IMAG

Interagency Modeling and Analysis Group

NIH
- NIBIB
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- NIGMS
- NIMH
- NINDS
- NLM

NSF
- Eng
- Bio
- CISE
- MPS

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DOE
- BER
- ASCR

DOD
- Army
- DARPA
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Interagency Modeling and Analysis Group (IMAG)

Multiscale Modeling (MSM) Post-Award Meeting Materials

Materials include:
Award Listing
Scientific Area Groupings
Comparison of Scales
Modeling Methods Groupings
Answers to the Questionnaire
Existing Environments
Individual Project Profiles

MSM Awardees Directory

PI Name	Proposal Title	Institution
Victor Barocas	Multiscale Mechanics of Bioengineered Tissues	University of Minnesota
James Bassignthwaighte	Adaptive Multi-Scale Model Simulation, Reduction and Integration for Cardiac Muscle Physiology	University of Washington
Daniel Beard	Multiscale Modeling of the Heart in Metabolic Syndrome and Cardiovascular Disease	Medical College of Wisconsin
James Brasseur	Micro-scale Transport as a Critical Link between Molecular-scale Absorption and Macro-scale Mixing in Gut Physiology and Function	The Pennsylvania State University
Marco Cabrera	Time Course of Metabolic Adaptations during Loading and Unloading	Case Western Reserve University
David Cai	Collaborative Research: Cortical Processing across Multiple Time and Space Scales	Courant Institute
Yoonsuck Choe	Multiscale Imaging, Analysis, and Integration of Brain Networks	Texas Engineering Experiment Station
James Glazier	Multiscale Studies of Segmentation in Vertebrate Embryos	Indiana University
Trent Guess	Dynamic Simulation of Joints Using Multi-Scale Modeling	University of Missouri - Kansas City
Teresa Head-Gordon	Multiscale Models to Study How Spatial Organization of Cellular Components Influences Signaling	UC Berkeley
Roger Kamm	Multi-scale Analysis of Cellular Force Transmission and Biochemical Activation	MIT
George Karniadakis	A Stochastic Molecular Dynamics method for multiscale modeling of blood platelet phenomena	Brown University
Denise Kirschner	A multi-scale approach for understanding antigen presentation in immunity	University of Michigan
Robert Kunz	Multiscale Human Respiratory System Simulations to Study the Health Effects of Aging, Disease and Inhaled Substances	Penn State University
Anthony Ladd	Multi-scale modeling of chemical-to-mechanical energy conversion in actin-based motility	University of Florida
Ching-Long Lin	Multiscale simulation of gas flow distribution in the human lung	University of Iowa
Ernst Georg Luebeck	Scales of carcinogenesis: cells, crypts and cancer	Fred Hutchinson Cancer Research Center
Andrew McCulloch	Multi-scale modeling of the mouse heart: from genotype to phenotype	UCSD
Peter Ortoleva	Intercellular Genomics of Subsurface Microbial Colonies	Indiana University
Niles Pierce	Coarse-graining DNA Energy Landscapes for the Analysis of Hybridization Kinetics	Caltech
Jay Schieber	CISE: Multiscale Modeling To Develop A Cyberinfrastructure For The Dynamics Of Flexible And Stiff Entangled Macromolecules	Illinois Institute of Technology
Stanislav Shvartsman	Collaborative Research: Multiscale analysis of epithelial patterning: modeling and experiments	Princeton University
Michela Taufer	DAPLDS: a Dynamically Adaptive Protein-Ligand Docking System based on Multi-Scale Modeling	UTEP
Bridget Wilson	Mapping and Modeling ErbB Receptor Membrane Topography	University of New Mexico Health Sciences Center

MSM Awardees- Science Areas

Cardiovascular			Subject
Victor Barocas	Multiscale Mechanics of Bioengineered Tissues	University of Minnesota	*Tissue Engineering*
James Bassingthwaighte	Adaptive Multi-Scale Model Simulation, Reduction and Integration for Cardiac Muscle Physiology	University of Washington	*Muscle Physiology*
Daniel Beard	Multiscale Modeling of the Heart in Metabolic Syndrome and Cardiovascular Disease	Medical College of Wisconsin	*Metabolism*
Marco Cabrera	Time Course of Metabolic Adaptations during Loading and Unloading	Case Western Reserve University	*Metabolism*
George Karniadakis	A Stochastic Molecular Dynamics method for multiscale modeling of blood platelet phenomena	Brown University	*Blood*
Andrew McCulloch	Multi-scale modeling of the mouse heart: from genotype to phenotype	UCSD	*Physiology*
Robert Kunz	Multiscale Human Respiratory System Simulations to Study the Health Effects of Aging, Disease and Inhaled Substances	Penn State University	*Lung*
Ching-Long Lin	Multiscale simulation of gas flow distribution in the human lung	University of Iowa	*Lung*

Other Systems			Subject
James Brasseur	Micro-scale Transport as a Critical Link between Molecular-scale Absorption and Macro-scale Mixing in Gut Physiology and Function	The Pennsylvania State University	*Gastrointestinal*
David Cai	Collaborative Research: Cortical Processing across Multiple Time and Space Scales	Courant Institute	*Brain*
Yoonsuck Choe	Multiscale Imaging, Analysis, and Integration of Brain Networks	Texas Engineering Experiment Station	*Brain*
Trent Guess	Dynamic Simulation of Joints Using Multi-Scale Modeling	University of Missouri - Kansas City	*Musculoskeletal*
Denise Kirschner	A multi-scale approach for understanding antigen presentation in immunity	University of Michigan	*Immunology*
Ernst Georg Luebeck	Scales of carcinogenesis: cells, crypts and cancer	Fred Hutchinson Cancer Research Center	*Cancer*
Bridget Wilson	Mapping and Modeling ErbB Receptor Membrane Topography	University of New Mexico Health Sciences Center	*Cancer*

Biological			Subject
James Glazier	Multiscale Studies of Segmentation in Vertebrate Embryos	Indiana University	*Developmental*
Teresa Head-Gordon	Multiscale Models to Study How Spatial Organization of Cellular Components Influences Signaling	UC Berkeley	*Developmental*
Roger Kamm	Multi-scale Analysis of Cellular Force Transmission and Biochemical Activation	MIT	*Signaling*
Anthony Ladd	Multi-scale modeling of chemical-to-mechanical energy conversion in actin-based motility	University of Florida	*Micromechanics*
Peter Ortoleva	Intercellular Genomics of Subsurface Microbial Colonies	Indiana University	*Actin*
Niles Pierce	Coarse-graining DNA Energy Landscapes for the Analysis of Hybridization Kinetics	Caltech	*Mircobial*
Jay Schieber	CISE: Multiscale Modeling To Develop A Cyberinfrastructure For The Dynamics Of Flexible And Stiff Entangled Macromolecules	Illinois Institute of Technology	*DNA*
Stanislav Shvartsman	Collaborative Research: Multiscale analysis of epithelial patterning: modeling and experiments	Princeton University	*Polypeptides*
Michela Taufer	DAPLDS: a Dynamically Adaptive Protein-Ligand Docking System based on Multi-Scale Modeling	UTEP	*Polypeptides*

Scales Comparison – Time

Each Multiscale Modeling project covers multiple scales, but each project is different. These tables summarize the different scales covered by each project in time, length, and biology.

Cardiovascular	ns	μs	ms	s	min	hrs	days	months	years
Barocas	x	x	x	x	x				
Bassingthwaighte		x	x	x	x	x			
Beard		x	x	x	x	x	x	x	
Cabrera			x	x	x	x	x	x	
Kunz		x	x	x	x	x	x		
Karniadakis		x	x	x	x	x	x	x	x
Lin		x	x	x	x				
McCulloch		x	x	x	x	x	x	x	

Other Systems	ns	μs	ms	s	min	hrs	days	months	years
Brasseur			x	x	x	x			
Cai		x	x	x	x				
Choe									
Guess				x					
Kirschner		x	x	x	x	x	x		
Luebeck						x	x	x	x
Wilson		x	x	x	x	x			

Biological	ns	µs	ms	s	min	hrs	days	months	years
Glazier				x	x	x	x	x	
Head-Gordon	x	x	x	x	x	x	x		
Kamm		x	x	x	x	x	x		
Ladd		x	x	x	x	x	x	x	x
Ortoleva			x	x	x	x	x		
Pierce		x	x	x	x	x	x	x	
Schieber	x	x	x	x	x				
Shvartsman				x	x	x			
Taufer	x	x							

Scales Comparison – Length

Cardiovascular	*nm*	*µm*	*mm*	*cm*	*dm*	*meter*
Barocas	x	x	x	x		
Bassingthwaighte	x	x	x	x	x	x
Beard		x	x	x	x	
Cabrera	x	x	x	x	x	
Kunz		x	x	x		
Karniadakis		x	x	x	x	
Lin		x	x	x	x	
McCulloch	x	x	x	x		

Other Systems	*nm*	*µm*	*mm*	*cm*	*dm*	*meter*
Brasseur	x	x	x	x	x	
Cai		x	x	x	x	
Choe		x	x	x		
Guess		x	x	x	x	
Kirschner	x	x	x	x		
Luebeck		x	x	x	x	
Wilson	x	x	x	x		

Biological	nm	µm	mm	cm	dm	meter
Glazier		x	x	x	x	
Head-Gordon	x	x	x	x		
Kamm	x	x	x	x		
Ladd		x	x	x	x	
Ortoleva	x	x	x	x	x	
Pierce	x	x	x			
Schieber	x	x				
Shvartsman	x	x	x			
Taufer	x					

Scales Comparison – Biological

Cardiovascular	***atm***	***mol***	***mol-comp***	***sub-cell***	***cell***	***multi-cell***	***tissue***	***organ***	***organ sys***	***organism***	***pop***
Barocas	x	x	x	x	x	x	x				
Bassingthwaighte				x	x	x	x	x	x		
Beard		x	x	x	x	x	x	x	x	x	
Cabrera				x	x	x	x	x	x	x	
Kunz		x	x	x	x	x	x	x	x		
Karniadakis					x	x	x	x	x		
Lin							x	x	x		
McCulloch		x	x	x	x	x	x	x	x		

Other Systems	***atm***	***mol***	***mol-comp***	***sub-cell***	***cell***	***multi-cell***	***tissue***	***organ***	***organ sys***	***organism***	***pop***
Brasseur		x	x	x	x	x	x	x	x		
Cai				x	x	x	x				
Choe		x	x	x	x	x	x	x			
Guess							x	x	x		
Kirschner		x	x	x	x	x	x	x	x		
Luebeck					x	x	x	x	x	x	x
Wilson		x	x	x	x		x				

Biological	atm	mol	mol-comp	sub-cell	cell	multi-cell	tissue	organ	organ sys	organism	pop
Glazier		x	x	x	x	x	x	x	x		
Head-Gordon		x	x	x	x	x	x				
Kamm		x	x	x	x	x	x				
Ladd		x	x	x	x						
Ortoleva				x	x	x					
Pierce		x	x	x							
Schieber	x	x	x	x	x						
Shvartsman				x	x	x	x	x			
Taufer	x	x	x								

Categories by Modeling Methods

- Finite Element Methods
  - Barocas, Beard, Glazier, Kamm, Lin, McCulloch
- Reduced model formulation, sys ID, integration across scales
  - Bassingthwaighte, Cabrera, Kunz, Pierce
- Dynamic - ordinary and partial DE
  - Beard, Cabrera, Glazier, Kirschner, McCulloch, Ortoleva, Shvartsman
- Numerical Methods, fast algorithms, stochastic
  - Brasseur, Cai, Glazier, Head-Gordon, Kamm, Kirschner, Karniadakis, Ladd, Luebeck, Pierce, Schieber, Shvartsman, Taufer, Wilson
- Image processing
  - Choe, Lin

