PDE and ODE Modeling of the Molecular Clock, Boolean Network Simulation of Genetic Regulation, ODE Modeling of Delta-Notch Signaling.*

IMAG

PI: Teresa Head-Gordon

Title: Multiscale Models to Study How Spatial Organization of Cellular Components Influences Signaling

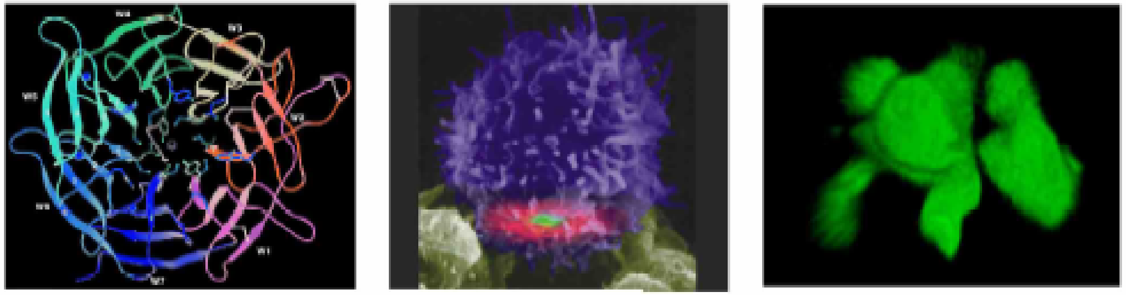
Institution: UC Berkeley

Funding Agency: NIH/NIGMS

Multiscale Models to Study How Spatial Organization of Cellular Components Influences Signaling

T CELL BIOLOGY: FROM MOLECULES TO TISSUES

Integration of multiscale modeling with genetic, biochemical and imaging experiments to enable discoveries



Protein	Cells & Signaling	Tissues & Organs
Crystalography Electron microscopy	Digital imaging Immunochemistry Genetics	Two photon microscopy Non-invasive imaging
Atomic structure prediction	Statistical physics Stochastic simulations	Stochastic dynamics

Head-Gordon (UCB)

Arkin (UCB), Chakraborty (MIT), Geissler (UCB), Oster (UCB)

Dustin (NYU) – experimental collaborator

PI: Head-Gordon

Four specific aims that bridge multiple scales

(1) Develop hybrid Molecular dynamics/Brownian dynamics methods that can study formation of multi-protein signaling complexes initiated by receptor engagement.

(2) Develop models that can describe cytoskeletal dynamics triggered by intracellular signaling and those involved in endocytosis of cell surface receptors.

(3) Develop efficient hybrid algorithms combining stochastic and mean-fled treatments for studying signaling and cell migration in a structured environment.

(4) Integration of scales and testing against biological experiments.

Progress-to date

(1) An analytical electrostatic model for salt-screened interactions between proteins. I. Lotan & T. Head-Gordon (2006). J. Comp. Theo. Chem. accepted.

(2) A hybrid stochastic-deterministic algorithm for cell signaling under the influence of fields. D. Wylie, Y. Hori, A. Dinner & A.K. Chakraborty, J. Phys. Chem. subm.

(3) Developing algorithm that combines signaling and migration (Chakraborty).

(4) Developing a method for modeling cytoskeletal rearrangements (Geissler).

(5) Developing a method for receptor endocytosis (Oster).

Model and Software Sharing Environments

- **Software Development; Languages and Tools:** C++, python, CVS, open MP, compiled and run on everything from Linux, C++ workstations and clusters to HPC platforms.

--> **We would be interested in software collaborations that aid in the dissemination of our models and algorithms**

- **Algorithmic challenges:**

  (1) To succinctly define and model processes of direct biological relevance.

  (2) To enable seamless algorithmic integration of multiple spatio-temporal scales.

- **Model Validation challenges:**

  (1) Identifying trends that clearly distinguish among different physical pictures.

  (2) Determining an acceptable level of quantitative agreement (parameter sensitivity).

  (3) Close collaboration with experimental biologists.

- **Multidisciplinary Collaboration challenges:**

  (1) Understanding the language and tools used by each discipline

  (2) Developing strong synergies between tools rooted in different disciplines

  (3) Familiarity with experiments.

PI: Head-Gordon

IMAG

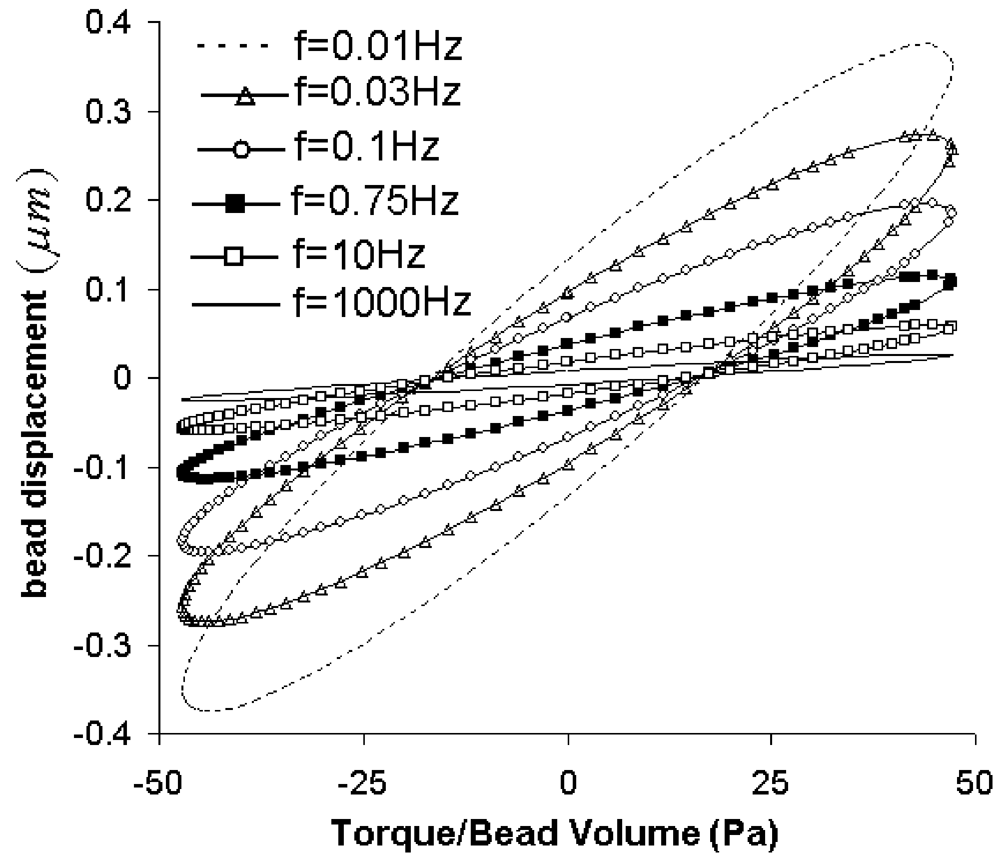
PI: Roger Kamm

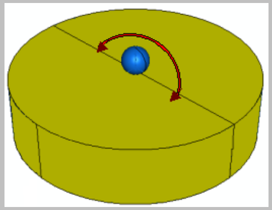
Title: Multi-scale Analysis of Cellular Force Transmission and Biochemical Activation

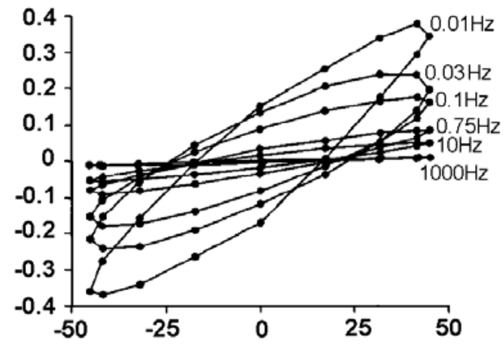
Institution: MIT

Funding Agency: NIH/NIGMS

Continuum finite element modeling -- soft glassy material constitutive law







Soft glassy material constitutuve law:

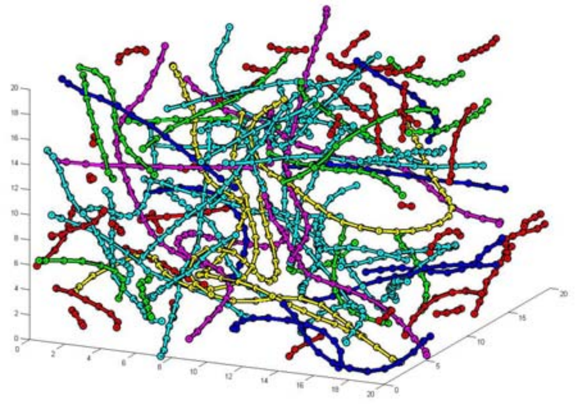
$$G^* = G_0\left(\frac{\omega}{\omega_0}\right)^{x-1}(1+i\bar{\eta})\Gamma(2-x)\cos\left[\frac{\pi}{2}(x-1)\right]+i\omega\mu$$

Modeling the cytoskeleton: Brownian dynamics modeling

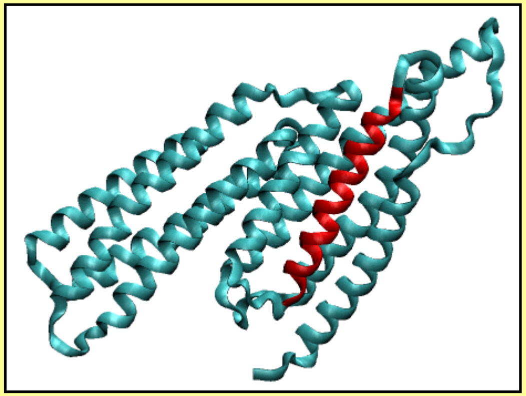
Using the Langevin equation:

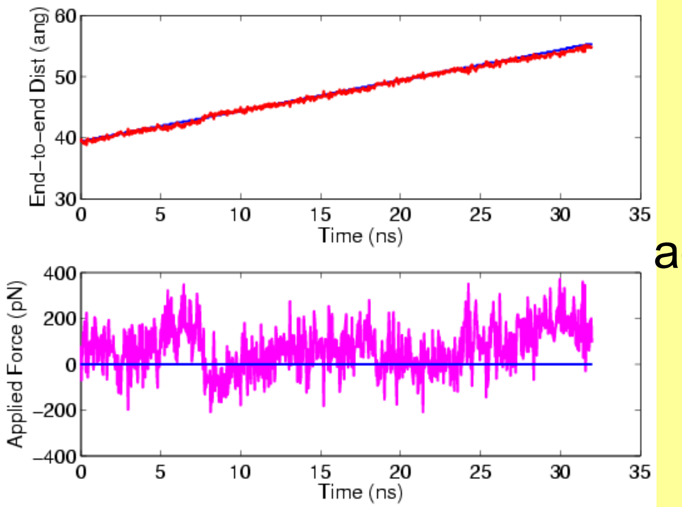
$$m\frac{d^2\vec{r}}{dt^2}=\sum_{i\neq j}\vec{f}_{ij}-\zeta\frac{d\vec{r}}{dt}+\vec{d}(t)$$

a 3D matrix of “actin” filaments is formed.



Atomistic simulations: Talin, one of the proteins within a focal adhesion



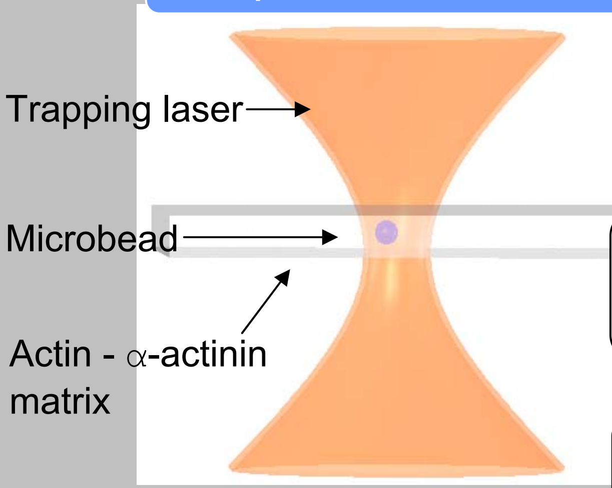


Force-extension curves for various actin binding proteins can be computed using molecular dynamics

Multi-scale Analysis of Cellular Force Transmission and Biochemical Activation **P.I., Roger D. Kamm**

Viscoelasticity of actin networks with α-actinin

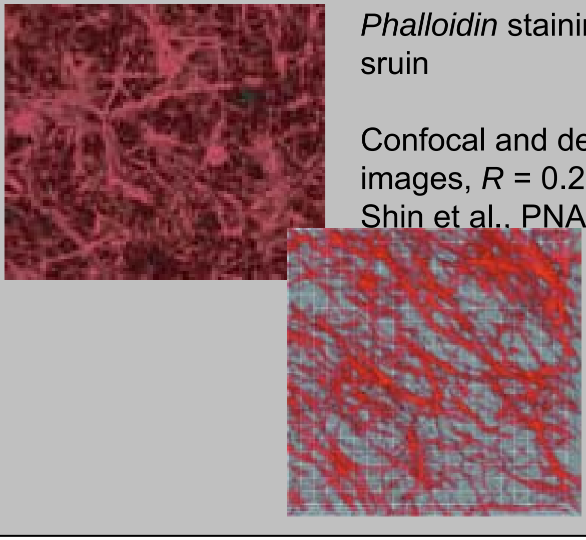
Optical tweezer microrheology



Prepare actin matrix with different concentrations

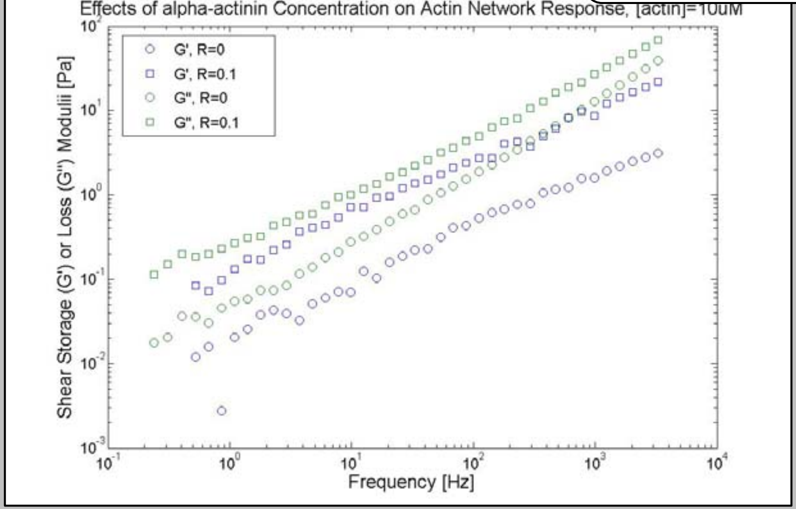
Optical tweezer measurement
1. Confined brownian motion
2. Transient step response

