IP0

Public Lecture: Reinventing the Sacred: Science, Faith and Complexity

I propose to discuss three topics. Several alternative theories and experimental work bear on the origin of molecular reproduction (here we at least think we know what we are talking about). Second, we discuss agency, the capacity of organisms to act on their own behalf, hence doing (here molecular reproduction causes value to enter the biosphere). Third, I discuss the evolution of the biosphere by Darwinian preadaptations, which, I believe, is partially beyond natural law. On the first topic I will discuss the classical view that life must be based on template replicated DNA, RNA or their cousins, the RNA world, the membrane-cell first world, my own work on the emergence of collectively autocatalytic sets of organic molecules and polymers, experimental evidence for collectively autocatalytic sets of DNA and peptide sequences, and our own and other workers’ evidence that random peptides fold, at least to molten globules, hence may well have catalytic activity. The study of emergent phenomena such as the emergence of molecular reproduction in collectively autocatalytic sets is an area of current mathematical research. On the second topic I will discuss the tentative definition that a minimum molecular autonomous agent is a self reproducing molecular system that also does at least one thermodynamic work cycle. Work cycles are necessarily non-equilibrium, so agency is non-equilibrium, and in life links exergonic and endergonic processes. More, work is the constrained release of energy into a few degrees of freedom. But it typically takes work to construct those very constraints. Something new enters physics here - propagating organization of process where work constructs constraints on the release of energy until a cycle of these processes closes on itself and a cell builds a rough copy of itself. We have no theory for propagating organization of process. Moreover, maximal work cycle efficiency is adiabatic, infinitely slow. Agents would reproduce infinitely slowly. I suggest instead that cells may maximize work per unit time hence power per unit fuel. On the third topic I will discuss Darwinian preadaptations in the biosphere, human economy and culture and try to show that these cannot be predestined, let alone predicted. Then if a natural law is a compact description of the regularities of a process, these aspects of evolution appear to be partially beyond natural law, and perhaps are not mathematizable. In their place is a ceaseless creativity where, I hope, we can find a sharable, fully natural, sacred.

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IP1

Protein Trafficking in Neurons

Neurons are amongst the largest and most complex cells in biology. Their intricate geometry presents many challenges for cell function, in particular, the efficient trafficking of newly synthesized proteins from the soma to distant locations on the axon or dendrites. In this talk I describe recent work on the mathematical modeling and analysis of one important aspect of protein trafficking, namely, glutamate receptor transport within dendrites. Glutamate receptors mediate the majority of excitatory synaptic transmission in the central nervous system. The regulation of glutamate receptor trafficking is an important mechanism for synaptic plasticity, whereas a breakdown in trafficking appears to be a contributory factor to a number of neurodegenerative diseases associated with memory loss including Alzheimer’s.

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IP2

Magnetic Resonance Elastography

Many disease processes such as cancer cause profound changes in the mechanical properties of tissues, yet none of the conventional medical imaging techniques such as CT, MRI, and ultrasound are capable of delineating this property. Magnetic Resonance Elastography (MRE) is an emerging diagnostic imaging technology that uses a special MRI technique to image propagating acoustic shear waves in tissue. Inversion algorithms are used to process the wave images to generate quantitative maps of tissue mechanical properties such as stiffness, viscosity, and anisotropy. Several clinical applications of MRE are now well-established, while others await the development of more effective inversion algorithms.

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IP4

Modeling and Inference of Transcriptional Regulatory Networks

Living systems are manifestations of their underlying complex dynamical networks of molecular interactions. A paramount problem is to understand how functional cellular behavior and interaction with the cell’s environment is mediated by these complex molecular systems. Recent advances in measurement technologies allow us to interrogate biological systems and collect massive amounts of heterogeneous information under a variety of experimental conditions. Integrating this information and constructing predictive models of system behavior are the central goals of systems biology. I will discuss our efforts focused on the inference of models of transcriptional regulatory networks from high-throughput measurement data, integration of multiple sources of evidence, network simulation and visualization tools, and the use of such models for gaining insight into the nature of cellular behavior in health and disease.

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IP6
The Mechanics of Tissue Dynamics
Tissues grow, change shape, and differentiate, function normally or abnormally, get diseased or injured, repair themselves, and sometimes atrophy. This complex suite of behaviors is governed by a complex suite of controls. Nonetheless, we can identify some general principles at work in the dynamics of tissues. Our goal is to understand how a tissues mechanics and biology regulate each other. Our models use a biologically-based continuum framework to track the mechanics, biology, and mechanobiology of the component cells, fluids, signaling molecules, and extracellular matrix materials. The presentation will describe our modeling approach, reveal some of the general principles we have identified, and discuss some of the questions our findings have raised about specific morphogenetic systems.

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IP7
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IP8
Coercion and the Emergence of Cooperation
One of the major challenges for the theory of natural selection is to explain the evolution of cooperation. Such cooperation exists at many levels, among self-replicating molecules, cells, individuals or societies. Coercion is a major factor promoting the collaboration of competing individuals; policing and sanctioning are widespread in human and insect societies, and can also be found in other biological communities. But sanctioning exploiters is costly. How can such spiteful behaviour emerge? In this talk, a variety of deterministic and stochastic models for the emergence of costly punishment is discussed. Remarkably, the evolutionary dynamics of finite populations shows such behaviour can emerge much more easily if the joint effort is optional, rather than compulsory.

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MS1
Measurement of Mechanical Properties with Ultrasound Vibrometry
Evaluation of tissue elasticity and viscosity non-invasively and quantitatively has important medical applications. A method is presented to quantify both elasticity and viscosity of a homogeneous tissue by fitting a Voigt dispersion model to the measured shear wave speed at multiple frequencies. Ultrasound radiation force is used to generate harmonic shear waves of various frequencies in the studied medium. Shear wave speed versus frequency is estimated from the phase difference detected by pulse echo ultrasound over a known propagation distance. This method provides a virtual biopsy of tissue elasticity and viscosity one location at a time. A special pulse sequence is developed to allow a single array transducer to both generate and detect tissue vibrations. In vitro and in vivo tissue experiments demonstrate the feasibility of this technique. Practical considerations and challenges in possible medical applications are also discussed.

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MS1
Constructing Images of Linear and Nonlinear Elastic and Viscoelastic Tissue Parameters
Recent advances in imaging technology allow remarkably accurate and detailed measurements of in-vivo tissue deformation under different types of loading. For example using ultrasound it is now possible to accurately (less than 1% noise) determine the displacement field in the interior of a breast compressed to 10 % strain with a resolution of about 100μm. This type of displacement data contains a wealth of information about the macroscopic mechanical properties of tissue. These properties are in turn closely connected to the health of the tissue. For example, cancerous tumors are often stiffer than their surroundings, fibrosis in a liver is associated with a diffuse overall stiffening, and atherosclerosis literally means the hardening of a blood vessel. In this talk I will describe our efforts to determine the spatial distribution of the mechanical properties of tissue from the knowledge of its displacement field. This process involves the solution of an inverse problem, where an appropriate mechanical model for tissue response is assumed and the spatial distribution of the material parameters is sought. I will focus on different types of mechanical models (linear elastic, viscoelastic and non-linear elastic models) and on efficient techniques for solving the resulting inverse problem.

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MS1
Mapping and Characterization of the Electromechanical Wave Propagation in the Left Ventricle in Vivo
Non-invasive conductivity mapping of the live myocardium
could constitute an invaluable tool for diagnosis of cardiac abnormalities. Using ECG-gated echocardiography to achieve ultra-high frame rates, it is possible to estimate and image, in a full 2D-view of the left ventricle, otherwise undetectable transient displacements initiated by the electrical activation of the myocardium. This electromechanically-coupled phenomenon can be assessed through imaging of the resulting wave in the left ventricle beginning at the QRS peak. In this work, we propose to characterize the properties of this wave and study its potential for indirect evaluation of conduction properties of the myocardium.

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MS1
The Statistics of Shear Wave Speed Images Obtained from Wave Front Arrival Times

Elastography is a non-invasive method which measures the mechanical properties of tissue. Often this is accomplished by generating a shear wave that propagates in the tissue, using ultrasound to measure the interior displacement of the shear wave. The goal is to image the speed of the shear wave. The arrival times of the shear wave front satisfy the Eikonal equation. In this talk we address how to find the shear wave speed given the arrival times using the Eikonal equation. Unfortunately, the shear wave speed is inversely proportional to the gradient of the arrival times. When Gaussian noise is added to the arrival times, in high speed regions the noise in the recovered shear wave speed is often Cauchy like, and this leads to instabilities. These high speed regions are usually the most interesting regions. We give an alternative level set description using curves of constant arrival time. With the level set description, we show that when Gaussian noise is added to the arrival times, the noise in the recovered wave speed is also approximately Gaussian, and that the level set description automatically increases the amount of smoothing in high speed regions to avoid instabilities.

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MS2
The Importance of Fluid Flow in Biofilm Modeling

In this talk, we explore biofilm models where the fluid flow field plays a more important role than simply a mechanism by which nutrients are delivered. Accounting for the flow field can alter the relative growth rate downstream, induce a directional influence for cell-to-cell signaling, and give differential rates for surface erosion. We present our results illustrating these effects, and our algorithms for efficiently expanding the size of the domain in which the solutions are computed by means of tiling.

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MS2
Title Not Available at Time of Publication

Current research has determined that the majority of bacteria in nature exist in structured communities termed biofilms rather than free swimming planktonic bacteria. Moreover, bacteria within biofilms are highly tolerant to typical antimicrobial and antibiotic treatments. These observations, coupled with the negative impacts of the presence of biofilms in medical, industrial and natural settings, have driven research into the processes that govern the formation, growth and development of biofilms. Because biofilms typically form in the presence of an externally driven fluid, the dynamics of the viscoelastic biofilm is inherently a fluid dynamics problem. Biofilms are physically and biologically heterogeneous with a range material properties, making any mathematical treatment both challenging and engaging. This talk will describe the incremental process of extending a classical technique used to solve coupled flow problems (BIM) to incorporate the growth and material properties of the biofilm. The goal of the research is to provide insight into the mechanisms of bacterial tolerance and the development of more effective methods for removal of the bacteria.

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MS2
A Reaction-Diffusion Model for Resistance of Biofilms to Antibiotics

It is an established fact that biofilm formations are more resistant to antibiotic agents than free swimming suspended bacteria. Several causes have been proposed in the literature to explain this diminished susceptibility: diffusive resistance, slow growth of a portion of the microbial population, existence of persister cells. Our proposed model is continuous and considers the influence of spatial effects on disinfection processes. It is based on a system of highly nonlinear reaction-diffusion partial differential equations. A substrate controlling biofilm growth (typically oxygen), an antibiotic, as well as active and inert biomass are considered in the prototype version of this model. The diffusivity of biomass inside the biofilm phase takes mainly two effects into account: fast diffusivity in areas saturated with biomass, and singularity at 0 similar to that in porous media equation at the interface between biofilm and liquid phases. Some aspects of the mathematical analysis (due to singularities existence of solution is far from trivial) are handled as well as some numerical issues are discussed.”

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MS2
Modelling Flow Dynamics in Biofilms

A continuum modelling approach is used to describe 2-dimensional biofilm growth within “typical” flow chamber experiments using conservation laws, force balances and viscous flow. The modelling also takes into account the role of nutrient and bacterial cell-cell signalling, both important factors in the normal development of biofilms. The resulting model consists of a highly coupled system of nonlinear partial differential equations with a moving interface. Numerical solutions will be presented and key results discussed.

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MS3
Multiscale Modeling of Neural Subcircuits in the Retina

We mathematically model the subcircuits of the outer plexiform layer of the retina. We investigate if feedback effects in the cone photoreceptor’s synapse are driven by electrical (ephaptic) or chemical (neurotransmitters, e.g., GABA) mechanisms. We formulate and analyze a partial differential equation system that includes the horizontal cell syncytium and its numerous dendritic spines into cone pedicles, and compare simulation results with spatial enhancement data from cat retina for different test regions.

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MS3
A Stage Population Model for Dendritic Spines

We formulate a cable model for the stage transitions between stubby, mushroom, and thin dendritic spines. In this model multiple spine types may coexist simultaneously at points along the dendrite, and the model allows for the study of population dynamics between spine types. A continuum formulation is used for tracking the interaction between the many activity-dependent spines and for studying the impact of their individual and collective dynamics on the output properties of the dendrite.

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MS3
Diffusion-Trapping Model of AMPA Receptor Trafficking Along a Spiny Dendrite

We model AMPA receptor trafficking between multiple dendritic spines distributed along a dendrite. Receptors diffuse laterally within the dendritic membrane between soma and spines, and can bind to scaffolding proteins within spines. Surface receptors are exchanged with local intracellular pools both at the soma and spines via exo/endocytosis. We derive a reaction-diffusion equation for receptor trafficking whose solution determines synaptic receptor numbers along the dendrite, and hence how lateral diffusion contributes to synaptic strength.