Desired Collaborative Environment

- Communication, interaction, meetings
- Access, information distribution
  - Interactive, centralized website
  - model repository, documentation
  - tool repository for models
  - threaded online discussion
  - Grid resource
- Model validation
- Organization, oversight, modular, long-term maintenance, common formats
- Communication between groups of graduate students
- Special conferences, journal publications, collaborative proposals

Challenges for Sharing Models

- Model documentation
- Interoperability of coding languages, validated models
- Platform dependence
- Solutions
  - Standard data formats to archive and share models
  - CellML with FieldML
- Models are scale, science, goal specific
- Integrate models that are **modular**, flexible and user-friendly
- Framework for easy replication of results
- Patient and task-specific biomechanical models
- Different scientist working on same biological problem
- Culture of adopting standard code

Challenges for Multi-disciplinary Collaboration

- Starting the conversation, speaking the same language, using the same terminology, tools, mutual appreciation, break down cultural barriers
- Mutual understanding of relevant problems, goals and objectives
- Focus on synthesis rather than analysis to fill gaps in different domains
- Broaden expertise and knowledge of collaborators
- Different approaches (hypothesis-driven vs. analytic models)
- Engineers oversimplifying the biological system, biological phenomena across laboratories
- Mathematicians not eager to understand meaning of biological error, need to be familiar with experiments
- Biologist not eager to understand modeling process and meaning of equations, fear of mathematics
- Biologist focused on phenomena in local laboratory
- Extend collaborations beyond 3 years
- Lack of suitable trainees with multidisciplinary background
- Identifying biologists studying small RNAs with interesting hybridization kinetics
- Time commitment for developing mutual understanding
- Statistical description of structure versus deterministic description of structure

Challenges for Linking Scales

- Understanding mechanisms when bridging scales, rather than methods
- Good input data, reliable data translation from in vitro to in vivo
- Scales varying by orders of magnitude – stiff problems
- Composite models at the same level with common parameterization
- Reduced robustness of higher level models
- Biological, physical and mathematical reductions and integrations
- Dynamic effects affecting properties across scales (rigid vs. flexible, sampling issues)
- Integrated data collection across scales
- Identify bridging phenomena at each scale to integrate scales
- Common tools, common variables, integration of existing models
- Define geometric, spatial and time scale separations and their coupling
- Creation of discrete-continuous algorithms
- Visualizing results at multiple scales
- Small scale effects on long-time
- Small scale effects on large scales
- Automatic 3D meshes across scales
- Statistical issues across scales
- Available functional and structural data
- Efficiently mapping free energy landscapes

Challenges for Model Validation

- Acquiring a good test case/problem, quantitative data of high reliability and variety
- Common definition of “validation”
- Variability of biological samples – in vivo measurements and in vivo testing
- Validation at one scale, not necessarily valid at other scales
- Validation for one phenomena, not necessarily valid with other phenomena
- Interactive data annotation environment, distributed and web-based
- Access to electronically available data
- Confirming simulation results that cannot be measured
- In vivo to in vitro translation for simulation and validation
- Computational scientists working at different scales should work on same biological problem
- Identify trends that distinguish physical pictures
- Acceptable standards and metrics for quantitative agreement, common validation tools
- Multidisciplinary collaboration
- Linking validation studies, validation experiments
- Differences between animal and human models and data acquisition
- Technology for single cell genome wide assays not available
- Expensive biological experiments
- Building multi-channel single-molecule fluorescence microscopy instruments
- Time intensive automated image analysis methods

Existing Sharing Environments

Cardiovascular

- www.physiome.org – model repository, CellML, JSim (Bassingthwaighte, Beard, McCulloch)
- Cell Modeling Database (Beard)
- NIH Center for Modeling Integrated Metabolic Systems (Cabrera)
- Adaptive finite element software platform (Barocas)
- PSU Exterior Communications Interface (Kunz)
- MPICH-G2/TeraGrid (Karniadakis)

Biological

- CompuCell3D (Glazier)
- Peer-to-peer (P2P) file sharing (Brasseur)
- CHARMM for molecular dynamics (Kamm)
- NUPACK (Nucleic Acid Package) www.nupack.org (Pierce)
- DAPLDS project and several other environments (Taufer)

Other Systems

- Musculoskeletal model databases (Guess)
- MIT website for Multiscale Modeling and Mechanobiology (Kamm)
- SIMBIOS – SIMTK (Larkin)

Project Profiles

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Co-PIs and Collaborators
N/A

Project Title
Multiscale Mechanics of Bioengineered Tissues

Grant Details and Funding Agency
Grant Number: 1 R01 EB005813-01
Agency: National Institute for Biomedical Imaging and Bioengineering (NIH-NIBIB)
Program Officer: F. Wang

Scales Examined

Time Scales

☒	Nanosecond and below (ns)
☒	Microsecond (μs)
☒	Millisecond (ms)
☒	Second (s)
☒	Minutes
☐	Hours
☐	Days
☐	Months
☐	Years and above

Biological Scales

☒	Atomic
☒	Molecular
☒	Molecular Complexes
☒	Sub-Cellular
☒	Cellular
☒	Multi-Cellular Systems
☒	Tissue
☐	Organ
☐	Organ Systems
☐	Organism
☐	Population
☐	Behavior

Length Scales

☒	Nanometer and below (nm)
☒	Micrometer (μm)
☒	Millimeter (mm)
☒	Centimeter (cm)
☐	Ten Centimeter
☐	Meter

Disease Focus
N/A

Organism of study
N/A

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus
50%, Artificial tissues with application to cardiovascular tissue engineering, How fiber diameter affects macroscale properties within engineered cardiovascular tissues, Biomechanics, tissue engineering, materials.

Modeling Methods and Tools (MMT) Areas and Percent Focus
50%, Finite element methods, Using volume averaging theory, applying to system, Adaptive finite element methods, high performance parallel computing, the last two will bridge between scales – using statistical parameters to solve detailed model, resulting in pseudo-physiologically realistic.

Software Development
Languages and Tools: n/a
Framework / Sharing Environment: Collaborators are in the process forming an adaptive finite element software platform, Interested in user interactive framework as well as developer framework.
Available Resources: n/a

Project Summary:
The major challenges in biopolymer-based engineering of load-bearing tissues are mechanical-strength and stiffness. In vitro, as in vivo, properties are controlled by composition and architecture, on the nm-mu m scale of the fibril network. The functional scale is much larger, mm-cm. We will create, implement, validate, and disseminate a computational tool to predict functional scale mechanics based on a network-scale model of engineered tissues. The model will use volume-averaging theory to couple across scales, yielding a macroscopic equation set informed by microscopic behavior. The theory allows study of different systems by varying only the microscopic model. Coupling will occur at Gauss points of the macroscopic finite elements. P-adaptivity will be used to optimize distribution of Gauss points, and the software will operate in parallel to meet the computational demands of many microscopic-scale model solves. Experimental validation will be performed by comparison with two systems. Acellular fibrin-collagen co-gels have two distinct, relatively well-characterized networks. Cultured fibrin-based model tissues, in which entrapped smooth-muscle cells have secreted collagen and elastin, will be more difficult to characterize, but they will be a key step towards the goal of a general model of engineered tissue micromechanics. The program announcement identifies three critical expectations: collaboration, scale-bridging, and new understanding. Some of the team members have worked together in the past, but this project is a new link between mechanics, computational science, and tissue engineering. Likewise, it will link the microscopic scale (most easily controlled by the tissue engineer), and the macroscopic scale (needed for tissue performance). The lack of clear understanding of even simple artificial tissues presents an opportunity for major advancement by drawing on the microstructure to describe the material. This project is highly relevant to public health because of the large potential impact of engineered tissue, particularly structural cardiovascular tissue. Many people need replacement arteries or valves, and there are severe flaws with existing options, creating the need for a new generation of artificial tissues. Understanding, predicting, and controlling the mechanical properties of those tissues will be a critical step forward.

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

Grant Details and Funding Agency
Grant Number:
Agency: National Science Foundation (NSF)
Program Officer: S. Demir

Scales Examined

Time Scales

☐	Nanosecond and below (ns)
☒	Microsecond (μs)
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☒	Cellular
☒	Multi-Cellular Systems
☒	Tissue
☒	Organ
☒	Organ Systems
☐	Organism
☐	Population
☐	Behavior

Length Scales

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☒	Centimeter (cm)
☒	Ten Centimeter
☒	Meter

Disease Focus
Cardiovascular and Skeletal Muscle disorders

Organism of study
Mammalian systems

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus
Biological Systems Analysis (50%); Cardiorespiratory Modeling (40%); Simulation Software development (10%)

Modeling Methods and Tools (MMT) Areas and Percent Focus
Model development (40%); Reduced model formulation and optimization (30%); Automating model substitution (30%)

Software Development
Languages and Tools: JSim, Simulation software package for algebraic, ordinary, and partial differential equations; optimization; data fitting; sensitivity and behavioral analysis.
Framework / Sharing Environment: JSim is open use software downloadable at http://nsr.bioeng.washington.edu. Will become open source. Runs on linux, unix, Windows, Macintosh OSX.
Available Resources: Archive and resource for biological models. Source code and documentation available for models at both websites. Current planning is to move all model to the Physiome website, www.physiome.org.

Project Summary:
This proposal is to develop a novel approach to carrying out simulations with continuous monitoring and dynamic control of the computing at subsidiary modules. The project will develop innovative methods for adaptive multiscale modeling, simulation and model reduction. It involves a combination of (a) modeling for cardiomyocyte- smooth muscle cell-endothelial cell interactions and the signals controlling these, (b) automated model reduction allowing adaptation of these cell types to changing states and more efficient computation in pseudo-steady states, and (c) parameter identification at subcellular to overall systems levels. The result will provide computational strategies and technologies, and their application to cardiac and muscle physiology. The proposed approach to multiscale modeling extends naturally from the current efforts of each of four investigators, based on their extensive individual backgrounds (cardiovascular physiology and medicine (JBB), systems identification (HJC), signal analysis (LEA), and thermodynamics and biochemistry (HQ). New computational algorithms and methods for spanning multiple modeling scales (regulation of transcription, cellular energetic metabolism, cell-to-cell interactions, integrated organ contractile function) will be demonstrated. The intellectual impact of this work includes these new methods and algorithms, as well as the resulting multi-scale simulation. The resulting simulation will also yield new insights into the behavior of this physiological system. It will provide highly integrated models of cardiac and skeletal muscle systems showing adaptive responses to lowered or raised oxygen and substrate supplied, changed demand for contractile work, sympathetic and parasympathetic neuronal input levels, and encompass the remarkable heterogeneity of normal regional flows and metabolic function that exists in both heart and skeletal muscles. In addition to the applicability of this work to physiological problems, the algorithms, source code, manuals and tutorials, all of which will be open source and widely disseminated, will be useful to a wide range of investigators.

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Co-PIs and Collaborators

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Project Title

Multiscale Modeling of the Heart in Metabolic Syndrome and Cardiovascular Disease

Grant Details and Funding Agency

Grant Number: 1-R01-EB-005825-01
Agency: National Institute for Biomedical Imaging and Bioengineering (NIH-NIBIB)
Program Officer: G. Peng

Scales Examined

Time Scales

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☒	Microsecond (μs)
☒	Millisecond (ms)
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Biological Scales

☐	Atomic
☒	Molecular
☒	Molecular Complexes
☒	Sub-Cellular
☒	Cellular
☒	Multi-Cellular Systems
☒	Tissue
☒	Organ
☒	Organ Systems
☒	Organism
☐	Population
☐	Behavior

Length Scales

☐	Nanometer and below (nm)
☒	Micrometer (μm)
☒	Millimeter (mm)
☒	Centimeter (cm)
☒	Ten Centimeter
☐	Meter

Disease Focus

Cardiovascular Disease

Organism of study

N/A

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus
50%. We are exploring the role of energy metabolism and cardiac substrate selection in metabolic syndrome, cardiovascular disease. We with to understand the coupled metabolic, electrical, and mechanical response of heart to physiological challenges, including ischemia, hypoxia, and acidosis.