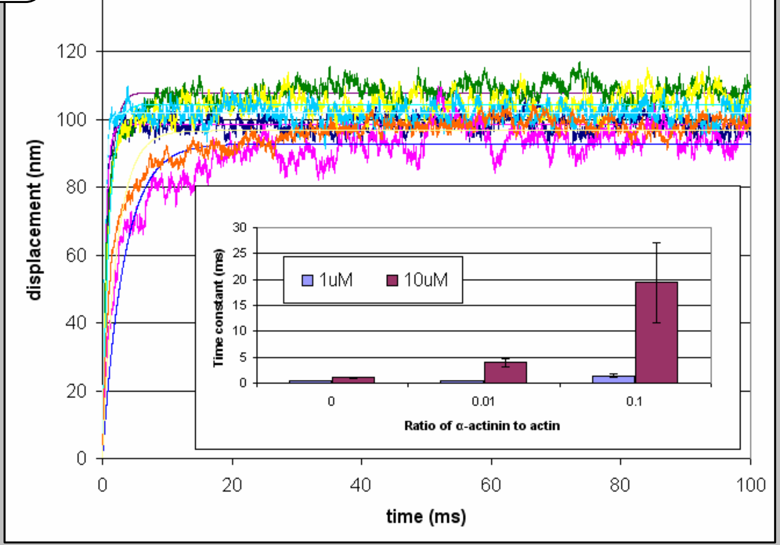
Mechanical properties of actin network with α-actinin



Texas red Phalloidin staining; actin + sruin

Confocal and deconvolved images, *R* = 0.2
Shin et al., PNAS, 2004





Multi-scale Analysis of Cellular Force Transmission and Biochemical Activation

P.I., Roger D. Kamm

IMAG

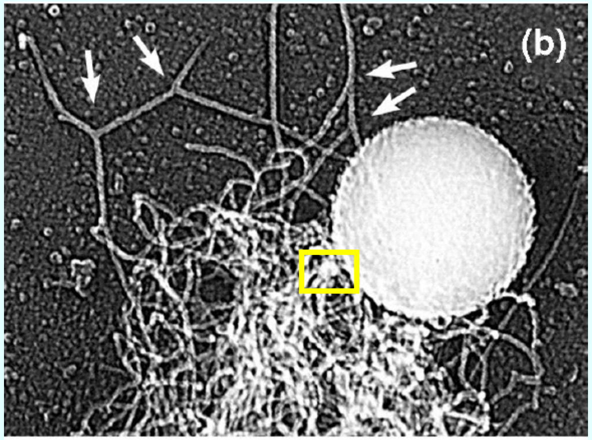
PI: Anthony Ladd

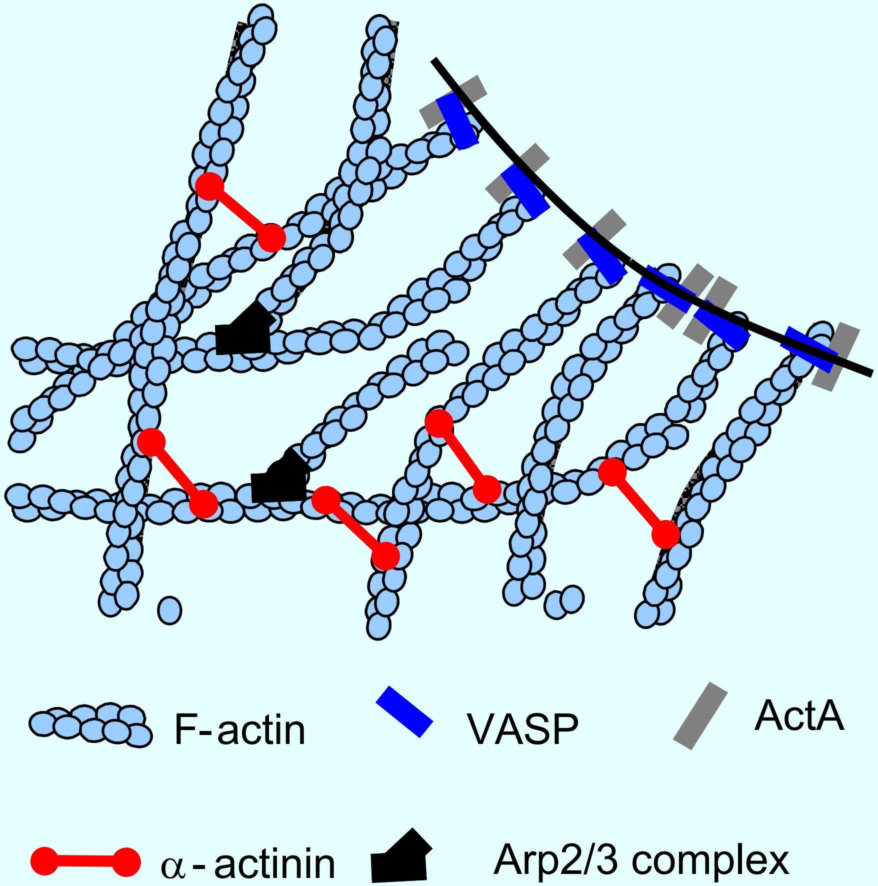
Title: Multi-scale modeling of chemical-to-mechanical energy conversion in actin-based motility

Institution: University of Florida

Funding Agency: NSF/CTS

Biochemical model of an actin network: Where does the force generation come from? Filaments remain attached (Dickinson and Purich)





<u>Forces</u>

Intramolecular:-Kirchoff rod

Intermolecular:-DVLO, Coulomb

Cross-links:-Rigid or elastic rods including orientation along rod

Hydrodynamic:-FLBE

Opportunities for code sharing

Lattice-Boltzmann model for hydrodynamic interactions and thermal fluctuations: available on request (solid particles)

New code for polymer solutions based on FLBE (under development); scales linearly with chain length; 10^8 time steps

Close to real-time dynamics of flexible polymers (Kuhn-scale model of DNA)

Dynamics of interacting elastic rods (under development)

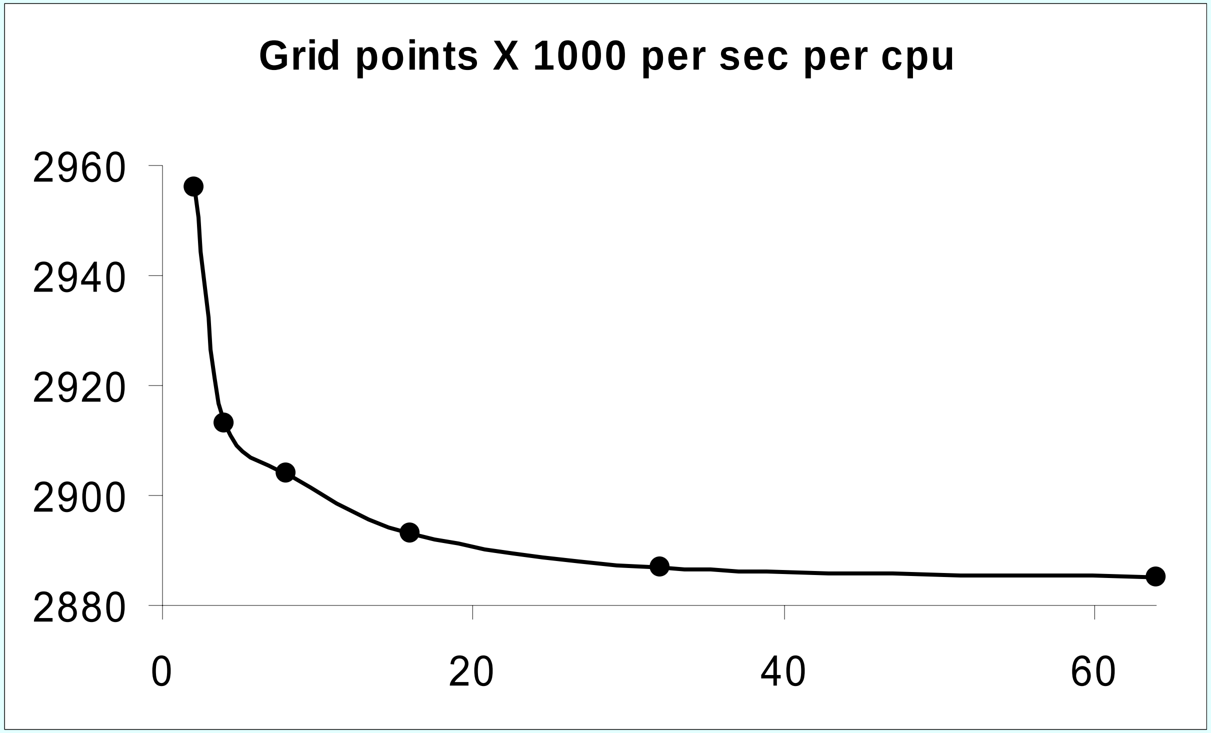
To be integrated with FLBE code.