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MS4
A Novel Neural Population Model for Investigating NREM/REM Sleep Regulation

In sleep/wake regulatory neuronal populations, microdialysis and microinjection experiments suggest that neurotransmitter dynamics play an important role in the initiation and maintenance of different behavioral states. However, traditional population firing-rate models have included synaptic coupling terms without explicitly modeling the dynamics of the neurotransmitters acting at these synapses. We investigate the mechanisms governing NREM/REM sleep regulation using a novel population modeling framework to capture the dynamic interplay between population activity and neurotransmitter concentration.

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MS4
A Computational Study of the Network Mechanisms Mediating Anesthesia-Induced Paradoxical Excitation

The anesthetic propofol paradoxically produces both behavioral and electroencephalographic manifestations of excitation at low doses. We model cortical interneurons and pyramidal cells using Hodgkin-Huxley-type conductances and track the evolution of network dynamics as we simulate propofol-induced GABAa-potentiation. Network dynamics that correlate with the introduction of low-dose propofol include increased post-inhibitory excitability of low frequency spiking neurons and the spontaneous formation of interneuron antisynchrony. These dynamics both depend on GABAa-induced reduction of the intrinsic membrane M-current.

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MS4
A Mathematical Model of the Sleep/Wake Cycle Based on Neurophysiology

We present a biologically-based mathematical model that accounts for several features of the human sleep/wake cycle. These features include the timing of sleep and wakefulness under normal and sleep-deprived conditions, ultradian rhythms, and the circadian dependence of several sleep variables such as the total sleep time and sleep-onset rapid eye movement sleep (SOREMS). Additionally, if the input from the neurotransmitter orexin is removed, the system exhibits more frequent switching between sleep and wakefulness, consistent with the sleep disorder narcolepsy. The model demonstrates how each of these features depend on interactions between a circadian pacemaker and a sleep homeostat and provides a biological basis for the two-process model for sleep regulation (Borbely, 1982; Daan et al., 1984). The model is based on previous "flip-flop" models for sleep/wake (Chou et al. 2001) and REM/NREM (Lu et al. 2006) and we explore whether the neuronal components of these flip-flop models, with the addition of a sleep-homeostatic process, are sufficient to account for the features of the sleep/wake cycle listed above. The model is minimal in the sense that, besides the sleep homeostat and constant cortical drives, the model includes only those nuclei described in the flip/flop models. However, in order to account for certain features of the ultradian rhythms, we found it necessary to add an additional hypothesis about the connections.

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MS5
Modelling the Effect of Amantadine on Influenza A Viral Dynamics in Vitro

We show that using a controlled experimental apparatus, the hollow fiber system, it is possible to develop accurate yet simple mathematical models of influenza infection in the presence of drug. The parameter estimates obtained from the experimental data are consistent with those obtained earlier for influenza infection in a human model. We estimated the maximum efficacy of amantadine in blocking viral entry to be ~74% which is likely due to the rapid emergence of resistance.

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MS5
Models of Acute Hepatitis B Infection: What
Causes Viral Persistence?

To understand the factors that govern disease progression in viral hepatitis B infection, we study acute stages of the infection where immune responses play an important role in determining whether the infection is cleared or becomes chronic. We develop mathematical models to test the contribution and role of various immune responses in viral control. We validate the model against experimental data to determine how well it represents the biological system and how useful its predictions are.

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MS5
HCV Infection and Hepatocyte Homeostasis

In recent research, several researchers have proposed that the distinct response of hepatitis C virus (HCV) viral load to antiviral therapy can be explained by the homeostatic proliferation of the target cell proliferation. In this talk, I’ll present a mathematical analysis of their model of HCV infection in the liver, and how differences in treatment efficacy and other host-dependent parameters alter the model’s bifurcation structure. In particular, a mathematical hypothesis explaining triphasic treatment responses will be presented.

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MS5
Analyzing the Kinetics of HIV Vaccines

Human immunodeficiency virus infects over 30 million people worldwide, and this pandemic continues to grow. The most affected regions are some of the poorest in the world. The best intervention strategy to curb this epidemic would be the advent of an effective vaccine. Although this has been difficult to achieve, many experimental studies have been conducted in the macaque model using a variety of approaches. We have been analyzing and modeling the dynamics of virus and the immune response in vaccinated vs. unvaccinated macaques. We have quantified the effects of a vaccine in reducing the depletion of CD4+ T-cells. Our studies also suggest that CD8+ T-cells do too little too late to prevent spread of virus within the host. This new approach of quantitative analyses of HIV vaccine data should contribute to a better process of rational vaccine design.

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MS6
Functional Localization of Calcium Machinery

We exploit the recent ability to dynamically monitor cytosolic calcium in the construction of a map of receptor and channel density. In particular, we 1) Infer from the change in cytosolic dye-buffered calcium fluorescence the affinities and diffusivities of all relevant exogenous and endogenous calcium buffering proteins, and 2) Infer from (1) the concentration of free calcium and so determine the distribution of ryanodine receptors and calcium extrusion pumps.

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MS6
Mitochondrial Modulation of Intracellular Ca2+ Signaling

In cells expressing highly dynamic Ca2+ signaling behavior, mitochondria can shape the spatiotemporal patterns. In addition, mitochondria have been shown to act as an independent network of Ca2+ oscillators. These phenomena are gaining attention as evidence points to mitochondrial dysfunction as a potential factor in diseases such as neurodegeneration. I will discuss efforts to model dynamic phenomena involving mitochondria, and in particular, depolarization waves thought to involve Ca2+ and the mitochondrial permeability transition.

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MS6
The Spatial Distribution of Ca2+ Release Channels Affects Ca2+ Dynamics: Insights into the Origins of Arrhythmias

Calcium (Ca) is released in cardiac cells through Ca release units (CRUs). The CRUs need to be spatially separated to prevent uncontrolled Ca release. Our large-scale simulations show that subtle (∼10%) changes in CRU spacing profoundly affect the stability of the Ca control system. We propose that changes in the spatial separation of CRUs underlie the high incidence of sudden cardiac death in heart diseases that have shortened CRU spacing.

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MS6  
Ca2+ Buffer Saturation Allows Facilitation of Ca2+ Transients by the Pre-Opening of Remote Ca2+ Channels

E. Neher proposed that activity-induced enhancement of neurotransmitter release could be explained by the gradual depletion of free endogenous Ca2+ buffers by the incoming Ca2+ influx. Recently we showed that this mechanism requires whole-terminal saturation of highly mobile buffers with rapid Ca2+ binding kinetics. We will examine implication of such global buffer saturation, in particular the ability of remote Ca2+ influx to influence Ca2+ elevation caused by the subsequent opening of local Ca2+ channels.

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MS7  
Computational Multi-Scale Modeling in Protein-Ligand Docking

In our multi-scale approach to protein-ligand docking, increasingly sophisticated docking models can be constructed along three scales of docking assumptions: (1) representation of the protein and ligand (potential energy function and flexibility of protein and ligand); (2) representation of the effect of solvent; and (3) sampling strategy. Computationally expensive docking models may be optimized for accuracy for difficult test cases, but may not improve results for simple test cases. It is our goal to increase the overall efficiency of docking by considering dynamic adaptations along these multi-scales to consider and evaluate new docking models. Using classifications of protein-ligand complexes based on the flexibility of protein and ligand, docking models can be dynamically adapted when more expensive models are required for sufficient accuracy. These classifications can be used to start an iterative search for adaptive docking models that optimize accuracy and minimize time to solution. The results of our project are being used to develop a Dynamically Adaptive Protein-Ligand Docking System (DAPLDS), which would be able to dynamically adapt to an appropriate docking model for new protein-ligand complexes or a large series of ligands. Our project Docking@Home (http://docking.cis.udel.edu/) uses the "volunteer computing" paradigm, which uses the Internet to harness the computing power and storage capacity of a volunteer computer resources owned by the general public. Given a variety of docking tasks, dynamic scheduling policies can selectively devote available resources based on computational expense to improve project throughput.

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MS7  
Coarse-Grained Molecular Models of Protein Complexation

A fundamental mathematical challenge relevant to biomolecular simulation is the quantitative description of protein complexation to derive molecular machines that control biological processes such as cell signaling. We have recently achieved a fundamental result in deriving an analytical solution for computing the screened electrostatic interaction between arbitrary numbers of proteins of arbitrarily complex charge distributions, assuming they are well described by spherical low dielectric cavities in a higher dielectric salty medium [I. Lotan and T. Head-Gordon (2006)]. An analytical electrostatic model for salt screened interactions between multiple proteins J. Comp. Theo. Chem. 2, 541-555]. By exploiting multipole expansion theory for the screened Coulomb potential, we can now describe direct charge-charge interactions and all higher-order cavity polarization correctly at all separation distances. Recently we have been extending this electrostatic model to new numerical formulations that better describe realistic shape of the protein molecules that span solutions from low to high spatial resolutions. While alternative numerical approaches are faced with an inherent trade-off between spatial resolution and memory and time requirements, which limits them to system of few macromolecules, we believe that our method is efficient and fast to compute even for many macromolecules, including frequent updates of changes in their charge distributions due to induced conformational changes. Ultimately, smooth and systematic increase in spatial resolution back to greater molecular detail of the dielectric boundaries will be the centerpiece of a multiscale scheme that converges on an atom centered solution [E.-H. Yap, N. Lux Fawzi, and T. Head-Gordon (2007)]. A coarse-grained a-carbon protein model with anisotropic hydrogen-bonding. Proteins, Struct. Func.. Bioinf. 70, 626-638]. We believe this will realize wide application in modeling complex materials problems including spatial organization of protein complexes.

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MS7  
Understanding Bionanosystems (BNS) via Multiscale the Basic Laws of Physics

The dynamics of a BNS involves processes across multiple time and length scales. While it is natural to understand these systems with the basic equations of molecular physics (e.g., the Liouville, Schrodinger, or Poisson-Boltzmann equations), the supramillion atom scale of these systems presents great challenges to direct molecular dynamics and quantum mechanics simulation. We illustrate how a multiscale analysis of the N-atom Liouville equation reveals essential principles of virology, and ultimately
yields an algorithm for computer-aided drug and vaccine
design and ways to optimize anticancer drug delivery via
nanocapsules.

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MS7
Analysis of Coarse-Grained Nucleic Acid Free-Energy Landscapes

We describe algorithms for analyzing the thermodynamic
and kinetic properties of coarse-grained DNA and RNA
free energy landscapes. The utility of these methods will
be demonstrated by elucidating the empirical behavior of
synthetic nucleic acid systems with metastable states.

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MS8
Multi-Modal Breast Imaging with Ultrasound Tomography

We report and discuss clinical breast imaging results ob-
tained with operator independent ultrasound tomography.
A series of breast exams are carried out using a recently
upgraded clinical prototype designed and built on the prin-
ciples of ultrasound tomography. The in-vivo performance
of the prototype is assessed by imaging patients at the
Karmanos Cancer Institute. Our techniques successfully
demonstrate in-vivo tomographic imaging of breast archi-
tecture in both reflection and transmission imaging modes.
These initial results indicate that operator-independent
whole-breast imaging and the detection of cancerous breast
masses are feasible using ultrasound tomography tech-
niques. This approach has the potential to provide a low
cost, non-invasive, and non-ionizing means of evaluating
breast masses. Future work will concentrate on extending
these results to larger trials.

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MS8
Motion Estimation Between Successive Sonograms

Elastography is an imaging modality where the strain of
tissues is estimated, when the tissues are subject to an
external or internal load. We present an algorithm to esti-
mate the motion between ultrasound images. The Jacobian
matrix of the cost function to be minimized is assembled
rapidly using a finite-element method. A global displace-
ment is retrieved, and spatial regularization allows to have
a strain estimate with a small amount of noise.

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MS9
Flocculating Infectious Bacteria: Smoluchowski and Sepsis

Klebsiella pneumoniae and Staphylococcus epidermidis are
common causes of intravascular catheter infections, the
most important sources of bacteremia. These bloodstream
infections dramatically increase the mortality of illnesses
and often serve as an engine for sepsis. Our current model
for the dynamics of the size-structured population of ag-
gregates in a flowing system is based on the Smoluchowski
coeagulation equations, which we are using to study prop-
erties of these flocculating bacteria. In this talk, I will
discuss the progress of several investigations into proper-
ties of our model equations as well as the comparison with
data. In particular, I will focus on the derivation of an
alternative fragmentation kernel in laminar flow as well as
the post-fragmentation aggregate size distribution.