Modeling Methods and Tools (MMT) Areas and Percent Focus
50%. We are developing differential equation-based deterministic models of cardiac cells and tissue and whole heart. To integrate cellular and mitochondrial electrophysiology, cytoplasmic and mitochondrial metabolism, cell mechanics, coronary substrate transport and blood tissue exchange, and whole-heart mechanics of contraction into a common framework, we must develop and extend models at each scale to merge together. Next, to make computations feasible on the resulting large-scale systems, we are developing parallel algorithms, and adaptive mesh methods.

Software Development
Languages and Tools: n/a
Framework / Sharing Environment: We believe that it is vital to provide past and current models to the community. Computer codes for all models used in publication will be made available for download on our website, and other archives where possible. We intend to made models available in multiple file formats when possible—including CellML and other exchange formats, as well at MATLAB and other computing languages.
Available Resources: n/a

Project Summary:
This proposal establishes a new collaboration spanning molecular, cellular, tissue, and whole-organ levels of modeling to develop a multi-scale model of cardiac metabolism. We have assembled a team of researchers at Medical College Wisconsin and University of Auckland with expertise in computational modeling and quantitative analysis of cardiac physiology necessary to develop a self-consistent integrated description of the relevant biophysical processes. We have assembled a team of researchers with expertise in computational modeling and quantitative analysis of cardiac physiology necessary to develop a selfconsistent integrated description of the relevant biophysical processes at molecular, cellular, tissue, and whole-organ levels of resolution. Our specific aims are: (1.) Cellular and subcellular modeling: we will develop a cellular model integrating myocardial energy metabolism, the cardiac action potential and the cellular contractile apparatus, to predict the cellular response to ischemia, hypoxia, hyperglycemia, and/or dyslipidemia; (2.) Integration of microvascular transport and coronary blood flow: whole-organ models of the coronary vasculature will be linked with models and associated numerical methods for simulating transport and exchange of solutes in the coronary capillary, network; and (3.) Modeling the beating heart in health and disease: metabolic and transport processes will be incorporated into the existing Auckland heart/model, which currently treats the electrophysiology and mechanics of cardiac contraction. The multi-scale integrative framework developed in this proposal will provide new insights

and enable prediction of the mechanisms of metabolic function and dysfunction in the heart. Our long-term goal (and indeed a major long-term goal of computation biology in general) is to develop the computational power to simulate the metabolic and regulatory mechanisms acting in disease and to quantify the impact of therapeutic agents on these mechanisms. By developing a platform to simulate whole heart function under a variety of pathophysiological settings, including hypertrophy, hypertension, hyperglycemia, and combinations of these factors, the developed model will serve as a prototype for the future applications in the computer-aided design and optimization of therapeutics.

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Co-PIs and Collaborators
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Nadine Smith, Penn State University
Jack Wood, Ohio State University
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Project Title
Micro-scale Transport as a Critical Link between Molecular-scale Absorption and Macro-scale Mixing in Gut Physiology and Function

Grant Details and Funding Agency
Grant Number: 506215
Agency: National Science Foundation (NSF)
Program Officer: M. Plesniak

Scales Examined

Time Scales

☐	Nanosecond and below (ns)
☐	Microsecond (μs)
☒	Millisecond (ms)
☒	Second (s)
☒	Minutes
☒	Hours
☐	Days
☐	Months
☐	Years and above

Biological Scales

☐	Atomic
☒	Molecular
☒	Molecular Complexes
☒	Sub-Cellular
☒	Cellular
☒	Multi-Cellular Systems
☒	Tissue
☒	Organ
☒	Organ Systems
☐	Organism
☐	Population
☐	Behavior

Length Scales

☒	Nanometer and below (nm)
☒	Micrometer (μm)
☒	Millimeter (mm)
☒	Centimeter (cm)
☒	Ten Centimeter
☐	Meter

Disease Focus
Gastrointestinal

Organisms of study
Animal Studies, Human Function

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus
Intestine function and physiology, digestion, gut absorption, gastro-intestinal diseases/50%

Modeling Methods and Tools (MMT) Areas and Percent Focus
Lattice-Boltzmann numerical algorithms, molecular dynamics, multi-grid methods, micro-coil magnetic resonance imaging, animal experiments/50%

Software Development
Languages and Tools: To be developed: objects containing lattice-Boltzmann, molecular dynamics code, geometry models, and image analysis software.
Framework / Sharing Environment: A dissemination plan, including peer-to-peer (P2P) file sharing, will be implemented.
Available Resources: Personal Linux cluster; Penn State University Linux clusters, 7 Tesla horizontal bore magnetic resonance imaging (MRI) system, 14.1 Tesla vertical bore MRI system, 1.5 and 3 tesla whole body MRI scanners.

Project Summary:

Digestion and pharmaceutical efficacy of the small bowels depends on the transport of molecules originating in the bulk flow across the mucosal epithelium, and the transport of secreted molecules to the bulk flow with macro mixing at the 1-2 cm scale. Absorption and secretion are rate-limited by diffusion of molecules to/from epithelial cells covering multitudes of finger-like protuberances ~100-500 μm (villi) that line the gut mucosa. The epithelial cells are, in turn, lined with "microvilli" ~ 1 μm directly involved in absorption. The process of digestion therefore relies on highly coupled multiscale transport and mixing processes that span several orders of magnitude from the macro scale (~ 1-2 cm), to the micro scale (villi~100 - 500 μm), to sub micron scale (microvilli ~ 1 μm), and ultimately to the molecular scale. Net diffusive resistance to the epithelium is measured by an effective "unstirred water layer" (UWL) thickness. *In vitro* estimates of UWL thickness are too high, however, to be consistent with normal digestion. Recent *in vivo* estimates suggest the existence of micro-mixing that may be associated with motions of the villi induced by embedded smooth muscle fibers under enteric neuromuscular control. The details of villi motion *in vivo*, however, are unknown. We hypothesize that villi motions generate a controlled "micro-mixing layer" (MML) that enhances molecular transport to/from the epithelium, and that the strength of MML mixing is sensitive to the space-time details of villi motion. The hypothesis implicates neuromuscular disease in malabsorption through pathological alterations to villi motion and micro mixing. We propose a focus on the details and neurophysiological controls of absorption and secretion through systems models that integrate the entire range of scales from macro-mixing to molecular absorption, centering on villi-induced micro-transport as a critical link to absorption. Coupled macro-to-micro models will be integrated with animal experiments in which micro-coil magnetic resonance imaging (MRI) will be used to quantify space-time mucosal and villi motion *in vivo*.

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Project Website: to be created

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Project Title

Time Course of Metabolic Adaptations during Loading and Unloading

Grant Details and Funding Agency

Grant Number: TBD
Agency: NASA
Program Officer: R. White (Acting)

Scales Examined

Time Scales

☐	Nanosecond and below (ns)
☐	Microsecond (μs)
☒	Millisecond (ms)
☒	Second (s)
☒	Minutes
☒	Hours
☒	Days
☒	Months
☐	Years and above

Biological Scales

☐	Atomic
☐	Molecular
☐	Molecular Complexes
☒	Sub-Cellular
☒	Cellular
☒	Multi-Cellular Systems
☒	Tissue
☒	Organ
☒	Organ Systems
☒	Organism
☐	Population
☐	Behavior

Length Scales

☒	Nanometer and below (nm)
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☐	Meter

Disease Focus

Chronic Physical Inactivity, Diabetes

Organism of study

Human and Rat

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus

Space & exercise physiology - 40 %; cellular, tissue/organ & whole body metabolism - 40 %; biochemical reactions, pathways & metabolic control - 20%

Modeling Methods and Tools (MMT) Areas and Percent Focus

Ordinary differential equations - 70 %; system identification methods - 30 %

Software Development

Languages and Tools: MATLAB and FORTRAN

Framework / Sharing Environment: Presently involved with the assoc. director of NIH Center for Modeling Integrated Metabolic Systems. The multi-scale project will benefit from that involvement and it is planned to participate fully in the new framework by sharing both development strategies and software.

Available Resources: Itanium-based Computer Workstation and Rodent Physiology Lab

Project Summary:

The alterations in skeletal muscle structure and function induced by space travel or endurance training are the result of a chronic mechanical stimulus (or lack of it) and a series of metabolic interactions spanning from the cellular to the organism level. Reduced activation of the weight bearing muscles alters gene expression of myosin heavy chain isoforms to meet the functional

demands of weightlessness and results in muscle atrophy, reduced capacity to process fatty acids, and reduced muscle endurance. On the other hand, endurance training induces an up-regulation of oxidative enzymes and results in increased fatty acid oxidation capacity and muscle endurance. The few human and animal studies comparing skeletal muscle structure and function before and after unloading suggest that the adaptations are time and biological-level dependent. While some parameters may be altered within a week (muscle mass, insulin resistance), others may take longer to show changes (work efficiency, VO2max). Similar conclusions may be drawn from endurance training studies. Thus, to establish countermeasures aimed at restoring astronauts' work capacity, it is critical to determine: (1) the time course of muscle atrophy, (2) the bioenergetic, metabolic, and fuel-processing factors that contribute to the reductions in endurance associated with muscle atrophy, and (3) the effects of skeletal muscle atrophy on whole-body metabolism. To answer these questions a multi-scale model of energy metabolism -linking cellular to whole organism processes- is needed in combination with appropriate cellular to whole-body measurements collected during the period of adaptation. The objective of this proposal is to identify the time course of the adaptations to loading and unloading and to integrate them using a multiscale model of skeletal muscle and whole body metabolism, in order to predict the system integrated response after periods of space travel or endurance training.

Thus, the specific aims of this proposal are:
1) To identify and model the time course of the structural, metabolic and functional adaptations to loading and unloading.
2) To develop and validate a multi-level (cell-muscle-whole body) computational model of skeletal muscle metabolism in the context of the whole body.
3) To predict the integrated response of muscle fibers, whole skeletal muscle, and whole body during periods of loading and unloading, in particular astronaut's muscle energetics and function, as well as his/her whole body metabolism and performance.

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Project Title

Collaborative Research: Cortical Processing across Multiple Time and Space Scales

Grant Details and Funding Agency

Grant Number: 506396
Agency: National Science Foundation (NSF)
Program Officer: T. Russell

Scales Examined

Time Scales

☐	Nanosecond and below (ns)
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☒	Millisecond (ms)
☒	Second (s)
☒	Minutes
☐	Hours
☐	Days
☐	Months
☐	Years and above

Length Scales

☐	Nanometer and below (nm)
☒	Micrometer (μm)
☒	Millimeter (mm)
☒	Centimeter (cm)
☒	Ten Centimeter
☐	Meter

Biological Scales

☐	Atomic
☐	Molecular
☐	Molecular Complexes
☒	Sub-Cellular
☒	Cellular
☒	Multi-Cellular Systems
☒	Tissue
☐	Organ
☐	Organ Systems
☐	Organism
☐	Population
☐	Behavior

Disease Focus

N/A

Organism of study

N/A

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus
Physiological phenomena in primary visual cortex (50%)

Modeling Methods and Tools (MMT) Areas and Percent Focus
Fast algorithms, Statistical formalisms for computational scale-up and effective dynamics (50%)

Software Development
Languages and Tools: User-friendly Graphic interface for modeling tools
Framework / Sharing Environment: n/a
Available Resources: n/a

Project Summary:
The primary visual cortex (V1) is a complex integrated circuit that performs fundamental tasks in processing of visual information by the brain. The central theme of this proposal is to investigate how the neuronal responses of V1, ranging from feature selectivity to illusory perception, are induced and influenced by network components at many scales - from detailed intracellular membrane dynamics, to local input areas of networks that encompass only short-range interactions with fast conductance times, to large cortical areas that encompass many orientation hypercolumns with long-range connections and diverse synaptic time-scales, to multilayer dynamics with strong inter-layer couplings. In this complex system, each scale has its own distinct dynamical characteristics, but function emerges from interaction across all of these scales. To model this functional hierarchy, novel coarse-grained effective representations will be developed for capturing the dynamics of large-scale neuronal networks with heterogeneous structures. By bridging between multi-compartment models of single neurons and large-scale effective network descriptions that have orientation-specific couplings, new hybrid representations will be developed to interpret new multi-mode, multi-scale ensemble measurements. These formalisms will be built upon mathematical asymptotic mode-reduction and statistical physics methods, and will address emergent biological functions by going beyond the traditional analyses that involve only a small number of scales. Fast and adaptive numerical algorithms will be developed for evolving large-scale network dynamics that exploit modular and coarse-grained representations of fine scales. The associated software will form a general simulation platform of a hierarchical computational V1 model that is validated for many well-characterized physiological processes and is capable of possessing predictive power for functions emerging out of its many scales.