Computational issues

Wide range of time scales require fine-grained parallelism

At present we get linear scaling with 10^6 nodes per cpu (97%)

Need to improve parallelism down to 10^4 nodes per cpu



Ladd: Actin motility

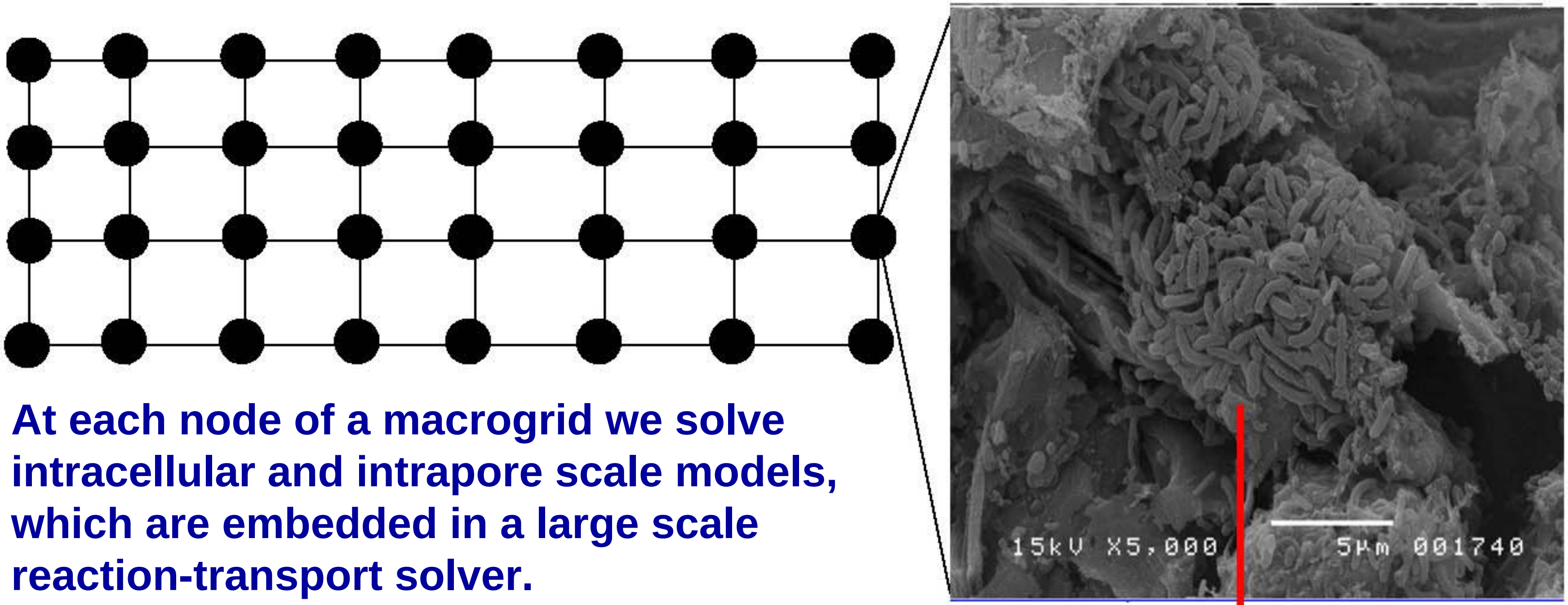
IMAG

PI: Peter Ortoleva

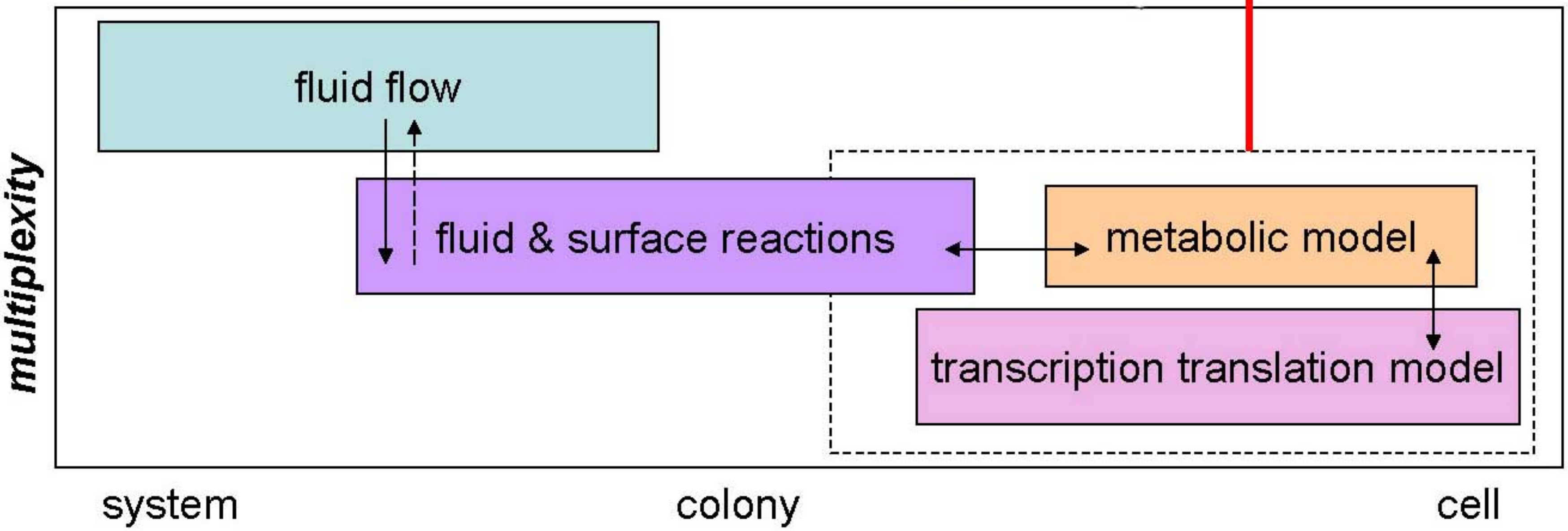
Title: Intercellular Genomics of Subsurface Microbial Colonies

Institution: Indiana University

Funding Agency: DOE/ASCR



At each node of a macrogrid we solve intracellular and intrapore scale models, which are embedded in a large scale reaction-transport solver.