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MS8
Mathematical Data Analysis for MRE

MRE (magnetic resonance elastography) is an instrument
which is expected to realize doctors’ palpation inside living
body. It measures waves inside living bodies. It can also be
applied to many problems in rheology. The mathematical
data analysis for MRE is to give an appropriate mathe-
matical model for the waves and a scheme to recover the
viscoelastic properties of the living body. We will propose
a mathematically rigorous data analysis for MRE.

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MS9
Biofilm Control with Probiotics

Traditionally, probiotics have been used as functional foods (e.g. in dairy products) but recently some interest developed in the potential of this concept for medical purposes, e.g. as alternative to antibiotics. Since many bacterial infections are caused by pathogenic biofilms and some probiotics form biofilms as well, one deals with a dual-species biofilm system of a pathogen and a probiotic. Modeling this leads to a system of highly nonlinear partial differential equation which we will study in computational experiments.

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MS9
Soft Materials Approach to Measuring the Viscoelastic Properties of Biofilms

We combine methods from computational mathematics and the science of soft matter to determine the viscoelastic properties of biofilms on the micron scale in which structural heterogeneity has been reported. Using image processing coupled with microfluidics we convert confocal microscopy images to statistical quantification. These properties have typically been difficult to characterize by bulk experimental techniques. These new data support appropriate mathematical modeling approaches to predict properties such as fracture dynamics under shear stresses typical of the vascular system.

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MS9
Biomechanics and the Limitations of Compartmental Models in Bloodstream Infections

Bloodstream bacterial infections are common, rapidly progressive, and frequently lethal illnesses. The fundamental mechanism of bacteremia is organism-wide distribution of pathogens carried in the blood stream, a process well suited for compartmental analysis. However, in animal and human disease there are experimental limitations that preclude simple modeling. The most important of these relate to compartments that are either hidden (in humans) or whose sampling is destructive (in mice), meaning that individual multicompartmental trajectories can never be measured. In this presentation, I’ll provide an overview of this important disease, discuss modeling options and a Monte Carlo strategy for parameter estimation, and, by highlighting how key assumptions needed for compartmental modeling are violated in reality, lay the groundwork for the other minisymposium talks on modeling bacterial communities.

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MS10
Signal Transduction Model Update via Sensitivity Analysis

Sensitivity analysis has traditionally been used to determine important mechanisms of a system and parameters to estimate. However, these traditional applications of sensitivity analysis assume that the model accurately describes a system. This paper presents a new application of sensitivity analysis for guiding model development. Sensitivity analysis is used to determine which parts of signal transduction models should be modified to improve the model predictions of experimental data.

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MS10
Embedding Global Sensitivity Analysis within Global Optimization to Constrain Parametric and Structural Model Uncertainty

Mathematical modeling of cellular processes requires resolving the appropriate degree of complexity while constraining relevant structural detail and parameter uncertainty. Active use of sensitivity screening methods for rapid assessment of feasibility and global sensitivity analysis coupled with global optimization searches for data compatibility can result in model structure alterations, parameter range reduction or experiment design. Models of T cell signaling and cardiac myocyte metabolism will serve to illustrate the application of these techniques.

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MS10
Sensitivity Analysis Based Adaptive Search-Space Reduction for Parameter Estimation Applications

One of the central aspects in systems biology is the estima-
tion of parameters based on experimental data. Due to the high dimensionality of the search space, often encountered for biochemical models, it is of great interest to reduce the numbers of parameters that need to be estimated. Here, we present a new method that, based on sensitivity analysis, allows to iteratively adapt the search space to the most important parameters.

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MS10
Analytical Advantages of Canonical Models for the Assessment of Cellular Responses

Nature has not provided us with guidelines for selecting mathematical representations for biological phenomena. In relatively simple cases, a possible choice is a model designed from first principles of physics. However, most biological systems are too complicated for this approach, leaving as alternatives ad hoc and canonical models. Canonical models are directly based on approximation theory and offer very significant analytical and computational advantages. I illustrate these advantages with power-law models within Biochemical Systems Theory.

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MS11
Product form Stationary Distributions for Complex Balanced Chemical Reaction Networks

The dynamics of chemical reaction networks can be modeled either deterministically or stochastically. The deficiency zero theorem for deterministically modeled systems gives conditions under which a unique equilibrium value with strictly positive components exists within each stoichiometric compatibility class (linear subset of Euclidean space in which trajectories are bounded). The conditions of the theorem actually imply the stronger result that there exist concentrations for which the network is “complex balanced”. That observation in turn implies that the standard stochastic model for the reaction network has a product form stationary distribution. Examples will be given showing the applicability of such results in the analysis of the dynamics of systems with multiple time-scales.

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MS11
Injectivity and Monotonicity in Chemical Reaction Networks

Details of the kinetics and values of rate constants are rarely known with great accuracy for biochemical reaction networks. In this context any claims which can be made based on reaction network topology are particularly important. For a broad class of reaction networks it is possible to make strong statements in two areas based on network topology: 1) Claims about the nonexistence of multiple equilibria based on sufficient conditions for injectivity of networks, and 2) Claims about the nonexistence of stable periodic orbits, based on sufficient conditions for the networks to be monotone systems. Results in these areas will be presented with examples of their application. Techniques used in the proofs will be outlined.

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MS11
Treatment for Within-Host Virus Dynamics

We revisit a standard model describing the infection cycle of a virus in an individual. One example of this model is furnished by HIV, a retrovirus which infects a particular class of immune cells, the CD4+ T cells, giving rise to infected T cells that spawn off new virus. However, the dynamics of other infections such as hepatitis, influenza and even the malaria parasite P. falciparum can be described by the same model. We will discuss the effect of periodic treatment on the system, and give tight bounds for the drug efficiencies required to eradicate the infection. We will also consider the problem of finding optimal treatment schedules that minimize various measures of the burden of the treatment on the patient.

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MS11
The Dynamics of Protein Folding and Export from the Endoplasmic Reticulum

One third of proteins are folded and delivered to their respective pathways from the endoplasmic reticulum (ER). Mutations in ER export, folding and degradation proteins are the cause for many ER storage (or protein-misfolding) diseases. We have developed a model of protein maturation, misfolding and export to investigate ER storage diseases. There are currently two prevailing hypotheses in the field: ER stress can result either from deterioration of the transport proteins responsible of extracting protein from the ER. We explore these hypotheses to study the origins of ER diseases and predict strategies for restoring protein homeostasis in the ER diseases.

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MS11
Multiple Roles of Negative Feedback in Immune Response to Virus Attack

Recently developed model of the immune response to influenza A virus focuses on the control of the infection by the innate and adaptive immunity, represented by interferon-
induced resistance, the removal of infected cells by effector cells, and virus-specific antibodies. Each of the immune mechanisms suppresses the virus through a negative feedback loop, with a distinct character and effect. We explore the effect of the feedback loops on the severity and duration of the disease.

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MS12
Information Processing in Dendrites

Dendrites are the main site for synaptic input to neurons. They are usually considered as pure post-synaptic elements that serve as a spatio-temporal filter for the synaptic input to the soma. Here I will discuss how to compute this response function for realistic dendritic geometries, and in particular address the case when the tree has electrical resonances associated with the presence of HCN channels (that underlie the \( I_h \) current). When coupled to an active soma I will discuss the consequences of neuronal geometry and intrinsic membrane resonances in determining output spiking patterns. I will further show how this framework for computing dendritic responses can be extended to cover networks with dendrodendritic junctions. These are prominent in some brain areas, for example in the olivocerebellar system and the olfactory bulb. Here the presence of gap junctions means that the dendrites of cells function as both post and pre-synaptic elements simultaneously. Finally, I will discuss the derivation of STDP like learning rules in such networks via the maximisation of a given likelihood function with respect to some set of synaptic weights. Time permitting I will also address how to model active membrane in the dendritic tree in a computationally cheap fashion, and discuss the role of dendritic spikelets in information processing.

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MS12
Adaptive Coding of Visual Information in Neural Populations

Our perception of the environment relies on the capacity of networks neurons to rapidly adapt to changes in environmental stimuli. Examining how brief exposure, or adaptation, to a stimulus of fixed structure changes information processing by neuronal networks is essential for understanding the relationship between sensory coding and behavior. I will present experimental evidence that shows how brief adaptation changes the interneuronal correlation structure and the accuracy of population coding in primary visual cortex.

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MS12
Multiscale Effects of Ion Channels in Epilepsy

Seizures are thought to be caused by an imbalance between the excitatory and inhibitory processes in the brain. This imbalance leads to pathological synchronization of neuronal activity leading to a seizure. Homeostatic mechanisms in neurons try to keep these forces in balance. Some ion channels, such as the hyperpolarizing \( I_h \) current, are known to change in their density in epileptic animal models reflecting these homeostatic changes. To understand the effects of the \( I_h \) on the dynamics of the neuron and on the network, we have measured phase response curves of neurons with and without \( I_h \) added to the neuron using electrical knock-in via the dynamic clamp. \( I_h \)'s effect on the neuron is to shunt excitatory inputs early in the phase. This results in a phase dependent decrease in excitatory synaptic efficacy. The effect predicted on networks is to increase synchrony. This is a surprising finding, that a decrease in excitatory synaptic efficacy could increase synchrony. We hypothesize then that a neuron will modulate \( I_h \) differently depending on whether it is in a network with significant recurrent connections or a network receiving synaptic input from another population. We believe that this explains why \( I_h \) is found to be downregulated in Hippocampus in one model of epilepsy (Chen and Soltesz, 2001) while it is upregulated in the Entorhinal cortex (Shah and Johnston, 2004). If homeostatic mechanisms do not take the network structure into account, an attempt to dampen synaptic input by increasing \( I_h \) could increase network synchrony making the brain region more prone to seizures.

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MS12
Correlation and Synchrony Transfer in Integrate-and-Fire Neurons

We use perturbation techniques to study how pairs of neurons transfer correlated input currents into correlated spikes. For spike correlations, or synchrony, over rapid timescales, correlation transfer increases with both spike time variability and rate. We show how this dependence on variability disappears at large observation time scales. We demonstrate that this result persists for a nonlinear membrane model and for heterogeneous cell pairs, and uncover strong nonmonotonocities due to refractory effects. This analysis allows us to present consequences for the encoding of time-varying stimuli.

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MS13
Effect of Exercise on Skeletal Muscle and Whole-Body Metabolism

Exercise training induces structural, biochemical, physiological, and functional adaptations ranging from the molecular to the whole-body levels. The extent of the adaptation depends not only on the characteristics of the training session (modality, frequency, intensity, time), but also on the training program duration. To predict the long-term effects of exercise training, a multiscale model of metabolism has been developed that integrates processes and adaptations at the cellular, tissue-organ, and organismal level to simulate the metabolic response to acute exercise of a normal-sedentary and an endurance-trained individual.

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MS14
Multi-Scale Modeling of Collagen Gel Mechanics

Collagen gels consist of an interacting network of long, thin fibers, allowing even very dilute solutions (1-3 mg/ml) to solidify. The critical challenge in understanding the mechanics of these gels (and of collagenous tissues engineered from them or native tissues) is to incorporate the network behavior, which occurs on the micrometer length scale, into the tissue behavior, which occurs on the millimeter length scale. A two-scale scheme has been developed in which the average stress is calculated on a representative network at each integration point of a finite-element representation of the tissue. The strain from the finite-element model is used to generate boundary conditions for each micro-model, which in turn provides the stress for the macroscopic scale. Further developments include a biphasic formulation to account for interstitial and image-based construction of the networks.

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MS14
Multi-Scale Modeling of Blood Vessels Using a Fluid-Solid-Growth Framework

Blood vessels adapt and remodel in response to changes in their mechanical and biochemical environment during development and aging, and with diseases including atherosclerosis, aneurysms, and hypertension to name just a few examples. While computational methods have been utilized separately to quantify hemodynamic conditions and to simulate growth and remodeling processes, there is a pressing need for a unified approach to model vascular adaptation and disease in response to biomechanical and biochemical stimuli. This class of Fluid-Solid-Growth (FSG) problems are inherently multi-scale in time since the biomechanical forces due to the heart beat change on the scale of seconds whereas vascular adaptation can occur over days to weeks and diseases progress over months to years. In addition, FSG problems are multi-scale in space since biomechanical forces and biochemical stimuli, sensed at a molecular and cellular scale, elicit adaptive and maladaptive responses from molecular to organ scales. We describe herein a novel computational method to model fluid-solid growth problems and illustrate this method by applying it to simulate the enlargement of a cerebral vascular aneurysm in response to shear and tensile stress.