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Co-PIs and Collaborators

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Stephen J. Smith - Stanford University

Project Title

Multiscale Imaging, Analysis, and Integration of Brain Networks

Grant Details and Funding Agency

Grant Number: 1-R01-NS054252-01
Agency: National Institute for Neurological Disorders and Stroke (NIH-NINDS)
Program Officer: Yuan Liu

Scales Examined

Time Scales

☐	Nanosecond and below (ns)
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☐	Minutes
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☐	Days
☐	Months
☐	Years and above

Biological Scales

☐	Atomic
☒	Molecular
☒	Molecular Complexes
☒	Sub-Cellular
☒	Cellular
☒	Multi-Cellular Systems
☒	Tissue
☒	Organ
☐	Organ Systems
☐	Organism
☐	Population
☐	Behavior

Length Scales

☐	Nanometer and below (nm)
☒	Micrometer (μm)
☒	Millimeter (mm)
☒	Centimeter (cm)
☐	Ten Centimeter
☐	Meter

Disease Focus

Primary focus: none; Secondary focus: cancer (in relation to microvasculature).

Organism of study

C57BL/6 mouse

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus

Data acquisition including: Heavy element staining for SBF-SEM (20%); En bloc staining with conventional stains (10%); SBF-SEM data acquisition (20%); KESM data acquisition (50%)

Modeling Methods and Tools (MMT) Areas and Percent Focus

Projection of data: modeling across multiple scales (SBF-SEM to KESM,KESM to MAP); Image processing and 3D reconstruction (polymerization algorithm for 3D reconstruction and compression: 10%, parallel fiber tracking: 10%); 3D brain atlas development (20%); Web-based database (20%) and cluster computing/distributed storage (20%). Integration from SEM to KESM and KESM to mouse atlas (20%)

Software Development

Languages and Tools: Fiber tracking using generalized cylinder model; Polymerization algorithm for seed point generation in fiber; tracking and branch arborization control; 3D brain atlas and web-based database; Data acquisition and instrument control; Cluster computing and distributed storage. Rapid development using FLTK;

Framework / Sharing Environment: Support for SWT, hoc, and other standard neuron morphology formats; Source revision control and dissemination using sourceforge.net open source community; Data download through main project web page and MBW database.

Available Resources: Dell Poweredge 2800 with 6GB memory and 1TB storage; Dell 5-node cluster with 2GB memory each, and combined 1TB storage; Knife Edge Scanning Microscope

Project Summary:

Detailed network connectivity maps do not exist at present for any mammalian brain circuit. This project will provide the first empirical map of mouse brain network connectivity, focusing on the individual cerebral cortical microcolumn (as determined by Serial Block Face Scanning Electron Microscope; SBF-SEM), and on the entire mouse cortex by integrating light microscopy data (from our Knife-Edge Scanning Microscope; KESM) with that of the SBF-SEM. The project will chart brain networks in the mouse at multiple scales of spatial resolution, and develop interfaces between these levels of description. The combined use of large-scale 3D microscopes, SBF-SEM and KESM, together with automated image analysis and reconstruction methods, will open the internal connectivity of brains of all species to measurement and modeling of brain architecture at a neuronal and subneuronal level of detail. The project will recruit mouse brain data from three sources at three scales: nanoscale (from SBF-SEM, Stanford University); microscale (from KESM, Texas A&M University); and macroscale (from the Mouse Atlas Project, UCLA). A key objective of this project is to develop seamless interfaces across the three levels. Staining, imaging, image processing, and reconstruction methods will be developed to interoperate across these multiple levels. At nanoscale: Stanford is developing high-contrast heavy-element staining methods to be used with a new, automated SBFSEM for tracing small and tightly packed axons and dendrites over the entire volume of a functional microcircuit. At microscale: We will use the KESM to scan the mouse brain at 300 nm resolution and create an aligned volume data set of select cortical areas. For these two levels, a common heavy element stain will be used. The KESM, in turn, can image conventionally stained tissue to compare to the pre-existing UCLA 3D mouse brain atlas (MAP). The data will be cast into the Mouse Brain Web (MBW), a web-based representation of the mouse brain network which will make possible multi-scale integration of circuitry information across these levels. The availability of such multi-scale information for the mouse will be strongly beneficial to our understanding of human brain function and development. Such information will also contribute to discovering better treatment of disorders, such as epilepsy, and potential regenerative abilities. Data from this project will be made public, along with the software for its integrative storage, retrieval, and analysis.

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Project Title

Multiscale Studies of Segmentation in Vertebrate Embryos

Grant Details and Funding Agency

Grant Number: 1-R01-GM-076692-01
Agency: National Institute of General Medical Sciences (NIH-NIGMS)
Program Officer: P. Lyster

Scales Examined

Time Scales

☐	Nanosecond and below (ns)
☐	Microsecond (μs)
☐	Millisecond (ms)
☒	Second (s)
☒	Minutes
☒	Hours
☒	Days
☒	Months
☐	Years and above

Biological Scales

☐	Atomic
☒	Molecular
☒	Molecular Complexes
☒	Sub-Cellular
☒	Cellular
☒	Multi-Cellular Systems
☒	Tissue
☒	Organ
☒	Organ Systems
☐	Organism
☐	Population
☐	Behavior

Length Scales

☐	Nanometer and below (nm)
☒	Micrometer (μm)
☒	Millimeter (mm)
☒	Centimeter (cm)
☒	Ten Centimeter
☐	Meter

Disease Focus

N/A

Organism of study

Chicken

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus

60% - Developmental Biology, Morphogenesis, Gastrulation, Somitogenesis, Cell Tracking, Cell Fate Determination, Cell Differentiation, Biological oscillators, Vertebrate Segmentation, Pattern Formation, Vertebral Precursors, Congenital Vertebral Diseases

Modeling Methods and Tools (MMT) Areas and Percent Focus

40% - Cellular Potts Model Ordinary Differential Equation Boolean Functions Partial Differential Equation Finite Elements Stochastic modeling

Software Development

Languages and Tools: Python, C++

Framework / Sharing Environment: Development of open-source software framework for developmental biology modeling, CompuCell3D

Available Resources: CompuCell3D is available as a download from SourceForge

Project Summary:

In vertebrates, segmentation during early embryogenesis forms somites, recurring tissue modules, distributed along the anterior-posterior axis. Segmental structures give rise to the ribs, vertebrae, limbs, associated muscles, and central and peripheral nervous system. Failures in segmentation can be lethal or cause serious developmental abnormalities. Somitogenesis relies on a molecular clock, growth factor gradients and the expression of cell-adhesion and extracellular matrix (ECM) molecules. Segmentation requires complex, large-scale (millimeter) coordinated movement of cells and ECM. Despite increasing knowledge of the molecular mechanisms underlying segmentation, the interplay of molecular-, cell- and tissue-level mechanisms during somitogenesis remains obscure. Because of the tight feedback between subcellular and large-scale processes, no single-scale model can simulate somitogenesis. Current models address only the subcellular or macroscopic levels and do so separately. A successful multiscale model will answer one of developmental biology's great open problems: how do the molecular mechanisms of fate determination couple to large-scale tissue deformations? The proposed work will test the hypothesis that during segmentation, physical forces and biomaterial properties must coordinate with a moving biological oscillator, the segmentation clock, for successful somitogenesis. We will both model and conduct experiments on key developmental mechanisms ranging from local regulation of cell adhesion proteins (micrometers) to global tissue deformations (millimeters). We will develop novel theories and modeling approaches to bridge these scales. Our methodology has four major components: 1) Identifying (discovering) mechanisms and relevant models at each scale. 2) Determining the parameters for each level of model. 3) Validating model results. 4) Testing model predictions of normal and abnormal behaviors, e.g. inhibition or overproduction of adhesion molecules. The techniques and insights the research will produce will apply to other developmental processes. The software we develop will form the core of an open-source, multiscale and general purpose Tissue Simulation Toolkit, which other researchers can apply to this and other developmental problems. The proposed research contributes to public health by addressing the causes of a significant subset of the developmental malformations which occur in approximately 150,000 infants born each year in the USA (1 out of 28 births). Disturbing somite formation results in Klippel-Feil syndrome.spondylocostal dysostosis.Jarcho-Levin syndrome, congenital scoliosis and kyphosis, Goldenhar syndrome, and spina bifida, among others disorders. Studying the developmental mechanisms in vertebral patterning will aid in the identification of protective or potentially disruptive factors for normal somitogenesis and could potentially impact treatments for the prevention of vertebral patterning disorders.

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Lorin Maletsky, University of Kansas
Terence McIff, University of Kansas Medical Center

Project Title

Dynamic Simulation of Joints Using Multi-Scale Modeling

Grant Details and Funding Agency

Grant Number: 506297
Agency: National Science Foundation (NSF)
Program Officer: K. Chong

Scales Examined

Time Scales

☐	Nanosecond and below (ns)
☐	Microsecond (μs)
☐	Millisecond (ms)
☒	Second (s)
☐	Minutes
☐	Hours
☐	Days
☐	Months
☐	Years and above

Biological Scales

☐	Atomic
☐	Molecular
☐	Molecular Complexes
☐	Sub-Cellular
☐	Cellular
☐	Multi-Cellular Systems
☒	Tissue
☒	Organ
☒	Organ Systems
☐	Organism
☐	Population
☐	Behavior

Length Scales

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☒	Millimeter (mm)
☒	Centimeter (cm)
☒	Ten Centimeter
☐	Meter

Disease Focus

Joint dysfunction (osteoarthritis)

Organism of study

Human: articular cartilage, medial and lateral meniscus, knee

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus: 40%

Modeling Methods and Tools (MMT) Areas and Percent Focus: 60%

Software Development
Languages and Tools: MSC.ADAMS, ABAQUS/EXPLICIT with VUMAT subroutines, PATRAN, MATLAB with Simulink, and Neural Network Toolbox, 64 bit MATLAB
Framework / Sharing Environment: development of modular application programming interface (API), sharing through a secure ftp repository with documents and programs for download
Available Resources: UNIX and windows based workstation class computers, eight compute-noded Linux/Beowulf cluster, 26 processor Sun 6500 server

Project Summary:

Dynamic loading of the knee is believed to play a significant role in the development and progression of tissue wear disease and injury. Macro level rigid body joint models provide insight into joint loading, motion, and motor control. The computational efficiency of these models facilitates dynamic simulation of neuromusculoskeletal systems, but a major limitation is their simplistic (or non-existent) representation of the non-linear, rate dependent behavior of soft tissue structures. This limitation prevents holistic computational approaches to investigating the complex interactions of knee structures and tissues, a limitation that hinders our understanding of the underlying mechanisms of knee injury and disease. The objective of this project is to develop validated neural network models that reproduce the dynamic behavior of menisci-tibio-femoral articulations and to demonstrate the utility of these models in a musculoskeletal model of the leg. The specific aims of this study are:

Aim 1: Develop finite element (FE) models from micro-structure based constitutive methods that bridge the nano-micro scale behavior at the tissue level

Aim 2: Develop neural network (NN) based models that learn from FE simulation of dynamic behavior of menisci-tibio-femoral articulations

Aim 3: Validate the NN models within a rigid body dynamic model of a natural knee placed within a dynamic knee simulator

Aim 4: Demonstrate the utility of the NN models by placing them within a dynamic musculoskeletal model of the leg to study the interdependencies of the menisci and other knee tissues

Aim 5: Distribute the validated NN models of menisci-tibio-femoral dynamic response and contact pressure for use in any rigid body model of the knee or leg

The final product will be Neural Network (NN) models that conform to a modular application programming interface (API) that can be exported to any commercial integrated development environment (IDE) or in-house multi-body model. The NN models will be built upon a multi-scale approach and describe the non-linear, rate dependent, non-homogenous dynamic response of menisci-tibio-femoral articulations in a computationally efficient modular package. The multi-scale modeling approach will be validated using a dynamic knee loading machine and the utility of the approach demonstrated by studying the interdependencies of menisci properties, tibio-femoral contact, and anterior cruciate ligament strain during a dual limb squat. A synergistic interdisciplinary team has been assembled to address the objective and aims of the proposed project comprising experts in rigid body dynamics and knee modeling, FE modeling, nano-micro scale material modeling, neural networks, and clinical and experimental biomechanics.