IMAG

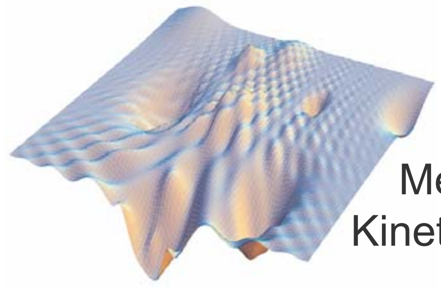
PI: Niles Pierce

Title: Coarse-graining DNA Energy Landscapes for the Analysis of Hybridization Kinetics

Institution: California Institute of Technology

Funding Agency: NSF/DMS

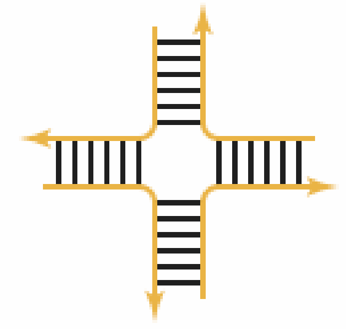
Nucleic Acid
Free Energy Landscape



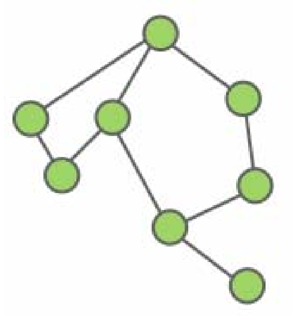
Equilibrium
Metastability
Kinetics

Characterize function of
- Synthetic DNA devices
- Regulatory RNAs

Secondary Structure Model



Set of base pairs



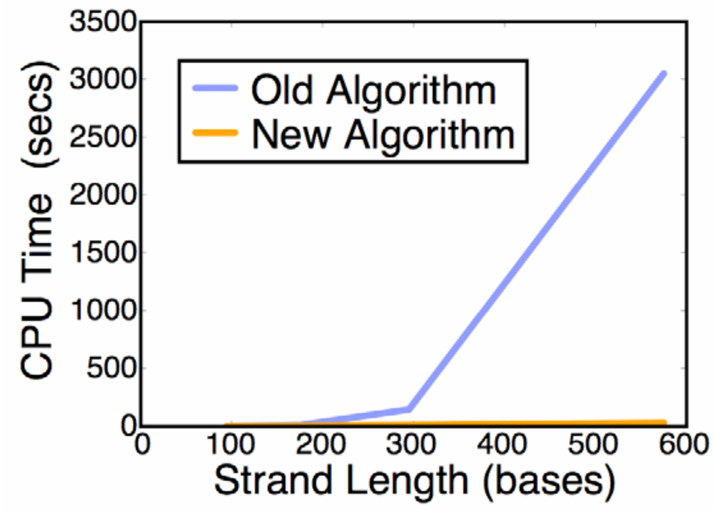
Landscape graph
- Node: 2° structure
- Edge: elementary step

Project 1: Fast Stochastic Kinetics

Consider a strand of length *N*

Landscape grows exponentially with *N*
- Infeasible to enumerate states

Explore using fast stochastic kinetics
- Generate trajectories from the exact probability distributions

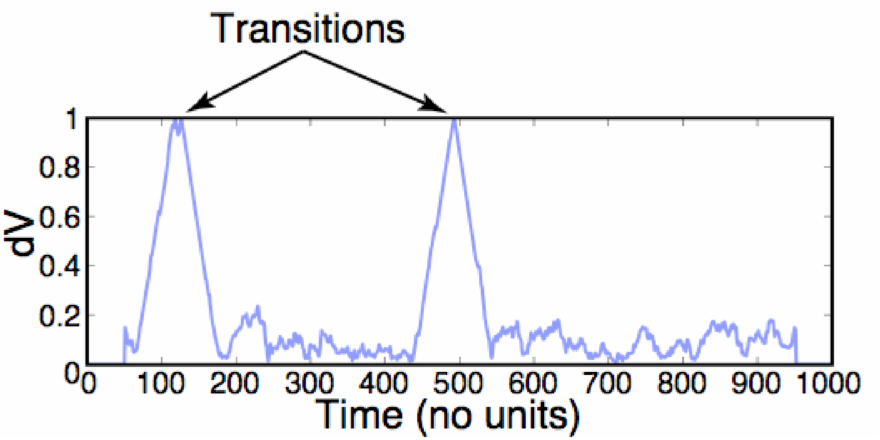


Old complexity: $O(N^5)$ (Flamm, *et al*., 2000)
New complexity: $O(N^3 \log N)$
New generality: multiple strands

Project 2: Trajectory-Based Coarse-Graining

Experiments often suggest that kinetics are dominated by a few macrostates

Identify transitions between macrostates on the fly by comparing occupancy distributions along trajectories

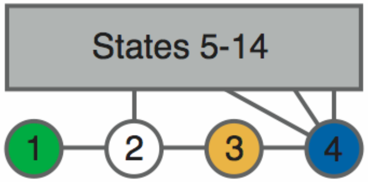


Combine repeated distributions into macrostates

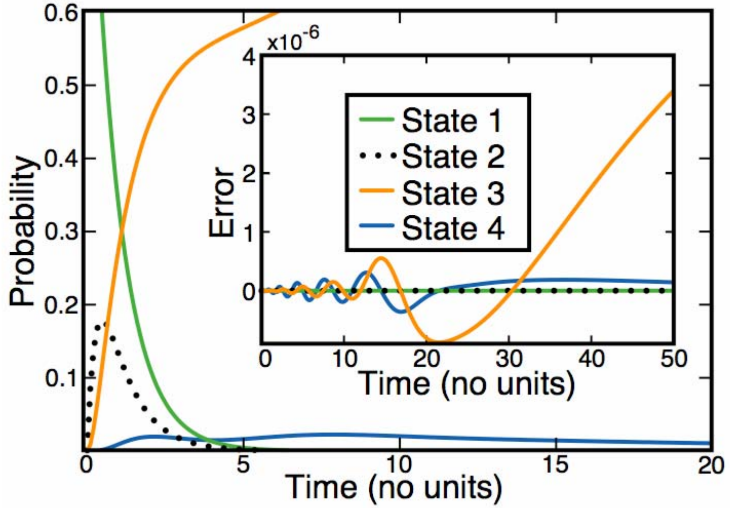
Estimate transition rates using local equilibrium approximation (Widom, 1965)

Project 3: Model Reduction of Subgraphs via Balanced Truncation

Treat subgraph (5-14) as a reservoir interacting with system of interest (1-4)



Reduce reservoir to 5 states (≈.00001 error) or 3 states (≈.01 error)



Attempt piecewise reduction of graphs

Project 4: Thermodynamic Analysis of Interacting Nucleic Acid Strands

Consider a test tube containing multiple strand species that interact to form multiple species of strand complexes

New multi-stranded partition function algorithm yields the equilibrium concentration of each complex species

The free energy landscape is convex when coarse-grained to complexes

Research Groups

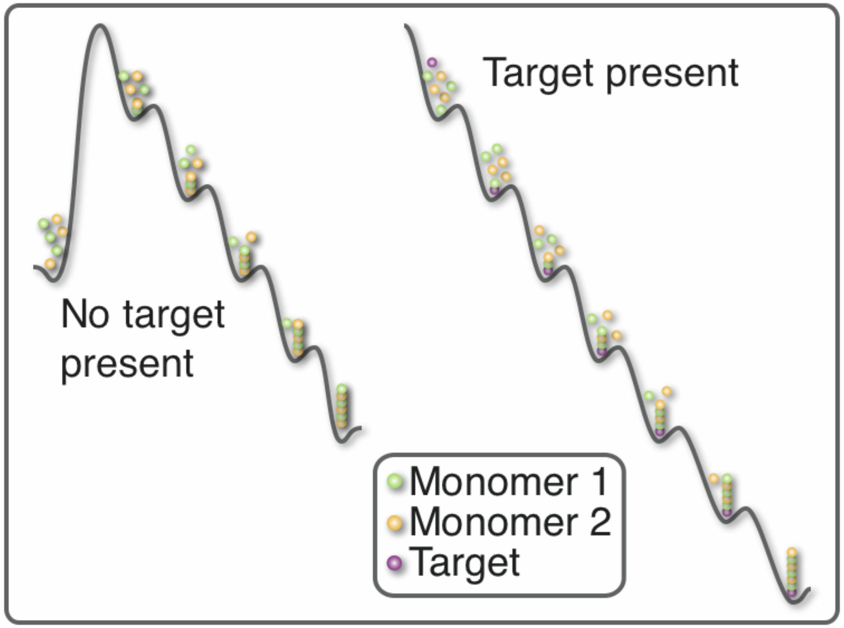
Hideo Mabuchi, Caltech
Niles Pierce, Caltech
Erik Winfree, Caltech
Bernard Yurke, Lucent Bell Labs