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**MS14**  
**Accurate Coarse-Graining of Red Blood Cell Models**

We develop a systematic coarse-graining procedure for modeling red blood cells (RBCs) using arguments based on mean-field theory. The three-dimensional RBC membrane model takes into account the bending energy, in-plane shear energy, and constraints of fixed surface area and fixed enclosed volume. The sensitivity of the coarse-grained model is investigated and its behavior is validated against available experimental data and in Dissipative Particle Dynamics (DPD) simulations of RBCs in microcirculation.

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**MS14**  
**Multi-Scale Modeling of Chemical-to-Mechanical Energy Conversion in Actin-Based Motility**

In actin-based motility, monomeric actin polymerizes into stiff filaments from surface-bound components, 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. The scientific goal of this project is based on the hypothesis that the structural and force-producing properties of the network are critically dependent on whether working filaments remain tethered by end-tracking proteins or remain untethered as required by the conventional Brownian Ratchet model. The computational goal of the project is to develop and validate a biologically relevant, multi-scale model of force generation by actin polymerization. We are designing a computational framework for modeling the mechanical properties of solutions of stiff biopolymers such as actin, accounting for its resistance to bending and torsion, position and orientation dependent chemical functionalization along the molecular backbone, and the coupling of the polymer dynamics to the surrounding solvent. In this talk I will outline the theory underlying the mechanical model of a stiff polymer and describe some tests of our numerical implementation. Parallel work developing the means of modeling the fluid-mitigated hydrodynamic interactions will also be described. At longer times a quasi-static approach can replace the detailed dynamic model and we are also developing Monte-Carlo simulations of thermally fluctuating filaments. Finally under high load thermal fluctuations may be ignored and the classical equilibrium theory of flexible rods used instead. I will show some preliminary calculations for individual filaments and simple filament networks.

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**MS14**  
**Multi-Scale Modeling of Calcium Responses in Realistic Cell Geometry**

Release of inflammatory mediators by mast cells in type 1 immediate hypersensitivity allergic reactions relies on the antigen-dependent increase in cytosolic calcium. Here we used a series of electron microscopy images to build a 3D reconstruction of a rat tumor mast cell, which then served as a basis for modeling of IP3-mediated calcium responses. Local proximity of the endoplasmic reticulum (ER) to both the plasma membrane and to mitochondria is considered. We found that local ER luminal calcium concentration during IP3R transport is markedly affected by nearby organelles. In addition to compartmental and PDE-based approaches, we describe the first application of stochastic reaction-diffusion modeling within a complete 3D cell geometry. These combined approaches help to bridge the gap between measured single molecule kinetic constants and overall calcium dynamics.

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**MS15**  
**Regularisation and Prior Knowledge in Diffuse Optical Tomographic Reconstruction**

Optical Tomography in highly scattering media is nonlinear and severely ill-posed. An increasingly widely used approach for image reconstruction is a parameter estimation method based on optimisation of a likelihood function. These kinds of problems always require regularisation which most generally should be interpreted in terms of Bayesian prior term. In this talk I will describe different regularisation techniques incorporating structural and statistical information. An emphasis will be placed on cross-construction with an auxiliary image representing a multimodality approach.

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**MS15**  
**Inverse Transport From Angularly Averaged Measurements**

Inverse transport consists of reconstructing the absorption and scattering coefficients in a domain from measurement of the outgoing density of particles at the domain’s boundary. Uniqueness and identification of the coefficients has been established in many settings where the source term and the outgoing measurements are allowed to depend on both the spatial and directional variables. In practice, however, the sources and the measured density of particles are often angularly averaged. I will present recent uniqueness and stability results in the latter context for continuous wave (time-independent) and modulated (or equivalently, time-dependent) sources. This is based on joint works with Alexandre Jollivet, Ian Langmore, and Francois Monard.

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MS15

Interferometric Synthetic Aperture Microscopy

Methods of computed imaging have historically provided new levels of insight and utility when coupled with established instrumentation. Examples include the growth of X-ray projections into modern computed tomography (CT), nuclear magnetic resonance spectroscopy into magnetic resonance imaging (MRI), and radar ranging into synthetic aperture radar imaging (SAR). Over the last 16 years, optical coherence tomography (OCT) has provided an alternative to physical sectioning and histology that allows for imaging of living samples and even in vivo examination of cell structure and dynamics. Applications range from monitoring the development of engineered tissues to the diagnosis of malignancies. The sectional imaging of OCT is achieved by direct visualization of raw data obtained in focused optical range finding. As a result, there is, in the OCT community, a widely held belief that there exists a trade-off between transverse resolution and the thickness of the volume that may be imaged with a fixed focal plane. The extreme manifestation of this effect may be seen in optical coherence microscopy (OCM) where a single plane is imaged using a highly focused beam to achieve micron scale resolution, but no sectioning is possible because of the defocus away from this plane. In this talk I will show that solution of the inverse scattering problem leads to algorithms that provide a three-dimensional reconstruction of the object with a spatially invariant point-spread function for the system. The spatial resolution is everywhere equal to the best resolution in the raw data (in the focal plane). Thus the supposed trade-off between resolution and depth of imaging is eliminated. The resultant reconstructions show a marked qualitative improvement in all regions and moreover are quantitatively meaningful. This new modality is formally related to SAR and we refer to it as interferometric synthetic aperture microscopy (ISAM). I will present the theoretical analysis, numerical simulations and experimental results for samples including a tadpole, a human tumor, and a titanium dioxide particle suspension.

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MS15

Reflectance Optical Tomography in Layered Tissues

We will discuss direct and inverse problems for light propagation in layered tissues. Light propagation in tissues is governed by the theory of radiative transport. This theory takes into account absorption and scattering due to inhomogeneities. A two layer half space is a useful tissue model because it allows one to prescribe different optical properties in superficial and deep regions of tissues. This difference between optical properties is necessary to model accurately light propagation through tissues systems comprised of a thin cellular epithelial layer supported by an underlying stroma. We discuss an inverse obstacle scattering problem in layered tissues with applications to detecting carcinomas in situ. This theory makes explicit use of the fact that tissues scatter light with a sharp peak in the forward direction.

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MS16

Boundary Integral Methods Biofilm/Fluid Systems: Growth and Viscous Interactions

Current research has determined that that the majority of bacteria in nature exist in structured communities termed biofilms rather than free swimming planktonic bacteria. Moreover, bacteria within biofilms are highly tolerant to typical antimicrobial and antibiotic treatments. These observations, coupled with the negative impacts of the presence of biofilms in medical, industrial and natural settings, have driven research into the processes that govern the formation, growth and development of biofilms. Because biofilms typically form in the presence of an externally driven fluid, the dynamics of the viscoelastic biofilm is inherently a fluid dynamics problem. Biofilms are physically and biologically heterogeneous with a range material properties, making any mathematical treatment both challenging and engaging. This talk will describe the incremental process of extending a classical technique used to solve coupled flow problems (BIM) to incorporate the growth and material properties of the biofilm. The goal of the research is to provide insight into the mechanisms of bacterial tolerance and the development of more effective techniques for the removal of the bacteria.

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MS16

Channel Forming Instabilities in Multiphase Flow Models of True Slime Mould

The true slime mold Physarum polycephalum is a single cell organism reaching up to meters in size. The cytoplasm shows periodic shuttle streaming through a network of tubular structures reaching velocities up to 1 mm/s. When the organism is small (< 100 microns) there is no streaming. As it gets larger, flow channels develop and streaming begins. We use a multiphase fluid model and discuss instabilities that produce flow channels within the gel.

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MS16

Theory of Swimming Filaments in Viscoelastic Media

Motivated by our desire to understand the biophysical mechanisms underlying the swimming of sperm in the non-Newtonian fluids of the female mammalian reproductive tract, we examine the swimming of filaments in the nonlinear viscoelastic upper convected Maxwell model. We
obtain the swimming velocity and hydrodynamic force exerted on an infinitely long cylinder with prescribed beating pattern. We use these results to examine the swimming of a simplified sliding-filament model for a sperm flagellum. Viscoelasticity tends to decrease swimming speed, and changes in the beating patterns due to viscoelasticity can reverse swimming direction.

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MS16
Modeling Yield in a Viscoelastic Network System

Abstract not available at time of publication.

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MS17
AMPA Receptor Trafficking and its Regulation During Synaptic Plasticity

AMPA receptors mediate the majority of fast excitatory synaptic transmission in the central nervous system, and there is growing evidence to suggest that the regulation of AMPA receptor trafficking is an important expression mechanism for synaptic plasticity. There are two major mechanisms of AMPA receptor trafficking: exo/endocytic exchange of surface receptors with intracellular receptor pools, and the lateral diffusion of surface receptors between the dendrite and spines. In this talk we present a biophysical model of these trafficking mechanisms under basal conditions and during the expression of various forms of synaptic plasticity including LTP/LTD and homostatic scaling.

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MS17
A Model of the Roles of Essential Kinases in the Induction and Expression of Late Long-Term Potentiation

The induction of late long-term potentiation (L-LTP) involves complex interactions among second messenger cascades. To gain insights into these interactions, a model was developed for L-LTP induction in the CA1 region of the hippocampus. The differential equation-based model represents actions of protein kinase A (PKA), MAP kinase (MAPK), and CaM kinase II (CAMKII) and activation of transcription by CaM kinase IV (CAMKIV) and MAPK. Simulations suggest supralinear stimulus-response relationships are essential for translating brief stimuli into long-lasting gene activation and synaptic weight increases. The model predicts results of experiments on L-LTP induction and expression, and helps clarify similarities between hippocampal L-LTP and synaptic strengthening in other systems.

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MS18
Automating Modular Construction of Multiscale
Models

Success in automating automating the construction of integrated models from databases of preconstructed modules (= modular model forms) would allow the extraction of thoroughly validated modules from well-curated databases, with assurance of clear documentation by acknowledged experts. Competing modules should similarly be available. To pull selected modules into a higher level model requires common ontologies, complete equations with boundary and initial conditions, completely defined units, and running examples. This requires serious collaborative planning, at the national and international levels. Total success in very general way is unlikely. The problems start with the fact that models stored in databases such as CellML, SBML or ours at Physiome.org or others, have not adhered to a common ontology. Having multiple synonyms for variable and parameter names would help, at some risk of loss of uniqueness. Suggestions for implementing such capabilities is the topic of this discussion.

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MS18
Exploiting the Biophysical Semantics of Biosimulation Models

Currently, the merging of validated physics-based modules into multiscale (molecules to organisms) and multidomain (chemical kinetics, fluid dynamics, etc.) biosimulation models depends on manual, code-level integration methods that scale poorly to the scope of the physiome. Providing computational assistance, or outright automation of model merging must rely on: (1) computable knowledge of the biophysical properties and property dependencies that models encode as, respectively, variables and equations, and (2) a corresponding bioinformatics architecture and tool set that can merge and encode models across disparate modeling languages while resolving pervasive curatorial errors. Toward these goals, we introduce (1) the Ontology of Physics for Biology (OPB) an ontology of biophysical and systems dynamical knowledge, (2) Semantic Simulation (SemSim) models light-weight ontologies that encode the biophysical semantic content of individual models in terms of the OPB and other knowledge resources, and (3) BioSem Builder software that semantically merges SemSim models and re-encodes the merged models into a variety of biosimulation languages. We anticipate that these bioinformatics knowledge resources and tools will greatly accelerate and facilitate automatic, or semi-automatic composition of patient- and pathology-specific biosimulation models.

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MS18
Distributing and Maintaining Models in CellML

Abstract not available at time of publication.

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MS19
The Impact of Behavioral Changes on the Spread of Pandemic Influenza.

Abstract not available at time of publication.

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MS19
Sustained Oscillations via Coherence Resonance Stochastic a Pandemic

Abstract not available at time of publication.

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MS19
The Diffusion Along a Genetic Space of Strains of Influenza

Abstract not available at time of publication.

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MS19
Antiviral Intervention During Pandemic Influenza: Prophylaxis and Treatment Coverage Levels Driven by Individual and Societal Interest

Abstract not available at time of publication.

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**MS20**

**Nonlinear Effects of Signal Transduction in Olfactory Sensory Neurons**

Using stoichiometric network analysis and bifurcation theory, we identify a calcium-induced negative feedback on the ion channel level that explains experimentally observed fast adaptation and oscillations in the signal transduction of vertebrate olfactory receptor neurons (ORNs) (Reidl et al., Biophys.J. 90 (2006)). The characteristic quasi-onedimensional geometry of the cilia of the ORN leads to a description in terms of interacting sensing modules. The effect of negative feedback on the dynamics and cooperation of these modules is examined (Gopalakrishnan et al., PRE 76 (2007)).