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Co-PIs and Collaborators

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Project Title

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

Grant Details and Funding Agency

Grant Number: 1-R01-GM-076730-01
Agency: National Institutes of General Medical Sciences (NIH-NIGMS)
Program Officer: P. Lyster

Scales Examined

Time Scales

☒	Nanosecond and below (ns)
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Length Scales

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Biological Scales

☐	Atomic
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☒	Molecular Complexes
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☒	Multi-Cellular Systems
☒	Tissue
☐	Organ
☐	Organ Systems
☐	Organism
☐	Population
☐	Behavior

Disease Focus

N/A

Organism of study

N/A

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus
Biomedical impact: protein-protein interactions, cytoskeletal dynamics, cell signaling dynamics, cell migration, T cell biology, the immune response, autoimmunity.

Modeling Methods and Tools (MMT) Areas and Percent Focus
Monte Carlo, molecular dynamics, Langevin/Brownian dynamics, particle methods, coarse-grained models, field theoretic techniques, worm-like chain, discrete-continuous dynamical models

Software Development; Languages and Tools: C++, python, CVS, open MP, compiled and run on everything from Linux, C++ workstations and clusters to HPC platforms.
Framework / Sharing Environment: n/a
Available Resources: n/a

Project Summary:
T cell activation underlies the adaptive immune response, and an understanding of how this is regulated has many potential benefits including production of better vaccines and treatment of autoimmune diseases. T cell activation is predicated on the binding of the T cell receptor to cognate ligands on antigen presenting cells. This interaction can stimulate intracellular signaling cascades that ultimately lead to the up-regulation of gene transcription factors. Recently, it has been demonstrated that spatial organization of membrane-associated molecules and intracellular signaling components plays a role in regulating T cell signaling. T-cell activation is an emergent property that results from collective dynamics involving interactions between multiple components. This inherent cooperativity and the complex spatial organization that can regulate the collective dynamics makes it difficult to intuit mechanistic insights from experimental data alone, and progress requires mathematical models that integrate phenomena ranging from molecular size and time scales to cellular scales. To address how spatial organization of cellular components influences T cell response to external stimuli, our proposed research includes four specific aims that bridge multiple scales: (1) Develop hybrid Molecular dynamics/Brownian dynamics methods that will enable the study of dynamical events leading to spatial localization of multimeric protein complexes that mediate signaling 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 algorithms that can treat the stochastic dynamics of signaling reactions and cell migration in a spatially heterogeneous and crowded molecular environment, and will require the creation of hybrid methods combining stochastic and mean-field descriptions. (4) While each of the above specific aims involves the development of new methodology that in itself requires a bridging of scales, our fourth specific aim involves an overall integration of scales using specific aims 1 and 2 as necessary input for the computations performed in specific aim 3. For example, models of cell signaling dynamics that will be developed in specific aim 3 require knowing whether a multimeric signaling complex forms sequentially or in a concerted fashion, which will be determined using the molecular scale methods developed in specific aim 1. The computational results will be tested directly against experiments.

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Project Title

A Stochastic Molecular Dynamics Method for Multiscale Modeling of Blood Platelet Phenomena

Grant Details and Funding Agency

Grant Number: 506312
Agency: National Science Foundation (NSF)
Program Officer: T. Russell

Scales Examined

Time Scales

☐	Nanosecond and below (ns)
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☒	Months
☒	Years and above

Biological Scales

☐	Atomic
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Length Scales

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☒	Centimeter (cm)
☒	Ten Centimeter
☐	Meter

Disease Focus

Cardiovascular / Thrombosis and platelet diseases

Organism of study

N/A

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus
Platelet Aggregation 50%

Modeling Methods and Tools (MMT) Areas and Percent Focus
Dissipative particle dynamics 50%

Software Development
Languages and Tools: Grid computing, CAVE
Framework / Sharing Environment: MPICH-G2/TeraGrid
Available Resources: 60-node PC Dell cluster

Project Summary:

Blood platelets play a central role in hemostasis and in the formation of thrombi, which may result in heart attack, stroke or sudden death. They are micron-size cells - smaller than red blood cells - and when activated they become adhesive for other activated platelets and they adhere to the vessel wall. Their strong interaction with nano-size proteins at the subendothelium matrix activates and reshapes them from passively traveling discoids to active spiny spheres. The length and time scales characterizing such interactions as well as platelet-blood flow interactions span several orders of magnitude.

We propose a multiscale modeling methodology with focus on flow-modulated phenomena such as cell adhesion and aggregation at the micron-scale, and including nanoscale effects representing the main protein interactions. We will develop an integrated approach by coupling multiscale representations of blood flow, ranging from a quasi 1D transient flow in compliant vessels at the largest scale, to unsteady 3D flows in curved and flexing vessels at the mm range, to multi micron-scale thrombus formation at a pressure in the lumen of such a vessel with an atherosclerotic plaque, to changes over short times (seconds and minutes) in the behavior of platelet structure, receptors and bonds in a developing thrombus-wall interaction. To this end, we will develop a coarse-grained molecular dynamics approach, based on recent formulations of dissipative particle dynamics (DPD), to seamlessly connect length scales from 10 nm to a few mm. Specifically, we will use DPD to simulate platelet activation and aggregation in blood ßow, including plasma, red cells, fibrin and other components. Below these scales we will employ molecular dynamics (MD) while above these scales we will interface DPD with Navier-Stokes equations and with a unique one-dimensional stochastic model of the entire arterial tree that our team has been developing. The new simulation approach will be validated systematically again two in vitro and one in vivo experiments of varying biological and computational complexity.

The potential impact of this work is great as it will provide a new simulation capability for studying biomolecular interactions in blood vessels, organs and the entire arterial tree in a few hours instead of days or even weeks on a supercomputer. This, in turn, will allow fundamental studies at the molecular and cellular level and interaction with macroscales not currently possible with existing methodologies. The development of DPD has largely been confined to Europe, so our work will popularize it in USA as well. In addition, our research will contribute to the ultimate objective of simulating the entire arterial tree, including rheology, stimulus, medicine intake, etc. in a comprehensive physiological simulation to determine the formation and remediation of thrombi.

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Co-PIs and Collaborators
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M. Miller, Consultant, Washington U
D. Ghosh, Co-PI, U Michigan
J. Linderman Co-PI, U Michigan

Project Title
A Multi-scale Approach for Understanding Antigen Presentation in Immunity

Grant Details and Funding Agency
Grant Number: 1-R01-LM-009027-01
Agency: National Library of Medicine (NIH-NLM)
Program Officer: V. Florance

Scales Examined

Time Scales

☐	Nanosecond and below (ns)
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☒	Second (s)
☒	Minutes
☒	Hours
☒	Days
☐	Months
☐	Years and above

Biological Scales

☐	Atomic
☒	Molecular
☒	Molecular Complexes
☒	Sub-Cellular
☒	Cellular
☒	Multi-Cellular Systems
☒	Tissue
☒	Organ
☒	Organ Systems
☐	Organism
☐	Population
☐	Behavior

Length Scales

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Disease Focus
Tuberculosis, Immunology

Organism of study
N/A

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus
n/a

Modeling Methods and Tools (MMT) Areas and Percent Focus
Ordinary Differential Equations (several non-linear types, all continuous, determistic approaches) and Agent-based Model (stochastic, discrete approach)

Software Development
Languages and Tools: n/a
Framework / Sharing Environment: Open source software used in the lab, not currently involved in development frameworks.
Available Resources: n/a

Project Summary:
The human immune response works to either clear or control pathogens upon infection. Antigen presentation s critical to the immune response and is the process by which peptide fragments of pathogens are taken up by cells and displayed on the cell surface. Events at multiple scales (genetic molecular, cellular, tissue, and organ) are involved in antigen presentation. Briefly, antigen-presenting cells (ARC) take up pathogens at the site of infection. Once they have been taken up, they are then processed into peptides within the APC. These peptides then bind proteins known as the major histocompatibility complex (MHC). These peptide- MHC complexes (pMHC) are then displayed on the surface of the APC for recognition by T cells. In addition, the dynamics of antigen presentation and recognition are influenced by the larger tissue-level context in which they occur, namely the structured environment of the lymph node and ultimately by external compartmental dynamics of blood and the lymphatic system. A comprehensive understanding of the process of antigen presentation during an immune response will require an integrated picture of events that are occurring over multiple spatial and time scales. Mathematical models are tools that allow for such a multiscale investigation. Not surprisingly, since pathogens meet APCs continually as a first line of defense, many have evolved ways to inhibit antigen presentation. One such intracellular bacterial pathogen is Mycobacterium tuberculosis. Upon entering the lungs, M. tuberculosis is taken up by resident macrophages and then replicates. To evade immune surveillance, M. tuberculosis is known to inhibit antigen presentation of its host macrophage. The mechanisms by which M. tuberculosis achieves this inhibition have not been completely elucidated. Our specific aims include: building mathematical and statistical models to: predict affinity of peptides for different MHCII molecules with particular emphasis on the role that peptide length plays in determining affinity; describe the processing and the presentation events occurring in a single APC; describe antigen recognition and some of the downstream events by capturing interactions of cells within a single lymph node; capture relevant immune dynamics in the body in two-compartments of blood/lymph node. Integrating the models over multiple scales will be a key goal as well as utilizing data from non-human primate and mouse systems. Our specific goal is to use the models developed above towards understanding antigen presentation during M. tuberculosis infection, the causative agent of tuberculosis, and the leading cause of death due to infectious disease in the world today. As the premise behind vaccines is to train the immune system to recognize pathogens (via antigen presentation) and to quickly respond, information gained from the studies described herein can be immediately applied to vaccine design for M. tuberculosis as well as for other pathogens.