Software

www.nupack.org

Project 5: Mapping the Free Energy Landscape for HCR

Hybridization chain reaction: triggered amplification for biosensing



DNA hairpins polymerize only in the presence of target molecules

Equilibrium and kinetics calculations critical to interpreting experimental data

IMAG

PI: Jay Schieber

Title: CISE: Multiscale Modeling To Develop A Cyberinfrastructure For The Dynamics Of Flexible And Stiff Entangled Macromolecules

Institution: Illinois Institute of Technology

Funding Agency: NSF/OCI

Multiscale Modeling To Develop A Cyberinfrastructure For The Dynamics Of Flexible And Stiff Entangled Macromolecules

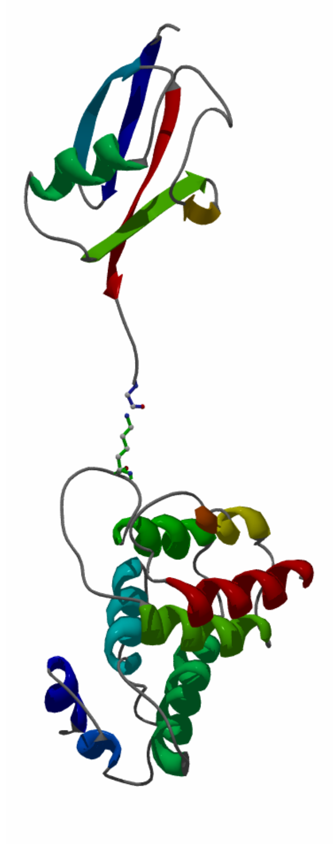
Jay D. Schieber

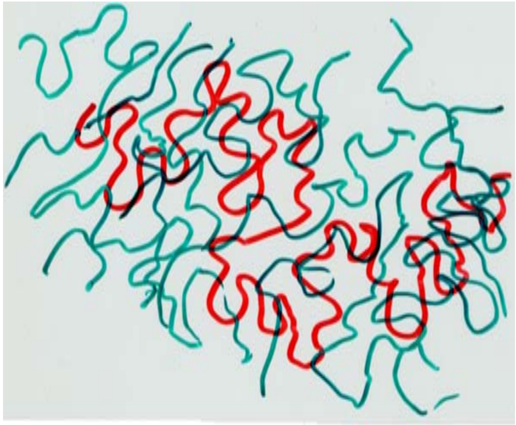
ILLINOIS INSTITUTE OF TECHNOLOGY

Transforming Lives. Inventing the Future.

Jorge Iñiguez-Lluhi

University of MICHIGAN



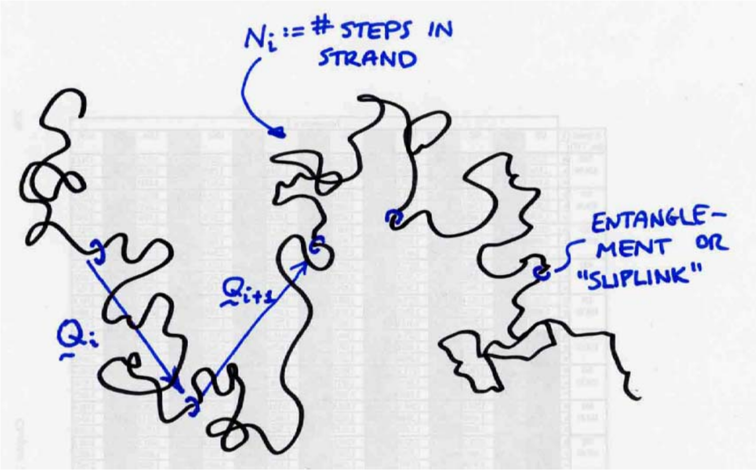


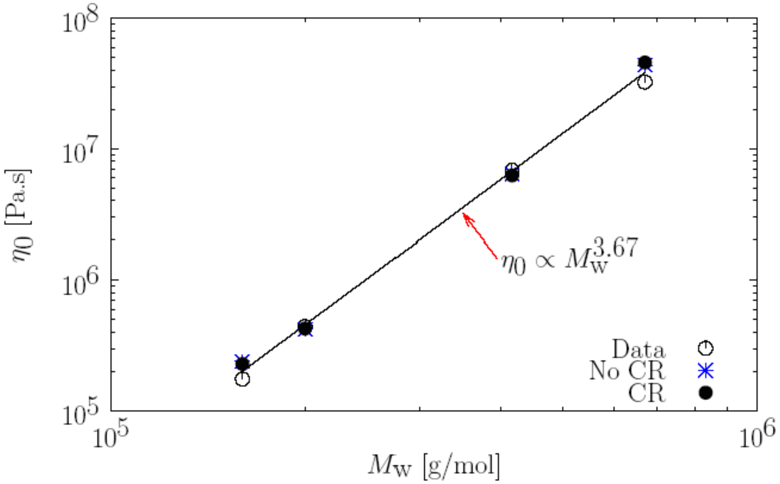
Study dynamics of single chain in concentrated environment.

Multiscale model to predict macroscopic behavior based on molecular architecture.

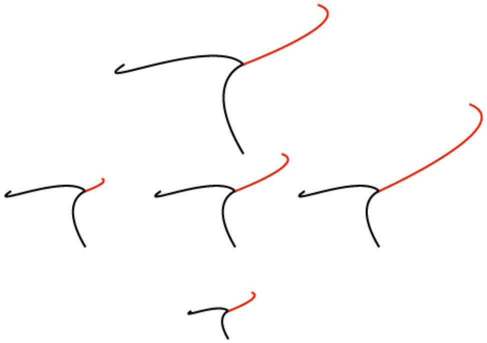
Theoretical

- Coarse-grained picture
- Stat. Mech. → Entropy
- Friction at entanglement
- Two parameter model
- Brownian Dynamics
- Linear and branched chains

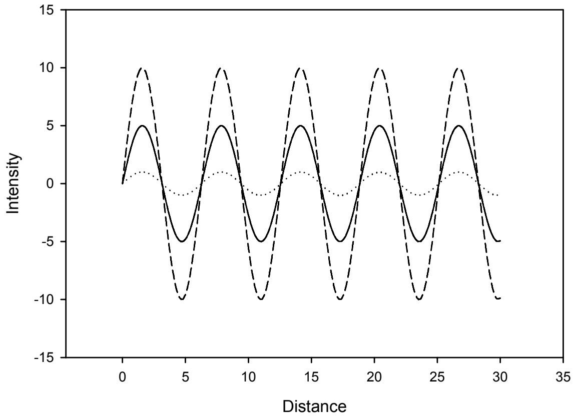




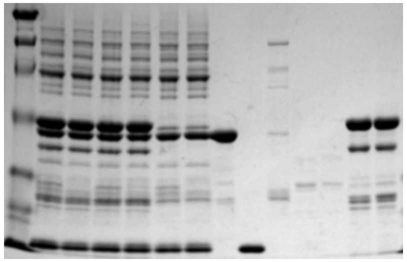
Experimental



- Novel Synthetic approach based on site-specific covalent attachment of Small Ubiquitin-like MOdifier proteins (SUMO).
  - Allows generation of defined branched architectures.



- Holographic grating technique (FRS)
  - To study diffusion of different protein architectures in well-characterized gels.



- Gel electrophoresis
  - To study the effect of architecture on electrophoretic mobility.