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**MS20**

**Axonal Pathfinding and Sorting in the Olfactory System**

The axonal pathfinding in the olfactory system is an example for an extremely precise sorting behavior: all axons of an odorant receptor of certain type project onto the same site in the olfactory bulb, the glomerulus. This process is described with a mathematical model with attractive and repulsive interactions between the growing axons. Simulations reproduce the observed sorting of the axons. Under certain conditions, the convergence into a sorted state can also be shown analytically.

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**MS21**

**Analyzing Dynamic Crosstalk Among Kinase Pathways with Fuzzy Logic**

We adapted fuzzy logic to analyze a dataset characterizing the dynamic behavior of kinase pathways governing apoptosis. Use of fuzzy logic enabled balance of mechanistic detail and ease of interpretation. Simulations of our model recapitulated most features of the data and generated several predictions involving pathway crosstalk and regulation. Additionally, we have demonstrated that fuzzy logic rules can be produced with empirical data, creating potential for automated and unbiased modeling with emphasis on conceptual interpretation.

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MS21
Analysis of the Regulators of Caspase Activation by Death Receptor Ligands

To understand ligand-induced cell death decisions in human cells, we combine single-cell and population-based measurements with ODE models of relevant protein signaling networks. We seek a quantitative understanding of what controls the completeness, rapidity and timing of caspase activation. Because these descriptors of caspase dynamics are more biologically relevant than time-dependent caspase activity profiles, we used numerical methods based on finite differences to analyze their sensitivity to changes in initial protein concentration and parameter values.

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MS21
Elucidating Mechanisms in Genetic Oscillators Via Inverse Bifurcation Analysis

Given a plausible ODE model that captures the known qualitative dynamics of an oscillatory gene network, one often would like to derive insights on how the system behavior is controlled by the various gene interactions. To address such issues, we formulate inverse problems whereby bifurcation phenotypes are mapped to biochemical mechanisms. For applications ranging from redox oscillations to circadian rhythm, there is a need to elucidate the mechanisms governing limit cycles solutions and their bifurcations (including period-doubling and Neimark-Sacker). In this talk, we show the mathematical formulations for tackling such problems and demonstrate the results of inverse bifurcation analysis to a number of oscillator models.

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MS22
Parameter Estimation for Bursting Neural Models

Parameter estimation for differential equation models is a challenging problem. This talk will consider parameter estimation for an ODE model of respiratory neurons that "burst". I'll discuss an approach which uses geometric features of the differential equation to aid the estimation. In particular, we formulate a geometric definition of bursting based upon multiple time scales in the ODE, and restrict to periodic burst solutions in our parameter search. The results suggest possible ways that the neuronal output may be modulated.

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MS22
Dynamic Integration of Distributed Biological Pathway Models Using Cytosolve

One prevailing strategy to model the whole cell is a bottoms up one: first integrate smaller biological pathway models to build larger models of cellular function and then link such larger models to produce a computational model of the whole cell. The current approach to realize this strategy is a monolithic one, where the model integrator manually merges the computer source codes of smaller biological pathway models to create one large monolithic computer program containing the merged source codes. The monolithic approach is not scalable for integrating the thousands of biological pathway models necessary to model the whole cell. We present Cytosolve, a new method that dynamically integrates a distributed ensemble of biological pathway models without the need to merge the source codes of the individual biological pathway models. Cytosolve allows each biological pathway model to reside at its own location on any computer worldwide, where the authors of each model can independently maintain and update the models source code. As more biological pathway models develop in a disparate and decentralized manner, Cytosolve provides a scalable method to integrate complex models of cellular function, and eventually to model the whole cell. In this talk, we will present the Cytosolve architecture and share two working examples: (1) integrating the EGFR pathway of Kholodenko, and (2) an integrative model of the IFN response to viral infection.

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MS22
Merging Cellular Biochemical Models Using Physicochemically Rigorous Rules

Simulations of cellular systems are optimally realistic and meaningful only when appropriate physical chemical rules are adopted. Since a great deal of information is available regarding the thermodynamic and ion-binding properties of biochemical reactants, it is possible to construct simulations of biochemical systems that properly incorporate these data. Specifically, realistic simulations of biochemical systems require accounting for: (i) the complex multiple equilibria of biochemical species and dynamic buffering of ions; and (ii) the pH and ionic dependence of enzyme kinetics and apparent equilibria and thermodynamic driving
forces for biochemical reactions. Using a formal method that treats these phenomena, we can develop and validate computational models of systems of unprecedented complexity. In addition, rigorous physical chemical rules facilitate non-ambiguous model integration while reducing uncertainty in parameter estimates and improving the reliability of model predictions. As an example we will show how a model of cardiac energy metabolism that tracks more than 100 species is developed, parameterized, validated, and used to generate hypotheses and understand emergent phenomena.

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MS22  
Robust Large-Scale Individual-Based Modelling in Biology

We are interested in the complex (emergent) behaviour of large numbers (millions) of interacting entities. The interactions might take place on the same length and time scale or on a hierarchy of length and time scales. The entities may be physical objects which are constrained to obey the laws of physics, and may have complex networks embedded within them. Examples include cell signalling networks (molecule level), tissue development, wound healing, and the development of malignancy (cell level), and the behaviour of ant colonies and macro-economic behaviour in human societies (society level). Our aim is to understand behaviour and predict the effect of intervention, in order to design therapeutic interventions or influence social policy. Properly engineered and robust software tools are essential if the goal is to use the software to inform clinical and policy decisions. We are developing FLAME (Flexible Large-scale Agent Modelling Environment, http://flame.ac.uk) to provide these robust software tools. The presentation will provide an overview of our approach to modeling complex systems and the aims of the software development team, and examples of model building using the software, including links to physics models and other modeling paradigms (e.g. COPASI).

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MS24  
Numerical Treatment of the Bidomain Equations in Large Scale Simulations

In deriving the conductivity tensor of cardiac tissue, we are forced to deal with very large Finite Element matrix systems. To cope with this problem we introduce a conjugate gradient method with dual search directions that exploits the structure of the Bidomain equations. The procedure accelerates the rate of convergence, guarantees convergence to a null residual and allows us to determine the influence of high resistive barriers on the conductivity tensor.

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MS24  
Origin and Spatiotemporal Organization of Cardiac Alternans

Cardiac alternans are period-doubling oscillations of heart activity with a well-established clinical link to sudden death. This talk will discuss recent progress made to understand the cellular origin of these oscillations and their complex spatiotemporal organization at the tissue scale, using both physiologically detailed and abstract models. The results shed light on the fundamental nature of the alternans bifurcation and the complex dynamics of phase-defects underlying the formation of an arrhythmogenic substrate.

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MS24  
Purpose and Methods of a Bidomain Reaction-Diffusion Model of the Human Heart

The first mathematical heart model consisted of a single dipole source. It is still used. More recent models couple millions of elements, each represented by a detailed membrane model. We pushed this further by making a bidomain reaction-diffusion model of the human heart with over 50 million elements. In this presentation we discuss how to make such a large bidomain system converge, and what are the useful applications of this large and resource-hungry model.

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MS24  
Spatial Heterogeneity and Atrial Arrhythmias

Atrial fibrillation is the most commonly encountered cardiac arrhythmia. The atria express great heterogeneity in terms of action potential duration and morphology, which can be further amplified by neural modulation. The consequences of two aspects of this heterogeneity are explored in a computer model. The role of action potential duration gradients in establishing reentry is discussed. Second, arrhythmogenic aspects of acetylcholine release in the sinoatrial node are explored.

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MS25  
Coarse-Grained Modeling and Simulation of Lipid Bilayer Membranes

Lipid molecules consist of a hydrophilic head group and a hydrophobic tail whose competition leads to intriguing phases. These include micelles, bilayered fluidic sheets, or enclosed vesicles with rich geometric structures having features over a wide range of length-scales. A fundamental challenge in studying lipid systems is to understand how molecular level interactions lead to observed large-scale phenomena. In this talk we shall discuss a coarse-grained
modeling and simulation approach which captures many of the features of lipid bilayers. We shall then discuss hydrodynamic phenomena related to bilayer membranes. In particular, the role of thermal fluctuations and the coupling of membrane deformations and lipid flow. We will also discuss the role of fluid-like features of the membrane in the dynamic coupling of protein inclusions within a bilayer.

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MS25  
Investigating Platelet Motion Towards Vessel Walls in the Presence of Red Blood Cells

Blood is a heterogeneous medium composed primarily of red blood cells and plasma. Although platelets make up only one percent of blood by volume, they are highly concentrated near vessel walls in vivo. This phenomenon has proven difficult to quantify. We use a lattice Boltzmann-immersed boundary method to investigate how shear rate, hematocrit, red cell deformability, as well as platelet size and shape affect lateral platelet motion.

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MS25  
Cell Quakes: Microrheology in Active Gels and Living Cells

The mechanics of the in vivo cytoskeleton is controlled in part by the details of its non-equilibrium steady-state. In this ‘active’ material, molecular motors (e.g. myosin) exert transient contractile stresses on the F-actin filament network. Since microrheology traditionally relies of the linear response properties of the soft materials in thermal equilibrium, this departure from equilibrium has profound implications for the interpretation of microrheological data from the interior of living cells and in vitro active networks. In active networks, such as the in vitro systems of Mizuno et al. [Science 315 (5810) pp. 370-373 (2007)], and in living cells, the underlying theoretical foundation of the interpretation of microrheology – the Fluctuation-Dissipation theorem – does not apply. New ideas are needed. In this talk, I review microrheology, and then discuss a new theoretical interpretation of microrheology in active (i.e. molecular motor driven) networks. I also explore how molecular motor activity can reversibly control the elastic properties of these active gels. The cytoskeleton points towards the development of new biomimetic materials whose elastic properties can be tuned by controlling the material’s non-equilibrium steady-state.

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MS25  
Equilibrium Shapes of Multicomponent Vesicles

Phase separation within a multi-component membrane can lead to the formation of domains with distinct mass concentration. The physical quantities such as bending stiffness and surface tension may adjust their values correspondingly. As a result, shape transformations occur. The classical theory on the equilibrium shapes focus on the competition between the bending energy and the line energy of the phase boundaries. Surface tension, another important mechanical property at small scales, usually is neglected. In this talk, we assume surface tension depends on the local mass concentration. We present a group of nontrivial equilibrium shapes induced by the competition between surface energy and the line tension. Our results show that, without bending, this competition gives rises to phenomena of domain-induced budding for a membrane with fixed surface area and volume.

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MS26  
Rapid Spontaneous Evolution of Modularity

Biological networks have an inherent simplicity: They are modular, with a design that can be separated into units that perform almost independently. Little is known about the evolutionary origin of modularity. We suggest a possible explanation for the origin of modularity in biology. We find that evolution under ‘modularly varying environments’ can lead to the spontaneous emergence of modular systems. We further find that varying environments can dramatically speed up evolution compared to evolution under a fixed environment.

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MS26  
Critical Dynamics in a Living Cell

Cells are dynamical systems of biomolecular interactions that process information from their environment to mount diverse yet specific responses. A key property of many self-organized systems is that of criticality: a state of a system in which, on average, perturbations are neither damped nor amplified, but are propagated over long temporal or spatial scales. Criticality enables the coordination of complex macroscopic behaviors that strike an optimal balance between stability and adaptability. Using an approach based on algorithmic information theory and applying it to global gene expression data from macrophages, we found that macrophage dynamics are critical, providing the most
compelling evidence to date for this general principle of dynamics in biological systems.

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MS26
Systems-Level Regulation of Immune Responses

The immune response is a complex intertwined network of interactions. We have examined a respiratory infection model system by synthesizing a network based on existing experimental information and integrating it in dynamic models based on Boolean formulation. Our model offers novel predictions regarding cytokine regulation, key immune components and clearance of primary and secondary infections; we experimentally validate few of these predictions. The model provides insights into the virulence and pathogenesis of disease-causing microorganisms and allows system-level analysis.

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MS26
Evolution of Complexity

Abstract not available at time of publication.

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MS27
Tracking Calcium Dynamics from Voltage Measurements

Using models of calcium dynamics in postsynaptic cellular stimulations by electrophysiological protocols, we show how one can verify and then validate models of those dynamical processes. The method, Dynamical Parameter Estimation, allows single measurements on networks of neurons to follow dynamical processes and verify and validate models of those processes.

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MS27
Phenomenological Model of Synaptic Plasticity Experiments


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MS27
Matching a Decision with Response: Learning to Solve the XOR Problem

Many cognitive tasks require particular responses to specific combinations or pairings of stimuli. Such paired responses require logic equivalent to XOR and formation of neurons responsive to specific stimulus pairs. We generate such neurons from an initially randomly connected network of spiking neurons. We find spike-timing dependent plasticity tends to over-associate. However, long-term potentiation of inhibition counters over-association by generating cross-inhibition that is essential for producing specificity and enabling solution of such stimulus-pairing tasks.