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Co-PIs and Collaborators

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Project Title

Multiscale Human Respiratory System Simulations to Study Health Effects

Grant Details and Funding Agency

Grant Number: 1-R01-ES-014483-01
Agency: National Institutes of Environmental Health Sciences
Program Officer: D. Balshaw

Scales Examined

Time Scales

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Length Scales

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☐	Ten Centimeter
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Biological Scales

☐	Atomic
☒	Molecular
☒	Molecular Complexes
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☒	Organ
☒	Organ Systems
☐	Organism
☐	Population
☐	Behavior

Disease Focus

Lung-related Disease

Organism of study

Human

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus
Lung structure and function, Gas and particulate toxicity, Effects of aging on lung structure and function, Effects of lung damage, 50%

Modeling Methods and Tools (MMT) Areas and Percent Focus
Integration of simulation data across dimensions and scales, Multiphase CFD, Statistical representation of respiratory units, quasi-1D modeling of geometric, diffusion, deposition in the lower bronchi, Software engineering and integration, HRCT, Micro-CT and CLSM technologies including postprocessing, Geometric/Topological Monte Carlo for coupling micro-CT/CLSM to Q1D functional models, 50%

Software Development
Languages and Tools: n/a
Frameworks / Sharing Environment: PSU Exterior Communications Interface will be adapted to accommodate multi-scale, multi-dimensional lung function modeling. The team includes co-developers, beta-users and integrators of open source software for project relevant modeling disciplines.
Available Resources: n/a

Project Summary:
A multi-scale strategy is proposed to develop, couple, apply, and validate multimodality 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 of the lung. Microscopic computed tomography ('CT), and confocal microscopy (CLSM), will be used to characterize the "microscale" global and cellular architectures of the respiratory units. Multiphase computational fluid dynamics and quasi-one-dimensional functional modeling will be used to simulate the multi-component fluid mechanics at the 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. A novel and critical element of the proposed research is that the interfaces between functional biological scales will be developed using recent dimension-reducing coupling strategies developed in the nuclear reactor safety/simulation community, and multidisciplinary data-exchange standards developed in the aerospace sciences community. Coupling technologies will be developed between macro- and microscales, and between imaging and physical modeling; these will yield a system-level model that accommodates the critical two-way coupling between convective respiration physics and uptake, deposition, and disease-state morphology. Such an integrated approach will elucidate heretofore inaccessible physical understanding, dependencies, and treatment implications. The coupling software to be developed will be modular and open-source so other investigators can "plug-in" their models at the macro- and micro-scales, and/or evolve the system to other organs or human systems such as the liver or kidney. The ultimate public health goal of the research is improved understanding of respiratory function and disease, and evaluation/assessments of the effects of therapies, injury, surgical intervention, and aging on lung structure and function. The physics-based coupling between multiple scales is a critical step towards a complete integrated physiological model of the human respiratory system: a "virtual human lung."

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Project Title

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

Grant Details and Funding Agency

Grant Number: 505929
Agency: National Science Foundation (NSF)
Program Officer: M. Plesniak

Scales Examined

Time Scales

☐	Nanosecond and below (ns)
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☒	Second (s)
☒	Minutes
☒	Hours
☒	Days
☒	Months
☒	Years and above

Biological Scales

☐	Atomic
☒	Molecular
☒	Molecular Complexes
☒	Sub-Cellular
☒	Cellular
☐	Multi-Cellular Systems
☐	Tissue
☐	Organ
☐	Organ Systems
☐	Organism
☐	Population
☐	Behavior

Length Scales

☐	Nanometer and below (nm)
☒	Micrometer (μm)
☒	Millimeter (mm)
☒	Centimeter (cm)
☒	Ten Centimeter
☐	Meter

Disease Focus

N/A

Organism of study: N/A

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus
Actin polymerization; mechanics of cytoskeleton, bacterial propulsion 60%

Modeling Methods and Tools (MMT) Areas and Percent Focus
Numerical simulations of solutions of chemically functionalized biopolymers.

Software Development
Languages and Tools: New algorithms for efficient simulations of polymer solutions.
Framework / Sharing Environment: n/a
Available Resources: n/a

Project Summary:
We propose to develop and validate a biologically relevant, multi-scale model of force generation by actin polymerization. In actin-based motility, monomeric actin polymerizes into stiff filaments from surface-bound components (such as the Listeria monocytogenes surface protein ActA), which crosslink and propel the surface forward. How the chemical energy involved in monomer addition is converted into mechanical work is critical in understanding cell motility, as well as for exploiting actin-based motility for micro-/nanoscale sensors and actuators. Co-PI's Dickinson and Purich recently described how filament end-tracking motors can capture energy from ATP hydrolysis to rapidly polymerize tethered actin filaments against significant forces, even at monomer concentrations near the equilibrium concentration for free filament-end elongation. The efficiency of chemical-to-mechanicial energy conversion for a given filament growth mechanism depends on filament-filament interactions and the mechanical properties of the generated filament network. We hypothesize that the structural and force producing properties of the network are fundamentally different depending on whether working filaments remain tethered by end-tracking proteins or remain un-tethered (as required by the conventional Brownian Ratchet model). To determine the differences, we propose to construct a multiscale model of actin polymerization and force generation, using detailed simulations of the actin filaments, and accounting for both elongation mechanisms. The polymer simulations will extend recent work by PI Ladd and co-PI Butler, where a new and much more efficient simulation of solutions of flexible polymers was tested. The new model will enable us to simulate the dynamics of stiff fibers, composed of many segments interacting thermodynamically and hydrodynamically. We also propose a sequence of experimental validations; first, determination of the viscoelastic properties of actin gels using microrheological experiments developed in co-PI Weitz's laboratory, and second, measurement of force generation by the polymerizing network (Purich and Dickinson).

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Co-PIs and Collaborators

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Project Title

Multiscale simulation of gas flow distribution in the human lung

Grant Details and Funding Agency

Grant Number: 1-R01-EB-005823-01
Agency: National Institutes of Environmental Health Sciences
Program Officer: G. Peng

Scales Examined

Time Scales

☐	Nanosecond and below (ns)
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☒	Minutes
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☐	Days
☐	Months
☐	Years and above

Biological Scales

☐	Atomic
☐	Molecular
☐	Molecular Complexes
☐	Sub-Cellular
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☐	Multi-Cellular Systems
☒	Tissue
☒	Organ
☒	Organ Systems
☐	Organism
☐	Population
☐	Behavior

Length Scales

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☐	Meter

Disease Focus

Lung-related Disease

Organism of study

Lung

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus
50%, Lung – air flow and gas transport from mouth to trachea to smallest airway, Experiment for taking gas washin/washout time constants.

Modeling Methods and Tools (MMT) Areas and Percent Focus
50%, Finite Element Methods – macro-scale airflow, super cluster high performance computing, coupling 3D FEM model with 1D gas transport model, coupling to provide boundary conditions to estimate higher generations of conducting airways (16 total generations), currently up to 3D 11 generations of airways. The breathing lung model will be achieved by numerical optimization of dynamic CT imaging 4D data.

Software Development
Languages and Tools: Fortran
Framework / Sharing Environment: Currently involved in framework – research software at UI, distributing soft code that couples 1D and 3D models.
Available Resources: high-end workstations, computer account on the National Center for Supercomputing Applications (NCSA).

Project Summary:
The ultimate goal of the project is to develop a comprehensive computational fluid dynamics (CFD) model for pulmonary air flow that utilizes subject-specific airway geometries, spans spatial scales from the largest bronchial airways to alveolar sac, and employs a Computed Tomography (CT) data-driven, multistage approach to provide accurate predictions of regional ventilation and gas transport through the entire moving airway tree. The approach integrates three-dimensional (3D) and one-dimensional (1D) fluid dynamic models supplemented with dynamic CT data through numerical optimization to achieve realistic multi-scale breathing lung simulations. The model will bring about new understanding of air flow, gas transport, and aerosol particle deposition in the lungs. The specific aims of the project are: (1) Establish efficient techniques for generating subject-specific computational meshes for CFD analysis; (2) Integrate the custom developed 3D CFD model to the 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 multi-scale simulation; (3) 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; (4) Make available the coupling algorithms and share the databases with the research and clinical communities. We will use the custom developed segmentation software to extract airway geometries from the CT data sets. The CT-image based geometries will then be supplemented with synthetic geometries using the volume filling technique and Voronoi meshing scheme. The 3D-1D coupled CFD simulations will be performed using the above airway geometries. The coupled CFD solutions will be validated through CT experiments and compared with those of the 1D model. The coupling software and databases will be made available to both research and clinical communities through the medical image file archive system. The applications of the model include, but are not limited to, improving pharmaceutical aerosol drug delivery, predicting subject-specific regional ventilation for diagnosis of patterns related to pathologic changes in airway geometry and parenchyma destruction, and predicting long-term effects of environmental pollutants on lung function where environmental exposure has been shown to alter airway structure in early development.

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Project Title
Scales of carcinogenesis: cells, crypts and cancer

Grant Details and Funding Agency
Grant Number: 1-R01-CA-119224-01
Agency: National Cancer Institute (NIH-NCI)
Program Officer: J. Couch

Scales Examined

Time Scales

☐	Nanosecond and below (ns)
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Biological Scales

☐	Atomic
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☒	Population
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Length Scales

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Disease Focus
Cancer

Organism of study
Human, mouse

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus
20% - Primary focus is on genetic, cytologic, and morphologic abnormalities observed in biopsies from pre-malignant neoplasms in Barrett's esophagus. Of interest is also the role of crypt structured epithelia in the pathogenesis of esophageal adenocarcinoma including the time and length scales of neoplastic clones.

Modeling Methods and Tools (MMT) Areas and Percent Focus
80% - Agent-based computational models of clonal evolution in normal tissues and neoplasms.

Software Development
Languages and Tools: Java
Framework / Sharing Environment: Stochastic 2D lattice population model generalizing the linear birth-death processe commonly used in multistage carcinogenesis. Sharing environment: dedicated wiki - Software environment and tools to provide both interactive as well as research/development framework.
Available Resources: n/a

Project Summary:
The main objective of this project is the development of a computational multi-scale model of carcinogenesis that spans spatial and temporal scales from the level of the cell to the level of the human population. Specifically, it includes the modular development of a multiscale and multistage carcinogenesis simulation model that consists of three major components: From a cell to a proliferative unit module. Checkpoint delays, repair processes, and the apoptotic sensitivity of stem cells are assumed optimized to delay the process of neoplastic progression. This 'optimization' problem will be addressed by both deterministic and stochastic descriptions of stem cell population homeostasis in a proliferative unit (crypt). From a proliferative unit to a tissue module. Mechanisms that disrupt tissue architecture and allow neoplastic clones to expand may generate distinct spatial distributions of genetic lesions. The multiscale model developed here will be used to explore the spatial and genetic patterns of clones produced by crypt bifurcations, epithelial restitution and cell migration with or without wound healing. From a tissue to a population module. The micro-simulation model at the tissue level will be employed to derive first-passage-times for the induction of clonal expansions, their spatio-temporal growth characteristics, and the first-passage-time distributions of malignant transformations. Consistency of the resulting multistage model with population level data will be tested by fitting the model to the incidence of esophageal adenocarcinoma in the SEER registry. Public health relevance: This project seeks to improve our understanding of how tissue architecture, in particular the crypt structure of intestinal epithelia, modulates the accumulation of genetic lesions, clonal expansion and evolution in neoplasms. Synthesizing the various aspects of this problem into a more informed theory of multistage carcinogenesis will require an interdisciplinary approach. Although the biological questions and mathematical models that address them are primarily formulated in the context of the pre-malignant condition Barrett's esophagus, which is one of the few human conditions in which neoplastic progression can be directly observed over time, this research has wider implications for understanding the role of tissue architecture in carcinogenesis. This includes consequences for cancer screening, early detection, and the testing of specific intervention and prevention strategies.

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Co-PIs and Collaborators

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Project Title

Multi-scale Analysis of Cellular Force Transmission and Biochemical Activation

Grant Details and Funding Agency

Grant Number: 1-R01-GM-076689-01
Agency: National Institute of General Medical Sciences (NIH-NIGMS)
Program Officer: P. Lyster

Scales Examined

Time Scales

☐	Nanosecond and below (ns)
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☐	Organism
☐	Population
☐	Behavior

Disease Focus

N/A

Organism of study

N/A

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus
Protein conformational change under force, Cytoskeletal mechanics, Actin dynamics, Mechanotransduction, Cell Migration.