IMAG

PI: Stanislav Shvartsman

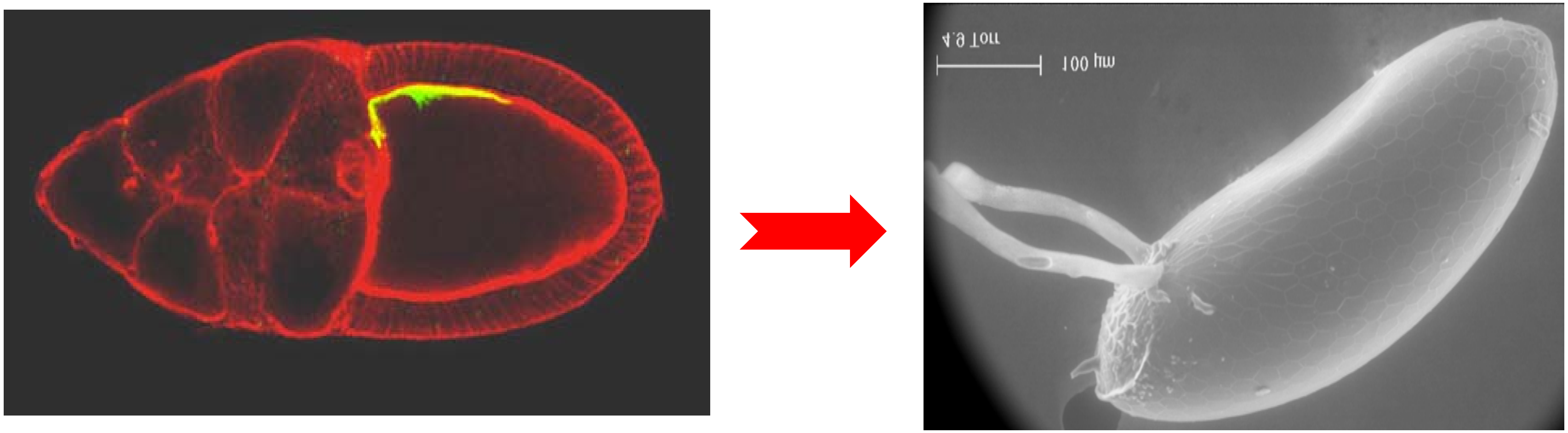
Title: Collaborative Research: Multiscale analysis of epithelial patterning: modeling and experiments

Institution: Princeton University

Funding Agency: NIH/NIGMS

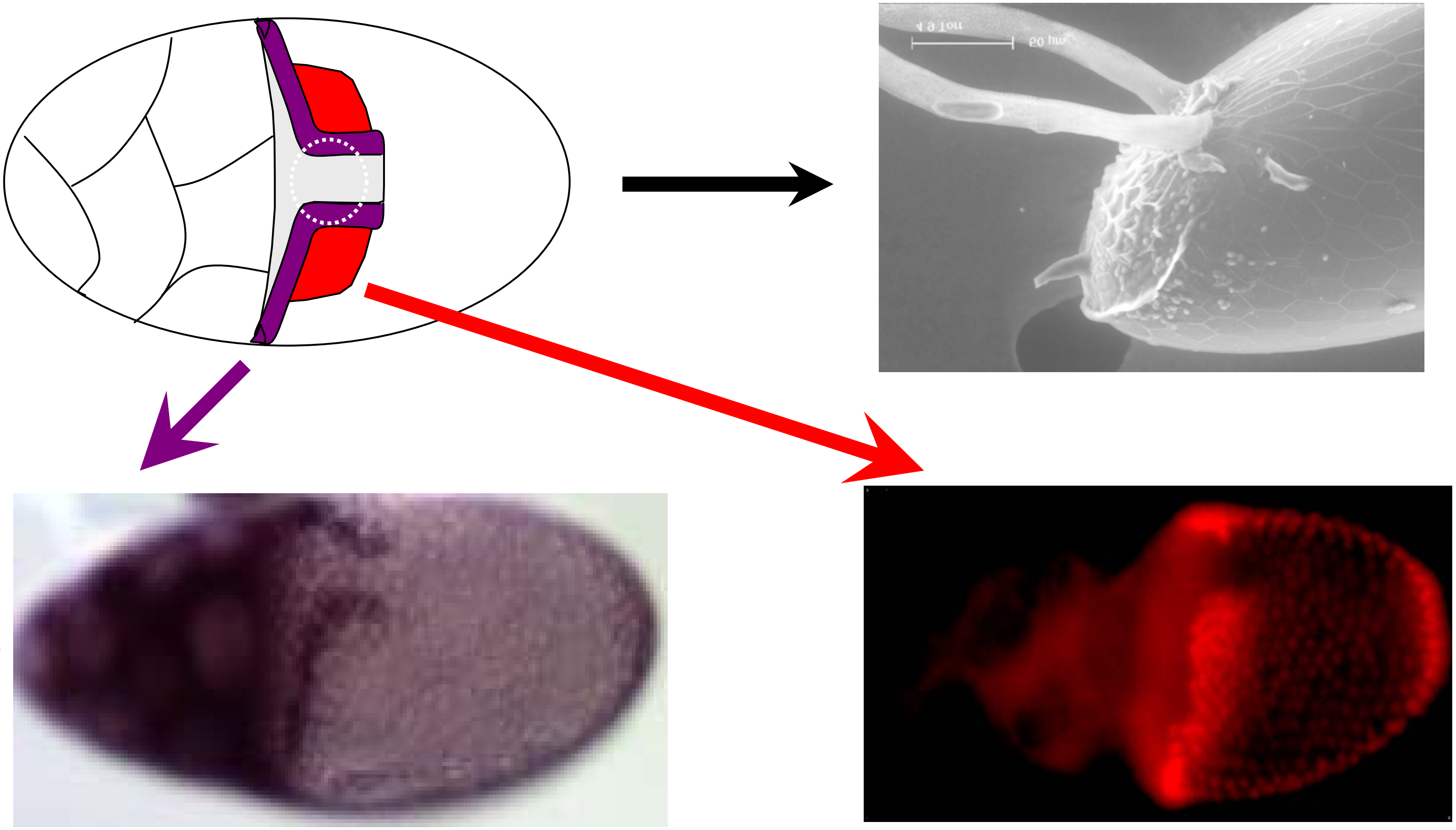
Experimental system

(DV patterning of the follicular epithelium)



1. Egg chamber: oocyte, 15 nurse cells, ~1000 epithelial cells
2. Eggshell: >10 cell fates (operculum, dorsal appendages, etc)
3. Morphology depends on cell-cell communication in oogenesis