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MS27
Reinforcement Learning in Populations of Spiking Neurons.

Averaging over fluctuations of many individual neurons within a population is a key mechanism for achieving robust information processing in the brain. However, in the context of reinforcement learning, single neuron performance is only loosely related to the population response, so that a global reinforcement signal based on the population response cannot reliably assess the performance of any single neuron. This results in a degradation of standard reinforcement algorithms with increasing population size. We suggest a novel, biologically realistic form of synaptic plasticity which overcomes such degradation.

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MS28
Multiscale Cancer Modeling

Based on the concept that tumors behave as complex dynamic and self-organizing biosystems, the talk will describe the development of a data-driven, agent-based multi-scale
and multi-resolution brain cancer model. This algorithm is designed to investigate how changes on the molecular level can percolate across the scales of interest, by impacting microscopic behavior as well as multi-cellular patterns. This project is part of The Center for the Development of a Virtual Tumor, CVIT.

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MS28
PreDiCT: Computational Prediction of Drug Cardiac Toxicity

Approximately 50% of the compounds developed by the pharmaceutical industry interfere with the heart (e.g., prolonging the QT-interval in the ECG). The regulatory agencies either restrict or decline the usage of these compounds for medical treatments. Products have been withdrawn from the market due to indications of cardiac toxicity. However, it is well-known that the QT-interval is not always a good metric and only little is known on the relation between drug properties and arrhythmia. We will present our multi-scale approach to predict the toxicity of drugs in the heart - ranging from the ion channel level to whole organ models. In collaboration with pharmaceutical industries we will investigate the interaction of various drug compounds on the main sodium, calcium and potassium ion channels. The modelling framework then leads to the possibility to examine the relation between the mode of action of the compounds and the arrhythmic events in the whole heart of rabbit and human.

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MS28
An Agent-Based Markovian Model for Angiogenesis

Angiogenesis is the process by which blood vessels form from an endothelial monolayer. Development of angiogenesis models is essential to understand the contribution of various factors (biochemical and biomechanical) involved in the process. Many existing models fail to account for cell-cell communication or the response of each cell to various angiogenic factors. Also, a comprehensive analysis of signaling pathways is lacking. This study aims at understanding the response of cell populations, wherein each cell is modeled by using Markov process, responding to certain global and local conditions. Thus, feedback loops (local and global) which are crucial to the biological process are an integral part of the model. The overall model is stochastic and the probabilities of transition between cell states (quiescent/migrating/dividing/dying) are based on output from the cue-signal-response model. The transition probabilities are functions of the current cell state and the cues added to the system. The direction of transition (migration/division) depends on matrix properties, which change every time step and affect the cell state in the following step. One mathematical challenge is dealing with the different timescales of intra-cellular and inter-cellular interactions. The overarching objective is to obtain a complete model of angiogenesis as it pertains to a controlled, in vitro experimental system with a reduced number of variables.

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MS28
Perturbations in Epithelial Tissue Renewal and Cancer; Modeling Clonal Expansions and Genetic Diversity in Carcinogenesis

Mathematical analysis of a general class of multistage carcinogenesis models reveals two basic phases in the age-specific cancer incidence function: a first exponential phase until the age of about 60 followed by a linear phase after that age. These two phases in the incidence curve reflect two phases in the process of carcinogenesis. Paradoxically, the early exponential phase reflects events between the formation (initiation) of premalignant clones in a tissue and the clinical detection of a malignant tumor, while the linear phase reflects events leading to initiated cells that give rise to premalignant lesions as a result of abrogated growth/differentiation control and/or perturbed tissue renewal due to damaging exposures inflicting wounding. This model is consistent with Knudson’s idea that renewal tissue, such as the colon, is converted into growing tissue before malignant transformation. The linear phase of the age-specific incidence curve represents this conversion, which can be the result of a recessive inactivation of a gatekeeper gene that maintains normal tissue architecture. Modeling Clonal Expansions and Genetic Diversity in Carcinogenesis Carlo C. Maley Carcinogenesis is a dynamic, multiscale process of clonal evolution in which genetic and epigenetic lesions (at the molecular scale) affect the expansion of clones and the accumulation of clonal diversity (at the organ scale). Most of the details of these dynamics remain unknown. For example, we do not understand how clones spread within a neoplasm or how clonal diversity changes over time as clones develop genetic instability and competition drives some clones extinct. These problems are important because suppressing clonal expansions would help to prevent cancer and we have shown that patients with more genetic diversity in their pre-malignant tumors are more likely to progress to cancer. Genetic diversity is also likely to be associated with therapeutic resistance, which is the cause of most cancer deaths. We have developed agent based models to explore the dynamics of clonal expansions and diversity in neoplasms. We are using these models to guide the development of experiments to measure these dynamics in vivo.

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MS28
Modeling Clonal Expansions and Genetic Diversity in Carcinogenesis

Carcinogenesis is a dynamic, multiscale process of clonal evolution in which genetic and epigenetic lesions (at the molecular scale) affect the expansion of clones and the accumulation of clonal diversity (at the organ scale). Most of the details of these dynamics remain unknown. For ex-
ample, we do not understand how clones spread within a neoplasm or how clonal diversity changes over time as clones develop genetic instability and competition drives some clones extinct. These problems are important because suppressing clonal expansions would help to prevent cancer and we have shown that patients with more genetic diversity in their pre-malignant tumors are more likely to progress to cancer. Genetic diversity is also likely to be associated with therapeutic resistance, which is the cause of most cancer deaths. We have developed agent based models to explore the dynamics of clonal expansions and diversity in neoplasms. We are using these models to guide the development of experiments to measure those dynamics in vivo.

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MS29  
Quiescent Phases and Their Impact on Predator-Prey Dynamics  
Abstract not available at time of publication.

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MS29  
Optimal Control of Lipid Production is Green Algae  
Abstract not available at time of publication.

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MS29  
The Potential Impact of Disease on the Migratory Structure of a Partially Migratory Bird Population  
Abstract not available at time of publication.

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MS29  
Saturation in Predation and Predation-Transmitted Infections  
Abstract not available at time of publication.

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MS30  
Tagged Magnetic Resonance Imaging for Evaluating Regional Cardiac Function: Data Acquisition and Processing Approaches  
Cardiac dysfunction or impaired relaxation/contraction of myocardium is associated with a variety of cardiovascular condition that leads to heart failure. Tagged magnetic resonance imaging (tMRI) is a cardiac imaging modality developed to assess region myocardial motion within the LV wall. This presentation summarizes the principle of tMRI, some of the sensitive motion estimators, including harmonic phase interference, and simple time-reversal model of left ventricle wall motion used for evaluating the cardiac performance using tMRI data.

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MS30  
Inversion Techniques for Magnetic Resonance Elastography  
MR elastography can quantitatively and non-invasively measure full vector displacements from propagating acoustic waves in vivo. From these data, inversion algorithms can calculate biomechanical tissue properties such as stiffness, viscosity, and anisotropy. An overview of inversion techniques proposed for this data and their relative strengths and weaknesses will be presented. Preliminary studies indicate that the technique has substantial potential as a diagnostic tool.

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MS30  
Reconstructing Tissue Elasticity Using a Lumped Parameter Model  
Lumped parameter system identification can be used to recover accurate mechanical properties of an anomaly in soft tissues such as a cancerous region in the brain or breast. The LPSID method competes with, and offers trade-offs to the current technology used in elastography where these primary advantages are 1) computational efficiency through exact linear solutions, and 2) the recovery of first and second derivative mechanical properties, namely damping and mass.

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MS30  
Detectability in Magnetic Resonance Elastography  
MR elastography may detect early stage small cancerous tissue, which is believed to be of 3.5 mm diameter. The detection of this small inclusion is challenging, because the inclusion is small relative to the typical wavelength (10-30 mm) of a low frequency excitation. This talk provides a theoretical bound of the smallest possible size of the detectable inclusion as a function of noise level, contrast ratio of the stiffness, and the excitation frequency.

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MS31
Optimal Flexibility in Flapping Appendages

When oscillated in a fluid, appendages such as insect wings and fish fins can produce large thrust forces while undergoing considerable bending. Can we determine the flexibility which produces maximum thrust and efficiency? We solve a general model for how flexible surfaces produce vorticity and bend passively in a fluid. We find a series of local thrust optima which are resonant peaks, and can be predicted with a scaling analysis. We discuss extensions to large-amplitude motions, and motions of actual fish fins.

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MS31
Simulating Cardiac Fluid-Structure Interaction by the Immersed Boundary Method

The immersed boundary (IB) method is a framework for modeling and simulating problems in which a viscous incompressible fluid interacts with an immersed elastic boundary. I shall describe an adaptive IB method that employs Cartesian grid adaptive mesh refinement (AMR) and present results from the application of this methodology to a model of the human aortic valve as well as a new medical imaging-derived model of the heart and nearby great vessels.

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MS31
Grow with the Flow: A Dynamic Tale of Blood Clot Formation

The body heals injured blood vessels and prevents bleeding by clotting the blood. Clots are primarily made of blood-borne cells and a fibrous material that is assembled at the site of injury in flowing blood. Clot composition and structure change with local chemistry and fluid dynamics, which in turn alters the flow. To better understand this fluid-structure coupling, we model the growing clot as a mixed porous material immersed in a dynamic fluid environment.

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MS31
The Lower Reynolds Number Limit of Flapping Flight

In this talk, the aerodynamic challenges of tiny insect flight and the possible morphological and kinematic adaptations insects use to increase lift forces will be discussed. Aerodynamic forces were studied over a range of Reynolds numbers using the immersed boundary method to numerically solve the two-dimensional Navier-Stokes equations with moving, flexible boundaries. For the smallest insects, flapping flight becomes less efficient as relative lift forces decrease and relative drag forces increase with decreasing Reynolds number.

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MS32
Mathematical Analysis of Error Regulation in Biological Systems

We develop a quantiative, stochastic thermodynamic analysis for the error rate of the DNA replication process inside a living cell. The analysis suggests that a flux-driven mechanism for the high fidelity according to the theory of “kinetic checkpoints”. It shows how it is coupled to energy input from the cell. Though we focus primarily on DNA replication, the model and mechanism are applicable to other biochemical processes.

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MS32
Specificity of Cell Signalling

Different cellular signal transduction pathways are often interconnected, so that the potential for undesirable crosstalk between pathways exists. Nevertheless, signaling networks have evolved that maintain specificity from signal to cellular response. In this talk, I will introduce a new framework on specificity for the analysis of networks containing two or more interconnected signaling pathways. Using this framework, along with existing and new experimental data, I shall study the mating pathway in yeast.

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MS32
Some Defining Quantities in Stochastic Gene Tran-
To examine how the environmental signals contribute to the regulation and noise of gene transcription, I will present a three states stochastic model. The transition between these states is characterized by several defining quantities, which decompose the stochastic nature of transcription activation into environmental signals, specific binding of transcription factors with promoter DNA, and the gene promoter stability. Some mathematical results and questions, along with their biological implications and challenges, will be discussed.

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MS32  
Robust Cell Polarization

Cells polarize components to specific locations leading to morphological changes in response to internal and external cues. Often, the external cue is a spatial chemical gradient. Sensing and responding to a chemical gradient present many challenges including sensitivity, dynamic range, tracking, and noise. In this talk, I will describe how we investigated in a systematic fashion the tradeoffs among these performance objectives.

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MS33  
Oscillations in Biochemical Reaction Networks

An important problem in cell biology is to predict the dynamics of interactions in biochemical reaction networks. If available, realistic mathematical models of oscillatory biochemical reactions are large systems of differential equations with many unknown parameters, making their analysis difficult. Subnetworks of cycles in a bipartite graph associated with a biochemical reaction are used to predict oscillations. Generalized network conditions for the two types of oscillations associated with negative and positive cycle will be presented.

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MS33  
Modeling Electrocortical Activity Through Integral Neural Field Equations

In many regions of mammalian neocortex, synaptic connectivity patterns follow a laminar arrangement. Recently there has been a growing interest in such models with delayed due to the speed of action potentials, and new progress has been made in one spatial dimension. In this study, we address the physiological importance of a model in two spatial dimensions with axonal delays, and obtain an equivalent PDE model used in several EEG modeling studies.