Modeling Methods and Tools (MMT) Areas and Percent Focus
Molecular dynamics, Brownian dynamics, Finite element methods, Coupling methods.

Software Development
Languages and Tools: Developing codes for the Brownian dynamics simulation. Both use and develop finite element codes.
Framework / Sharing Environment: Use CHARMM (public access) code for MD. Develop other codes in C++
Available Resources: n/a

Project Summary:
Numerous cellular processes occur at the interface between mechanics and biology. Such responses can range from changes in cell morphology to activation of signaling cascades to changes in cell phenotype. Although the biochemical signaling pathways activated by mechanical stimulus have been extensively studied, little is known of the basic mechanisms by which mechanical force is transduced into a biochemical signal, or how the cell changes its behavior or properties in response to external or internal stresses. While the approach proposed here has a computational emphasis, ongoing experiments will help to motivate and validate the computational studies. For example, studies have examined the change in internal structure that occurs when a neutrophil enters a capillary. An immediate reduction in stiffness is observed, followed by a progressive increase, sometimes leading to active protrusion. Mechanical deformation in this example initiates remodeling of the cell interior, activating signaling pathways that may or may not lead to a migratory response. Another example involves biochemically mediated reorganization of the intermediate filament network in the Panc-1 human pancreatic cancer cell which results in a three-fold reduction in the stiffness of the cell and a marked increase in the hysteresis in mechanical deformation; both of these factors are considered to facilitate cell mobility and cancer metastasis. The ultimate goal in this research is to capture such phenomena through quantitative modeling and simulation and use the results in developing new insights into the disease process and ultimately, new therapies. The primary aim of this project is to develop a broad but rigorous computational framework that links mechanical forces to conformational changes in single proteins by coupling biochemical activity with molecular dynamics simulations of protein deformation in a fully three-dimensional filamentous network. The prototypical problem is the simulation of cytoskeletal rheology and remodeling. Our specific aims are to: 1. Develop separate computational approaches at the nano-, meso-, and macro-scales, using molecular dynamics, Brownian dynamics, and finite element methods to simulate the mechanical and biochemical activity responsible for cytoskeletal rheology. 2. Construct and make available to the research community multi-scale algorithms that enable direct communication between the different computational platforms. 3. Extend this simple model to incorporate multiple reactions and to include the effects of signaling pathways necessary for models of mechanotransduction and cell migration. 4. Conduct experiments in reconstituted actin networks to provide a phenomenological basis for evaluation and validation of the computational models.

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Co-PIs and Collaborators
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Project Title
Multi-scale modeling of the mouse heart: from genotype to phenotype

Grant Details and Funding Agency
Grant Number: 506252
Agency: National Science Foundation (NSF)
Program Officer: S. Demir

Scales Examined

Time Scales

☐	Nanosecond and below (ns)
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Biological Scales

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☐	Population
☐	Behavior

Length Scales

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☐	Meter

Disease Focus
Cardiovascular Disorders

Organism of study
Mouse

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus
Genetically engineered mice (10%); cardiac anatomy and structure (10%); cardiac physiology (10%); cardiac myocyte biophysics (10%); signal transduction (10%)

Modeling Methods and Tools (MMT) Areas and Percent Focus
Regulatory network systems models (12.5%); cell biophysical models (10%); tissue continuum constitutive models (10%); whole organ finite element models (12.5%); circulatory systems dynamics models (5%)

Software Development
Languages and Tools: n/a
Framework / Sharing Environment: Builds on a large pre-existing software framework developed by the applicants, used by the community and supported by NSF and NIH over the past 15 years
Available Resources: n/a

Project Summary:
We propose to develop new multi-scale computational models of the mouse heart that integrate functionally and structurally across multiple scales of biological organization from molecular networks to organ system. We will develop new models of the electromechanics of the normal and genetically modified mouse heart that integrate across all five of the following biological scales and classes of mathematical model: biochemical models of molecular regulatory networks; biophysical models of whole excitation-contraction coupling, microstructural constitutive models of the regional anisotropic electrical and mechanical properties of multicellular cardiac tissue; three-dimensional anatomically detailed models of mouse ventricular geometry, fiber architecture and conducting system anatomy; and lumped parameter models of circulatory system hemodynamics. The new models will be genuinely integrative using efficient algorithms that simultaneously integrate and incorporate models at all five of these scales. State-of-the-art models integrate across at most three of these scales of biological organization. The proposed new models will extend the scales of spatio-temporal integration now possible by up to three orders of magnitude. This proposed research will involve an important new collaboration between UCSD and investigators at the University of South Carolina, where Drs. Thomas Borg and Robert Price will perform very large-scale three-dimensional acquisitions and reconstructions of whole mouse hearts at sub-micron resolution using confocal microscopy. From these new data in normal and transgenic mice, we will reconstruct highly detailed 3-D models of cardiac muscle fiber and sheet microarchitecture and cell connectivity via gap junctions. This will be used to construct threedimensional models with heterogeneous electromechanical properties. The fully integrated computational models will be used to predict the effects of specific molecular alterations in G-protein coupled receptor signaling pathways on whole ventricular electromechanical function in the mouse heart, and these predictions will be validated against measurements in transgenic mice over-expressing adenylyl cyclase type VI or Gαq, using magnetic resonance imaging and voltage-sensitive dye imaging.

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Dr. Christof Meile, University of Georgia, Athens

Project Title

Intercellular Genomics of Subsurface Microbial Colonies

Grant Details and Funding Agency

Grant Number: DE-FG02-05ER25676
Agency: Department Of Energy (DOE-ASCR)
Program Officer: D. Thomassen

Scales Examined

Time Scales

☐	Nanosecond and below (ns)
☐	Microsecond (μs)
☒	Millisecond (ms)
☒	Second (s)
☒	Minutes
☒	Hours
☒	Days
☐	Months
☐	Years and above

Length Scales

☐	Nanometer and below (nm)
☒	Micrometer (μm)
☒	Millimeter (mm)
☒	Centimeter (cm)
☒	Ten Centimeter
☐	Meter

Biological Scales

☐	Atomic
☐	Molecular
☐	Molecular Complexes
☒	Sub-Cellular
☒	Cellular
☒	Multi-Cellular Systems
☐	Tissue
☐	Organ
☐	Organ Systems
☐	Organism
☐	Population
☐	Behavior

Disease Focus

N/A

Organism of study

E.coli and *Geobacter* species

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus
50% bacterial gene regulatory networks, microbial colonies

Modeling Methods and Tools (MMT) Areas and Percent Focus
50% ODEs, PDEs for porous media, microarray analysis, gene ontology, phylogeny, and information theory

Software Development
Languages and Tools: n/a
Framework / Sharing Environment: Interdisciplinary approach to data/model integration for multi-scale systems
Available Resources: n/a

Project Summary:
Systems with multiple cells distributed in space and communicating via reaction transport processes present a multi-scale grand challenge for computer simulation. A key mode through which the cells communicate is via chemical signals that activate transcription factors and thereby couple genomic activity over large distances. With this vision we shall develop physico-chemical models of spatially-distributed, microbial colonies. We shall integrate our biomic (i.e. genomic, proteomic, metabolic) cell models/simulators, porous medium reaction-transport homogenization theory/software, and decades of experience in nonlinear dynamical phenomena in biological, chemical and geological systems. Thereby we will arrive at a deeper understanding of the spatiotemporal dynamics of subsurface microbial colonies. The software developed will be freely available to the wider environmental and energy sciences research communities. The driving biological problem is the interplay of pore fluid and mineral compositional gradients with microbial colonies and the resultant spatio-temporal dynamics in the subsurface. This proposal brings together the expertise of a group of researchers with modeling expertise at different spatial scales and with complementary scientific fields, including physical chemistry, computer science, microbiology and marine sciences. The investigation of feedback mechanisms between microbes and the environment requires the proposed multi-scale approach.

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Co-PIs and Collaborators

Hideo Mabuchi, Caltech; Erik Winfree, Caltech; Bernard Yurke, Lucent Bell Labs

Project Title

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

Grant Details and Funding Agency

Grant Number: 506468
Agency: National Science Foundation (NSF)
Program Officer: T. Russell

Scales Examined

Time Scales

☐	Nanosecond and below (ns)
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☒	Months
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Biological Scales

☐	Atomic
☒	Molecular
☒	Molecular Complexes
☒	Sub-Cellular
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☐	Organism
☐	Population
☐	Behavior

Length Scales

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☐	Meter

Disease Focus

N/A

Organism of study

N/A

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus

Analysis of DNA nanotechnology hybridization kinetics and analysis of mRNA hybridization kinetics (50%)

Modeling Methods and Tools (MMT) Areas and Percent Focus

Model reduction, balanced truncation, stochastic simulations, trajectory-based coarse-graining (50%)

Software Development

Languages and Tools: Software under development in C programming language

Framework / Sharing Environment: Published algorithms will be supplied to the research community on the NUPACK (Nucleic Acid Package) software site. In time, users will have a choice of running the algorithms via a web server or downloading the software to run on their own machines. The domain name www.nupack.org has been reserved for this purpose.

Available Resources: n/a

Research Overview

DNA is best known as the genetic storage medium for life. However, its unique structural properties make it an attractive material for engineering nanoscale structures and devices. Remarkably, synthetic DNA systems can be programmed to self-assemble into complex objects implementing dynamic mechanical tasks by appropriately designing the sequence of bases (A,C,G and T) comprising the constituent DNA strands. When mixed together, the strands "hybridize" to each other in prescribed ways by forming "base-pairs" between complementary bases (A pairing with T, C pairing with G). The field of DNA nanotechnology is devoted to exploring and developing these capabilities for applications in nanorobotics, nanofabrication, biomolecular computation, biosensing, nanoelectronics and nanomedicine.

In principle, the equilibrium and kinetic properties of a DNA strand can be elucidated by characterizing the features of its "free energy landscape". Structures that are likely at equilibrium are represented by deep valleys in the landscape, and the rate of conversion between two different structures is dependent on the nature of the valleys and ridges that separate them in the landscape. The dynamics of a folding DNA strand define a path that is somewhat analogous to that of a ball rolling over the landscape. In order to analyze functional DNA systems with moving parts, it is important to be able to identify the large-scale landscape features that dominate experimental behavior. Unfortunately, for problems of practical interest, existing physical models define free energy landscapes with a fine-grained level of detail that obscures these critical large-scale features. For example, it is not uncommon to encounter a DNA system with a theoretical landscape containing more states than there are atoms in the universe, even when experiments suggest that the landscape is dominated by a small number of features.

The proposed research will develop algorithms for efficiently exploring large landscapes that cannot be enumerated explicitly. Mathematical coarse-graining approaches will be developed to simulate the temporal evolution of physically meaningful "macrostates" without having to perform the simulations on the full "microstate" landscapes. These macrostate predictions will be used to guide and interpret experimental studies of DNA systems of fundamental interest to current nanorobotics and biosensing efforts. Custom-built fluorescence instruments will be used to probe free energy landscapes at the level of single molecules. While our expertise in DNA nanotechnology motivates our selection of experimental systems based on synthetic DNA constructs, the coarse-graining theory, computational algorithms, and experimental methods that we develop will be equally applicable to the analysis of natural RNA molecules (such as the mutant of human telomerase RNA that is thought to cause dyskeratosis congenita by altering the free energy landscape of a conformational switch).

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Co-PIs and Collaborators

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Project Title

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

Grant Details and Funding Agency

Grant Number: 0506305
Agency: National Science Foundation (NSF)
Program Officer: M. Heller

Scales Examined

Time Scales

☒	Nanosecond and below (ns)
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☐	Days
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☐	Years and above

Biological Scales

☒	Atomic
☒	Molecular
☒	Molecular Complexes
☒	Sub-Cellular
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☐	Organism
☐	Population
☐	Behavior

Length Scales

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Disease Focus

The branched proteins which are the subject of this project have been associated with multiple diseases that place a significant societal burden, including cancer and diabetes.