Pattern formation and morphogenesis



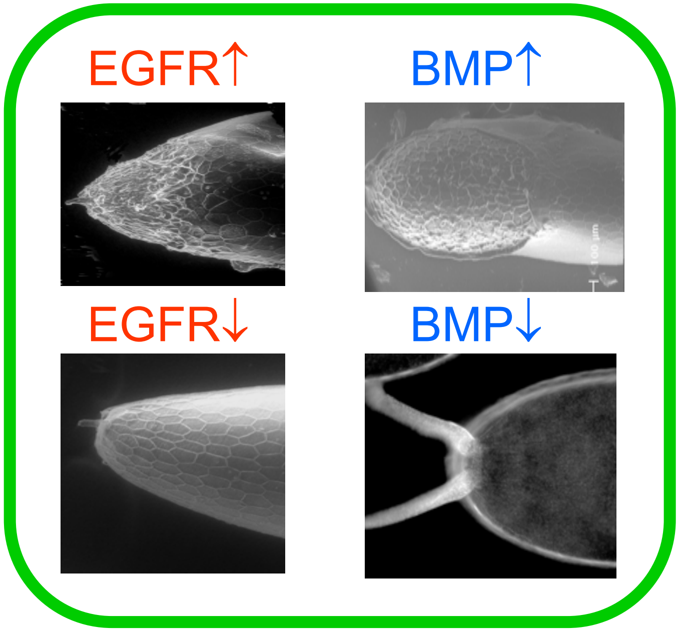
rho

Br

# of stripes = # of appendages

Microarray experiments

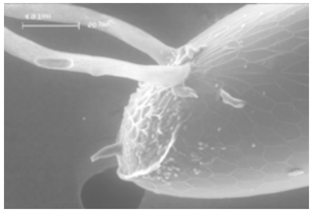
4 treatments

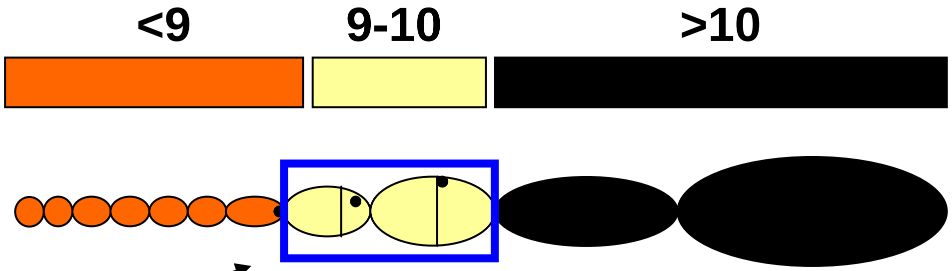


EGFR↑ BMP↑

EGFR↓ BMP↓

control





Analysis by “Golden Spike Method”
Choe S., *et al* Genome Biology 2005, 6:R16

(EGFR↑ OR EGFR↓) AND (BMP↑ OR BMP↓)

IMAG

PI: Michela Taufer

Title: DAPLDS: a Dynamically Adaptive Protein-Ligand Docking System based on Multi-Scale Modeling

Institution: UTEP

Funding Agency: NSF/OCI

Investigators, Objectives, and Research Fields

Investigators:

- Michela Taufer (UTEP). Patricia J. Teller (UTEP), Martine Ceberio (UTEP), Charles L. Brook, III (TSRI), David P. Anderson (UC Berkeley)

Objectives:

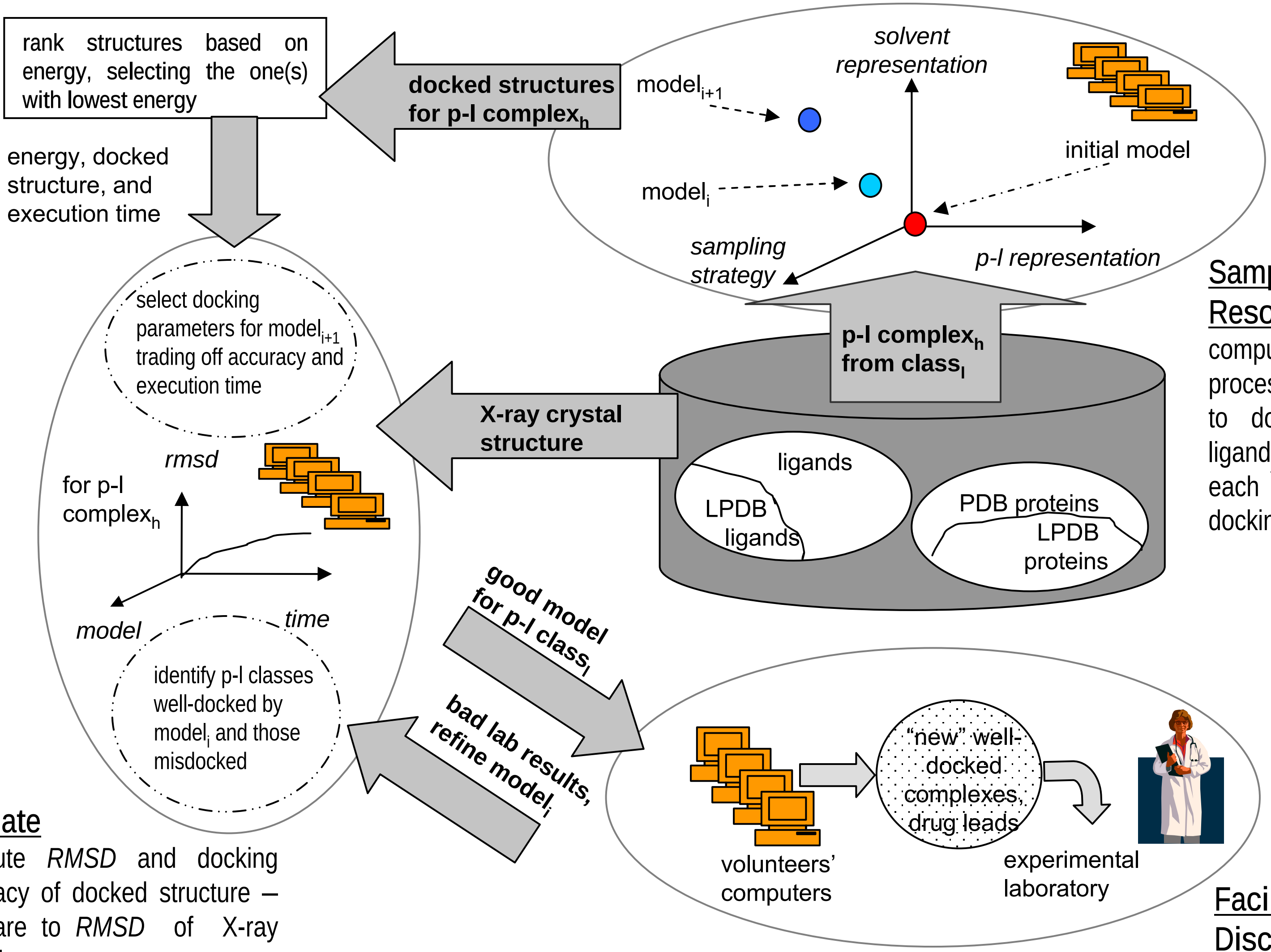
- to explore the multi-scale nature of algorithmic adaptations in protein-ligand docking
  - *protein-ligand representation*: spanning scale from rigid to flexible representation of protein-ligand interactions
  - *solvent representation*: spanning scale from less accurate to more accurate modeling of water treatment
  - *sampling strategy*: spanning scale from fixed to adaptive sampling of the protein-ligand docking space
- to develop cyber infrastructures based on computational methods and models that efficiently accommodate these adaptations

Research fields:

- docking methods (Drs. Charles L. Brooks III at TSRI and Michela Taufer at UTEP)
- decision theory (Dr. Martine Ceberio at UTEP)
- modeling for dynamic adaptation (Drs. Patricia J. Teller and Michela Taufer at UTEP)
- volunteer computing (Drs. David P. Anderson at UC Berkeley and Michela Taufer at UTEP)

Protein-Ligand Docking System based on Multi-Scale Modeling

Project Overview



rank structures based on energy, selecting the one(s) with lowest energy

docked structures for p-l complex$_h$

model$_{i+1}$

solvent representation

initial model

model$_i$

sampling strategy

p-l representation

energy, docked structure, and execution time

select docking parameters for model$_{i+1}$ trading off accuracy and execution time

p-l complex$_h$ from class$_l$

X-ray crystal structure

ligands

LPDB ligands

PDB proteins

LPDB proteins

rmsd

for p-l complex$_h$

model

time

identify p-l classes well-docked by model$_i$ and those misdocked

good model for p-l class$_l$

bad lab results, refine model$_i$

volunteers' computers

"new" well-docked complexes, drug leads

experimental laboratory

Sample using Volunteers' Resources

computer simulation of docking process using model$_i$ -- attempt to dock a transformation of ligand$_j$, orienting it differently on each attempt, at potential docking sites of protein$_k$

Validate

compute *RMSD* and docking accuracy of docked structure – compare to *RMSD* of X-ray crystal structure

Facilitate Drug Discovery

use model$_i$, which effectively well-docks p-l class$_l$, to identify "new" well-docked complexes from class$_l$

M. Taufer - SCI: Collaborative Research: DAPLDS - a Dynamically Adaptive Protein-Ligand Docking System based on Multi-Scale Modeling