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Oscillations in NF-kappa B Signalling Pathways

NF\(\kappa\)B oscillations were suggested by Hoffmann et.al from electro-mobility shift assays (EMSA) in population studies of I\(\kappa\)B\(-/-\) embryonic fibroblasts and simulated in a computational model. A common comment on the source of oscillations is the existence of negative feedback loops. However, this is not a sufficient condition. In this paper, we explore the source of oscillations by analyzing the dynamical properties of the computational model. We find that the computational model can be treated as a fast-slow system where the level of total I\(\kappa\)B Kinase (IKK) in the model is treated as a slow variable. Assume the level of total IKK does not change at all. We can view the level of total IKK as a parameter. Orbits in the true system trace attractors in this reduced model. We find that for a some range of the level of NF\(\kappa\)B, the reduced system experiences Hopf bifurcation twice while varying the level of total IKK. The damped oscillations come from the existence of a stable limit cycle or a stable spiral in the reduced system.

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A Coupled Hypercolumn Model Approach to Contour Grouping in the Visual Cortex

We use a coupled hypercolumn model to study how the primary visual cortex may accomplish the task of grouping a contour presented in visual space. An initial blip of attentional firing rate elevation spreads along neurons that contain the contour in their receptive field. Long range horizontal connections between hypercolumns are taken to be modulatory and orientation specific. Under this assumption, we can expand solutions to the coupled hypercolumn model in a small parameter representing the ratio of long range to local connection strength. Using perturbation theory we can solve for small order corrections to the homogeneous case.

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Dynamical Evolution of Spatiotemporal Patterns in Mammalian Middle Cortex

The spatiotemporal structure of brain oscillations are important in understanding neural function. We analyze oscillatory episodes from isotropic preparations from mammalian cortex which display irregular and chaotic spatiotemporal wave activity, within which spontaneously emerge spiral and plane waves. The evolution of these patterns are likely related to activity dependent ion concentration changes. The use of a principal orthogonal decomposition and Galerkin projection to show the modal interactions which underlie such persistent activity will be discussed.

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Waves and Synchrony in the Pinto-Ermentrout Model with Asymmetric Coupling

We investigate the Pinto-Ermentrout integro-differential equation model in the presence of asymmetric coupling. There is a parameter beta that appears in the equation, and we focus on values of beta for which the linearization around the rest state has complex eigenvalues. In this regime we study single pulse and multiple pulse waves, as well as the formation of synchronous oscillations which spread out spatially from a point of stimulus.

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Cortical Wave Dynamics Observed by Voltage-Sensitive Dye Imaging

I will start with showing cortical wave dynamics in rat brain slices and in vivo. Then I will discuss a new method we developed for characterizing spatiotemporal complexity of waves. We analyze angular distribution of spectral energy in the wave patterns, and quantify their complexity by the number of propagation modes of the waves. Compared to empirical orthogonal function (EOF) method, our method is more accurate when dealing with nonstationary waves.

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Quantitative Analysis of Gut Motion in an Animal Model using Dynamic MRI and 3-D Live-wire Image Segmentation

Conventional methods of quantifying segmental and peristaltic motion in animal models are highly invasive, involving the isolation of segments of small intestine either from dead or anesthetized animals. The present study was undertaken to non-invasively analyze these motions in the jejunum region of anesthetized rats using dynamic contrast enhanced magnetic resonance imaging (MRI), and quantify these motions using spatiotemporal maps. Dynamic images (1000 images at 6 frames per second) of the GE tract were acquired in vivo using a gradient echo imaging sequence. A semi-automated 2D spatial + time image segmentation algorithm based on 3D live wire and gradient vector flow analysis was implemented to accurately segment the dynamically acquired images. A 2D thinning algorithm was applied to the segmented images to compute the medial axis, which was used to compute the spatiotemporal map of the acquired image sequence. The spatiotemporal map, which is plot of the diameter of the gut along the length of the gut with respect to time, is a widely-used and a compact representation of the complex gut motion. The frequency (0.29 ± 0.05 Hz) and period of segmental contraction (3.14 ± 0.14 s) and average distance between segmental constrictions (4.56 ± 1.21 mm) were very similar in the jejunum region among different rats, showing little inter-animal variability. The frequency (0.46 ± 0.01 Hz) and period of peristaltic waves (2.18 ± 0.05 s) correlated well with the frequency (0.5 Hz) and period (2 s) of slow waves which have been described in previous literature, leading to the conclusion that in vivo short distance peristaltic type contractions are the result of slow waves generated by interstitial cells of Cajal. The speed of propagation of peristaltic wave (4.34 ± 1.03 mm/s) was found to be reduced under in-vivo conditions compared to in-vitro speeds. These represent the first quantitative in vivo results of the small intestine using non-invasive dynamic MRI approach. In this approach the segments of the GI tract are not isolated or exteriorized but are in true physiological conditions.

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High-throughput Imaging using Knife-Edge Scanning Microscope and Array Tomography, and Fast Algorithms for Multiscale Image Analysis and Reconstruction

Recent advances in serial-sectioning microscopy have enabled high-throughput imaging of massive volumes of biological microstructure at a very high resolution. One example is the Knife-Edge Scanning Microscope (KESM) we developed at Texas A&M, which is one of the few that combines serial sectioning and imaging in an integrated process. The KESM is capable of imaging biological tissue (about 1 cm3) at 300 nm x 300 nm x 500 nm resolution within 100 hours, generating data at a rate of 180 MB/s. The resulting data per organ (e.g., a mouse brain) can easily exceed tens of terabytes. Another example is a complementary microscopy method, Array Tomography, developed by our team at Stanford. Array Tomography allows the imaging of molecularly labeled objects in the brain tissue using fluorescent microscopy, and registered high-resolution imaging with scanning electron microscopy, enabling an accurate mapping across nano- to micro scale. Due to the massive amounts of data at multiple scales, morphological reconstruction algorithms that are fast, resource efficient, and accurate become necessary. We will present our latest results in large-scale microscopic neuronal circuit data acquisition in the mouse brain using KESM and Array Tomography, and discuss the fast algorithms we developed for tracing and analyzing neuronal morphology.

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Model-based Assessment of the Lung by Imaging

There has been a growing need for sensitive and objective measures of regional lung status both for detection of disease and for outcomes analysis. X-ray CT remains the imaging modality of choice for comprehensively evaluating the lung. Significant advances are being made in both temporal and spatial resolution. Scan apertures are at sub-cardiac cycle time frames, allowing for the imaging of not only anatomy but also ventilation and perfusion, providing structure-to-function correlations. We have brought together a multi-disciplinary team of investigators to develop a model/atlas of the normal human lung based upon these new measures. This atlas includes the lungs, lobes sublobar segments and airway and vascular branching structures of the lung and attached to each level of this structure will be the normal range of the CT-based measures of regional lung physiology including ventilation, perfusion, etc. This model/atlas of the normal human lung provides the comparative basis for detecting and quantitating pulmonary pathology. Imaging is serving an important role in the phenotyping of diseases such as Asthma, COPD in general, as well as other interstitial lung pathologies. As we are identifying specific differences amongst these patient populations, there is a growing interest to determine if computational fluid dynamics can provide insights into particular distribution patterns of pathology. In this talk we will discuss the growing interplay between CFD studies and the phenotyping of lung disease.

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Image-Based Patient-Specific Multi-Scale Modeling of the Failing Heart

The most significant recent advance in management of heart failure (HF) with a conduction block has come from CRT and defibrillator therapy. However, up to 30% of currently eligible patients fail to respond to CRT. Notably, exact estimation of the percentage of non-responders, or of factors predicting non-response, are difficult because of different criteria used to define ‘response’. Although these factors make it difficult to select optimally select patients for CRT, this remains of paramount importance to reduce unnecessary implants, procedural risks and healthcare expenses. We propose to develop new computational tools for optimally selecting patients for CRT, then for optimizing CRT to each individual patient. Having acquired...
IRB approval, two to five patients with NYHA Class III or IV will be recruited at the San Diego VA Medical Center. Implementing the strategy outlined above, we will develop patient-specific computational models of the human heart from detailed mapping, and test their ability to predict observed short-term functional improvements after CRT. The clinical procedures that we will perform include: cardiac contrast CT to obtain ventricular geometry; electroanatomic mapping of both ventricles to obtain ventricular activation patterns during native (dysynchronous) ventricular activation and during CRT; cardiac ultrasound to obtain dynamic ventricular (pseudo-) volumes and invasive dynamic pressure measurements during cardiac catheterization. Pressure-volume loops will be obtained during maneuvers to alter preload and afterload. Three and six months follow ups will be performed to assess long-term outcomes, to determine the predictive accuracy of our models, and also to provide an opportunity for the patient-specific models to optimize CRT in a patient-tailored fashion.

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MS36
Alcohol Drinking Dynamics in Distinct Risk Environments: Application to College Drinking
Abstract not available at time of publication.
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MS36
Modeling B Cell Dysfunction in HIV Infection
Abstract not available at time of publication.
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MS36
Nosocomial Infections: The Basic Reproduction Number Joke!
Abstract not available at time of publication.
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MS36
A Mathematical Model of Solid Tumor Regrowth
Abstract not available at time of publication.
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MS37
Multi-Scale Modeling of Spatiotemporal Dynamics of the Primary Visual Cortex
We discuss our large-scale (1 million neurons) computational modeling of the primary visual cortex (V1). In particular, we describe network mechanisms underlying stochastic, spatiotemporal dynamics associated with spontaneous on-going activity of the V1 and the line-motion illusion — which is the illusory motion sensation from a static cue of a flashed stationary square quickly followed by a stationary bar. Furthermore, we use a new analysis of coarse-grained event-chains to demonstrate the fine discriminability of orientation of V1.

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MS37
Optical Imaging of Tissue Culture Models of Cardiac Arrhythmias
Cardiac arrhythmias are associated with the abnormal initiation and/or abnormal propagation of the heart rhythm. By carrying out optical imaging of tissue cultures of spontaneously beating heart cells, it is possible to analyze macroscopic patterns of excitation with a goal of relating this to the cellular and subcellular electrophysiological properties of heart cells. In particular we have been able to observe transitions between rhythms in vitro, that model the normal and pathological rhythms in vivo. Optical imaging of tissue culture offers the benefit of providing a controlled environment that can be observed over long times, in which it is possible to systematically modify the geometry of the culture, the density of the culture, as well as change the physiology by the addition of pharmacological agents. The experimental work is complemented by theoretical studies of bifurcations and dynamics in mathematical models of excitable, heterogeneous systems. This work points to universal patterns of bifurcations underlying cardiac arrhythmias in humans.

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MS37
Multiscale Imaging Reveals Robustness and Capacities of the Human Respiratory System
System engineered organ representations based on multi-scale imaging provide insight into the evolutionary shaped design of the transport networks in terms of modularity, physical optimality and robustness. We have assembled a consortium of investigators to image, model and simulate functional properties of the human respiratory system. MDCT data of nine human lungs and a highly resolved cast, as well as micro-CT and light microscopic imaging was used to investigate dimensions and heterogeneities in geometric branching patterns, gas supply and diffusion capacities. We show that the dimensions of airways in these cases change systematically from area-preserving to area-increasing, thus they reflect multifractal properties. Airways are generally larger than predicted by the Hess-Murray law, providing up to four-fold less resistance as well as increase in robustness against perturbations. We show that resistance in the network topology of airways mediates a mismatch between anatomically demanded and
predicted oxygen supply, which offers an explanation for the excess diffusion capacity of human lungs. Robustness and capacities are important cornerstones for the development of solutions to improve diagnostics and intervention planning in aging and disease.

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MS37
Mapping and Modeling Receptor Topography During Signal Transduction

The ErbB family of growth factor receptors are widely expressed by cells of epithelial and mesenchymal lineages. EGFR and ErbB2 overexpression can lead to ligand-independent signaling and is linked to carcinogenesis. We use a combination of high resolution microscopy approaches to quantitatively evaluate the topography and behavior of resting and actively signaling ErbB receptors. Immunoelectron microscopy methods capture nanoscale spatial relationships between receptors and their intracellular signaling partners. Live cell imaging approaches, including single particle tracking of quantum dot probes, monitor differential properties of receptor monomers and dimers and provide evidence for cytoskeletal corrals. These data provide the foundation for our agent-based modeling efforts. Our stochastic modeling framework incorporates important spatio-temporal aspects of signaling, including protein clustering, protein motion and biochemical reactions within an idealized cellular geometry. We investigate mechanisms of receptor dimerization and activation as functions of time and receptor conformation, density and spatial distribution. For example, we have considered the effects of receptor clustering patterns of ErbB family members on both hetero- and homo-dimerization rates, using immunoelectron microscopy data. Simulation results suggest that partial spatial segregation of ErbB receptors has a profound impact on heterodimerization rates. We propose that membrane spatial organization is a significant contributor to the carcinogenesis process.