Organism of study

N/A

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus
Characterize mobility behavior of branched polypeptides during electrophoresis at various levels of entanglement with an immobile matrix / 35%

Modeling Methods and Tools (MMT) Areas and Percent Focus
Monte Carlo (MC), Molecular Dynamics (MD), Brownian Dynamics (BD) simulations / 65%

Software Development
Languages and Tools: FORTRAN
Framework / Sharing Environment: n/a
Available Resources: None yet

Project Summary:
A combined theoretical and experimental project is proposed to predict the dynamics and mobility of flexible, and semi-flexible macromolecular chains in a concentrated environment. The dynamics of polymers cover a large range of length and timescales, so they are not directly amenable to molecular dynamics studies. Instead, we implement a multiscale, coarse-graining approach utilizing slip-links to model entanglements on the mesoscopic level. The approach is robust, allowing consideration of lightly crosslinked elastic networks, semi-flexible mobility in gels, linear viscoelasticity of entangled chains, or nonlinear rheology of linear and star-shaped macromolecules. Parameters at the mesoscopic level are determined by Monte Carlo (MC) and Molecular Dynamics (MD) simulations, although the smallest characteristic time scale (τ_e) is more easily treated phenomenologically. The approach allows modeling of time scales from the atomic up to hundreds of seconds. The experimental component of the study takes advantage of recently acquired knowledge about the biosynthesis of branched proteins to generate a systematic collection of star-shaped proteins of defined architecture and molecular weight. The behavior of these proteins at various levels of entanglement with an immobile matrix will be explored by characterizing their mobility during electrophoresis. The biological properties of branched polypeptides are the subject of intense interest but their analysis has been hampered by their anomalous behavior in most analytical techniques. The proposed multiscale approach is uniquely suited to provide both a theoretical framework as well as the modeling tools to capture their dynamics and behavior.

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Project Websites: not yet available

Co-PIs and Collaborators
n/a

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

Grant Details and Funding Agency
Grant Number: 1-R01-GM-076690-01
Agency: National Institutes for General Medical Sciences (NIH-NIGMS)
Program Officer: P. Lyster

Scales Examined

Time Scales

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Length Scales

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Biological Scales

☐	Atomic
☐	Molecular
☐	Molecular Complexes
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☐	Organ Systems
☐	Organism
☐	Population
☐	Behavior

Disease Focus
Embryonic development

Organism of study
N/A

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus
50% - developmental biology, epithelial tissues, pattern formation, cell communication networks

Modeling Methods and Tools (MMT) Areas and Percent Focus
50% - reaction-diffusion models, PDEs, homogenization methods, optimal gids, asymptotic analysis

Software Development
Languages and Tools: n/a
Framework / Sharing Environment:
Publicly available database of gene expression patterns in the drosophila ovary, general purpose code for the solution of cell communication problems in epithelial layers
Available Resources: n/a

Project Summary:
Embryonic development is an intrinsically multiscale phenomenon that requires a highly coordinated processes at all levels of biological organization, from genes, to proteins, to cells, to tissues and, eventually, to the whole organism. Thus, multiscale approaches are indispensable for understanding the mechanisms responsible for development. This project proposes to combine experiments and modeling to study the mechanisms by which developing epithelia are patterned by the Epidermal Growth Factor Receptor (EGFR), an evolutionary conserved regulator of tissues in animals from worms to humans. Using Drosophila melanogaster as the experimental system, the PIs will quantify the transcriptional response to EGFR signaling, develop models of EGFR-mediated cell communication in epithelial layers, and use these models to analyze the EGFR system in Drosophila oogenesis, spanning the scales from genes to organs. The experiments will combine developmental genetics, genomics, and transcriptional profiling experiments. The computational approaches will include asymptotic, homogenization, and model reduction techniques. This integrative research will lead to the first experimentally validated model of EGFR signaling in tissues. The success of this effort relies on the combined expertise of the PI at bench experiments, modeling, and analysis across developmental scales. EGFR is essential for normal tissue development, but deregulated EGFR signaling has been associated with numerous diseases, including many types of human cancers. Hence, an integrative understanding of EGFR action in tissues is of direct relevance to a wide range of medical problems. In addition to addressing the fundamental questions of cell fate diversification in development, this work will lead to computational and data integration tools for a wide range of epithelial patterning problems. First, the PIs will develop Virtual Epithelium (VE), a publicly available software for the computational analysis of epithelial patterning systems. Second, the PIs will develop and make publicly available the Database of Drosophila Oogenesis (DODO) that will combine the heterogeneous datasets generated by their experiments with bioinformatics and biostatistics tools. VE will enable systematic modeling and exploration of the spatiotemporal dynamics of cell communication by diffusible chemical signals. DODO will complement the existing database of gene expression patterns in the embryo and form a starting point for a multiscale analysis of epithelial patterning in a large number of developmental contexts. The project will bring together researchers in biology, engineering and mathematics in an interdisciplinary research program aimed at bringing about new understanding of EGFR system.

PI and Contact Information

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Co-PIs and Collaborators

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Martine Ceberio (Affiliation: Computer Science Department at UTEP – Area of expertise: decision theory)
Charles L. Books III (Affiliation: Computational Biophysics and Chemistry at the Scripps Research Institute (TSRI) - Area of expertise: docking methods)
David P. Anderson (Affiliation: Science Space Laboratory at UC Berkeley – Area of expertise: volunteer computing)

Project Title

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

Grant Details and Funding Agency

Grant Number: 506429
Agency: National Science Foundation (NSF)
Program Officer: M. Heller

Scales Examined

Time Scales

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Biological Scales

☒	Atomic
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☒	Molecular Complexes
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Length Scales

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Disease Focus: N/A **Organism of study:** N/A

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus
Characterize mobility behavior of branched polypeptides during electrophoresis at various levels of entanglement with an immobile matrix / 35%

Modeling Methods and Tools (MMT) Areas and Percent Focus
Monte Carlo (MC), Molecular Dynamics (MD) simulations / 65%

Software Development
Languages and Tools: CHARMM, Berkeley Open Infrastructure for Network Computing (BOINC)
Framework / Sharing Environment: Electronic notebooks, a subversion repository, and a database portal for sharing software, publications, docking results, progress reports, and reference materials.
Available Resources: Ligand-Protein Data Base. http://lpdb.scripps.edu

Project Summary:
The DAPLDS or Dynamically Adaptive Protein-Ligand Docking System project involves collaboration among the University of Texas, El Paso, The Scripps Research Institute (TSRI), and the University of California, Berkeley. This project, through implementation and use of a cybertool, DAPLDS, that enables adaptive multi-scale modeling in a global computing environment (i.e., distributed, heterogeneous computing environment using "volunteer" PC computers), will further knowledge of the atomic details of protein-ligand interactions and, by doing so, will accelerate the discovery of novel pharmaceuticals. The goals of the project are: (1) to explore the multi-scale nature of algorithmic adaptations in protein-ligand docking and (2) to develop cyber infrastructures based on computational methods and models that efficiently accommodate these adaptations. The intellectual merit of the project derives from small molecules, called ligands, which play an essential role in turning protein functions on or off, or in providing substrates for chemical reactions catalyzed by enzymes. Knowledge of the atomic level details of the proteinligand docking is a valuable resource in the development of novel pharmaceuticals. The docking process depends on the characteristics of the protein-ligand complex involved and given a certain complex, the characterization and modeling of the docking process can affect both solution accuracy and model execution time. Based on characteristics of the protein-ligand conformations and the availability and reliability of computational resources, DAPLDS adapts, when appropriate, the model and/or the computational 3 system to optimize model accuracy and time to solution. The multi-scale modeling adaptation in DAPLDS comprises at least three spanning scales: (1) protein-ligand representation spanning scale from rigid to flexible representation of protein-ligand interactions, (2) solvent representation spanning scale from less accurate to more accurate modeling of solvent treatment, and (3) sampling strategy spanning scale from fixed to adaptive sampling of the protein-ligand docking space. Broader Impact: DAPLDS applies multi-scale modeling to the search for putative drugs and drug leads. Our project changes the way in which grand challenges are approached by implementing an adaptive cybertool that scales beyond the protein-ligand docking application, e.g., this tool can be adapted and used for protein folding and protein structure prediction. Moreover, the use of public computing resources promotes and disseminates science research and science knowledge among the users of PCs involved in this effort.

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Project Websites: not yet available (aligned with UNM Center for Spatio-Temporal Modeling, accessed at http://cellpath.health.unm.edu/stmc/)

Co-PIs and Collaborators

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Stanly Steinberg, Ph.D.
Janet Oliver, Ph.D.
Kimberly Leslie, M.D.

Project Title

Mapping and Modeling ErbB Receptor Membrane Topography

Grant Details and Funding Agency

Grant Number: 1-R01-CA-119232-01
Agency: National Cancer Institute (NIH-NCI)
Program Officer: J. Couch

Scales Examined

Time Scales

☐	Nanosecond and below (ns)
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Biological Scales

☐	Atomic
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Disease Focus: Cancer **Organism of study:** N/A

Biomedical, Biological and Behavioral (BBB) Areas and Percent Focus
50%, electron microscopy and protein measurements to map and quantitate changing distributions of ErbB receptors - associated signaling proteins in endometrial cancer cell lines. Phospho-proteomics in endometrial tumors (a measurement of steady-state levels).

Modeling Methods and Tools (MMT) Areas and Percent Focus
50%, including 20% model development and 30% application of models for simulations.

Software Development
Languages and Tools: n/a
Framework / Sharing Environment: Actively developing tools to link spatial stochastic membrane models to the intracellular environment.
Available Resources: n/a

Project Summary:
Our goal is to understand the topographical regulation of ErbB signaling in endometrial cancer, a disease where amplification of ErbB1 (the EGFR) and ErbB2 genes is associated with poor outcome. Specifically, we propose: 1) to map the topography of ErbB receptors and their associated signaling molecules using innovative electron microscopy techniques; 2) to apply rigorous biochemical and statistical analyses to establish quantities of signaling molecules, their distributions and their relationships; and 3) to use these spatial and quantitative data as a framework for multiscale simulations of the signaling process. Preliminary data show that, when expressed at modest levels, ErbB receptors are preclustered in the membranes of endometrial epithelial cells. We hypothesize that signal transduction by these preformed clusters is held in check by the low probability of interactions between receptors in the open, signaling-competent conformation. When ligand addition is simulated, the preclustered state accelerates dimerization, leading to trans-phosphorylation and activation. We predict that over-expression of ErbB receptors in cancer promotes the formation of large, mixed clusters that increase the probability of ligand-independent, productive dimerization. We further predict that the spatial relationships of receptors to downstream signaling molecules have profound effects on ErbB signaling to critical MAP kinase and AKT pathways. To test this, we will map steady-state distributions of ErbB1 and Erb2 under defined combinations of wildtype and mutant receptors. Ligand-induced changes in receptor distributions will be documented, focusing on cluster size and co-clustering, localization to caveolae and uptake by clathrin-coated pits. Double-labeling protocols will map receptor proximity to downstream signaling molecules. Effects of kinase inhibitors on receptor distributions will be determined. Our image processing and statistical toolbox will be applied to establish receptor distribution patterns, as well as estimates of relative concentrations of receptors and downstream components within signaling domains. We will simulate diffusion, clustering and internalization of receptors and signaling molecules using Monte Carlo and agent-based approaches. Spatially realistic simulations will predict rates of ErbB receptor homo and heterodimerization, and the efficiency of receptor-effector coupling. The model will fully explore the spatial and temporal aspects of ErbB signaling.