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MS38
Mathematical Models and Reconstruction Algorithms in Magneto-Acoustic Imaging

An acoustic wave can excite a local area of tissue placed in a magnetic field and induce an electrical current. Then Lorenz force causes a local current density. Some imaging modalities, such as the vibration potential imaging and the magneto-acoustic tomography with magnetic in- duction, are based on this physical phenomena. In this work, we provide the mathematical basis for these different magneto-acoustic imaging approaches and propose new algorithms for solving the inverse problem for these approaches. This is a joint work with Y. Capdeboscq, H. Kang, and A. Kozhemyak.

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MS38
A Method of Biological Tissues Elasticity Reconstruction Using Magnetic Resonance Elastography Measurements

Magnetic resonance elastography (MRE) is an approach to measuring material properties using external vibration in which the internal displacement measurements are made with magnetic resonance. A variety of simple methods have been designed to recover mechanical properties by inverting the displacement data. Currently, the remaining problems with all of these methods are that in general the homogeneous Helmholtz equation is used and therefore it fails at interfaces between tissues of different properties. The purpose of this work is to propose a new method for reconstructing both the location, the shape and the shear modulus of a small anomaly with Lamé parameters different from the background ones using internal displacement measurements. This is a joint with H. Ammari, P. Garapon, and H. Lee.

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MS38
SWIFT (SWeep Imaging with Fourier Transform), A New Paradigm for Near Simultaneous Transmit and Receive MR Imaging

SWIFT utilizes RF encoding sampled prior to completion of the RF pulse. Current hardware limits the switching between transmit and receive to the order of 10 micro seconds. The data handling is inherently different than conventional NMR, since the acquired data is the distribution of isochromats convolved with the RF pulse shape. The deconvolution is well behaved and the techniques have been found to offer increased detection of very short (T2) species, e.g. teeth, plastics and bone. Additionally the simultaneous acquisition of excited spins is beneficial for relaxing the B0 homogeneity demands. Theoretical and experimental data will be discussed.

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MS38
Conductivity Imaging from the Magnitude of One Current Density Field

This talk concerns the problem of Electrical Impedance Tomography when interior knowledge of the magnitude of the current density field is available. The current density field is generated by maintaining a given potential on the boundary and its magnitude can be determined from Magnetic Resonance measurements. Two non-material properties are related via a problem in the (non-smooth) calculus...
of variation. The mathematical tools used in the proofs range from harmonic measure theory to algebraic topology. This work is jointly with A. Nachman and A. Timonov.

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MS39
Modeling Multistrain Interactions: Cross Immunity and Antibody Dependent Enhancement

We investigate the dynamics of a model for multistrain diseases with strain interaction mediated by temporary cross immunity and antibody dependent enhancement (ADE). ADE increases the infectivity of secondary infections. While ADE alone is known to trigger chaotic outbreaks and desynchronization of the strains, we find that when both ADE and cross immunity are included, stabilization occurs for weak cross immunity. Large cross immunity leads to large amplitude chaotic outbreaks.

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MS39
Vaccinations in Disease Models with Antibody-Dependent Enhancement

As we increase our resources to fight disease, pathogens become more resilient in their means to survive. One example is antibody-dependent enhancement (ADE), a phenomenon in which viral replication is increased rather than decreased by immune sera. We study the complex dynamics induced by ADE in multi-strain disease models and investigate the effects of vaccine campaigns. In particular, we study the consequences of using single-strain vaccines, which would increase the virulence in other infections.

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MS40
Integration of Mitochondrial and Cellular Metabolism with Tissue-Level Substrate Transport to Explain Emergent Phenomena on Phosphate Metabolite Concentrations and ATP Hydrolysis Potential in the Heart

To understand how cardiac ATP and CrP remain stable with changes in work rate a phenomenon that has eluded mechanistic explanation for decades data from 31P-magnetic resonance spectroscopy (31P-MRS) are analyzed to estimate cytoplasmic and mitochondrial phosphate metabolite concentrations in the normal state, during hypoperfusion, and during acute ischemia and reactive hyperemic recovery. Analysis is based on simulating distributed heterogeneous oxygen transport in the myocardium integrated with a detailed model of cardiac energy metabolism. It is determined that baseline inorganic phosphate (Pi) concentration in the canine myocyte cytoplasm variable not accessible to direct noninvasive measurement is approximately 0.29 mM and increases to 2.3 mM near maximal cardiac work states. This variable is shown to be crucial in controlling oxidative metabolism in vivo. During acute ischemia (from ligation of the left anterior descending artery) Pi increases to approximately 2.8 mM and ATP consumption in the ischemic tissue is reduced to less than half its baseline value before the creatine phosphate (CrP) pool is 16% depleted. It is determined from these experiments that the maximal work rate of the heart is an emergent property and is limited not simply by the maximal rate of ATP synthesis, but by the maximal rate at which ATP can be synthesized at a potential at which it can be utilized.

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MS40
Multi-Cell Modeling of Biological Development Using the GGH Model and CompuCell3D Applications, Technology and Open Problems

While bioinformatics tools for the analysis of DNA sequences, reaction kinetics models of biomolecular networks and molecular dynamics simulations of biomolecules, are all widely used, multi-cell modeling of developmental processes at the tissue scale is still relatively undeveloped. One of the key reasons for this neglect has been the lack of widely-accepted modeling approaches and the computational difficulty of building such models. Now, a growing community of modelers has settled on the GGH Model, a modeling approach that derives from the familiar Potts model of statistical mechanics, as a convenient methodology to create sophisticated multi-cell simulations of tissue development, creating a de facto common modeling approach. The GGHs use of an Effective Energy and constraints to describe cell behaviors simplifies integration of multiple biological mechanisms, while the availability of open-source tools like CompuCell3D for building GGH models makes developing, validating and sharing such simulations much easier for non-specialists. I will introduce the GGH and the modeling environment CompuCell3D (http://www.compucell3d.org/), then apply the GGH to modeling somitogenesis in vitro (see pictures), illustrating some of the questions this type of modeling can address (e.g. error correction mechanisms in development) and discussing its application to other developmental-biology problems including tumor growth, gastrulation, and biofilms. I will also discuss some of the key mathematical and computational issues which GGH models and modeling environments still need to address.

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MS40
From Endothelial Signaling to Tissue Growth in Cerebral Aneurysms

Cerebral aneurysms are a result of growth and adaptation of the arterial wall tissue to a change in fluid shear stress at the surface of endothelial cells in cerebral arteries. In a contribution to the European FP6 aneurISt project (www.cilab.upf.edu/aneurist1/) we are modelling the signal transduction pathways that link changes in shear stress to collagen turnover and smooth muscle activity. Mixture theory is used to couple the changes in tissue composition, that result from these signalling pathways, to a fibre distribution constitutive law model which, in turn, is used in the large deformation mechanics finite element solution of wall stress.

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MS40
A Multi-Scale Approach Towards Understanding Antigen Presentation in the Immune Response to Mycobacterium Tuberculosis

The immune system and the process of antigen presentation in particular encompass events that occur at multiple length and time scales. Despite a wealth of information in the biological literature regarding each of these scales, no single representation synthesizing this information into a model of the overall immune response as it depends on antigen presentation is available. In this talk, I outline an approach for integrating information over relevant biological and temporal scales to generate such a representation for MHC class II-mediated antigen presentation. In addition, I begin to address how such models can be used to answer questions about mechanisms of infection and new strategies for treatment and vaccines.

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MS40
Modeling Multicellularity: from Cell Rheology to Gastrulation

I will present an overview of recent work focused on constructing computer models of developmental systems. In particular, we have devised an off-lattice algorithm, called the Subcellular Element Model, which is able to simulate large numbers (thousands) of deformable cells in three dimensions. I will describe the inner workings of the algorithm, and indicate that the method is capable of modeling developmental systems over a wide range of scales - capturing cell visco-elasticity at small scales, and long-ranged coordinated cell movement at large scales. Modeling of primitive streak extension in the chick embryo will be discussed as a concrete application.

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MS40
MAPK Signaling in Equations and Embryos

Exploring the robustness and evolvability of developmental signaling mechanisms is essentially impossible without computational modeling approaches. Successful models should integrate large amounts of data, test the feasibility of proposed modes of regulation, and lead to the formulation of new mechanisms. I will describe how we are combining imaging, modeling, and molecular genetics techniques in order to develop and experimentally test multiscale models of the Mitogen Activated Protein Kinase (MAPK) signaling pathway, a key regulator of development across species. We are using the terminal patterning system in the early Drosophila embryo as the main experimental model for studying the MAPK-mediated pattern formation. Our imaging results provide the first quantitative measurements of the gradient of MAPK signaling in the early Drosophila embryo and lead to the model where
this gradient is controlled by a cascade of diffusion-trapping systems. We tested this model in a combination of modeling, imaging, and genetic experiments. We are also exploring how the gradient of MAPK signaling is interpreted by giving rise to the gradients of biochemical modifications and subcellular locations of its biochemical targets. Our preliminary data suggest that a substrate competition mechanism coordinates the actions of the anterior and terminal patterning systems in the early embryo. I will present the results of genetic and computational tests of this mechanism.

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MS41
Modules and Roles: Towards a Cartography of Complex Biological Networks

In complex systems, individual components interact with each other giving rise to complex networks, which are neither totally regular or totally random. Because of the interplay between network topology and dynamics, it is crucial to characterize the structure of complex networks. Most real world networks display a marked modular structure, which means that, rather than being homogeneous in their connectivity, nodes tend to establish many more connections with a subset of the nodes in the network than with the remaining nodes. In my talk, I will discuss recent theoretical and computational developments that enable one to uncover the modular structure of complex networks. I will also discuss how, after identifying network modules, one can classify nodes into roles according to their pattern of intra- and inter-module connections. Finally, I will show that understanding the modular structure of biochemical networks sheds light onto their evolution, and has potential applications for the identification of drug targets.

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MS41
The Effect of Spatially and Temporally Correlated Input on Network Behavior

Recent work shows that spike-to-spike correlations amongst neurons receiving shared inputs increase as a function of the neurons’ firing rates. Thus, if different stimuli evoke different rates, they may also be expected to evoke different levels of correlation: in this sense, rate and correlation are co-tuned. I will explore the consequences of this co-tuning for the information that populations of neurons carry about the stimuli. First, the impact of correlation tuning on the Fisher information in the case of a single layer of cells will be considered. Previous work on the subject took into account changes in covariance, but not correlation. The results of an experimental study that illustrates how a single cell can read out information encoded using correlation tuning will be shown

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MS41
Reliability of Layered Neural Oscillator Networks

This talk concerns the reliability of large networks of neural oscillators in response to fluctuating stimuli. Reliability means that repeated presentations of a stimulus elicit essentially identical responses regardless of the system’s state at the onset of the stimulus; the degree to which a system is reliable impacts the precision of neural codes based on temporal patterns of spikes. Under what conditions is a network reliable? I will present recent work addressing this question for certain idealized neuronal networks with layers. The problem is studied on two scales: neuronal reliability, which concerns the repeatability of spike times of individual neurons embedded within a network, and pooled-response reliability, which concerns the repeatability of the total synaptic output from the network. It will be shown that individual embedded neurons can be reliable or unreliable depending on network conditions, whereas pooled responses of sufficiently large networks are mostly reliable. I will also discuss the effects of noise; our main finding here is that some types of noise affect reliability more seriously than others.

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MS41
Optimization of Metabolic Networks

Cellular metabolism occupies a central role in the processes that form the basis of life. Yet, the whole-cell behavior of the metabolic system remains widely unexplored because large-scale studies require establishing a mathematical and computational approach that goes beyond traditional biological research. Using a network-based approach, in this talk I will discuss intriguing recent results about the functional behavior of the metabolic system that follow from the interplay between network structure and network dynamics.

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MS42
The Role of Feedback in the Formation of Mor-
We consider a gene regulatory network that utilizes auto-activation and cross-inhibition to establish and maintain stable boundaries of gene expression. We find that in the presence of a general activator, neither auto-activation, nor cross-inhibition alone are sufficient to maintain stable sharp boundaries of morphogen production. The minimal requirements for a self-organizing system are a coupled system of two morphogens in which the auto-activation and cross-inhibition have Hill coefficients strictly greater than one.

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MS42
Germline Stem Cell Competition

In the ovarian niche of drosophila, there are two to three germline stem cells. They compete each other for occupancy. The experiment data show cadherin serve as a signal molecule to play an important role in this process. We use mathematical model to study the competition within the niche and the maintenance of the niche.

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MS42
Genetic Instability and Cancer Growth

Carcinogenesis (cancer generation) relies on a sequence of mutations that transforms cells, leading to their unchecked growth. An important phenomenon in cancer is genetic instability, or an increased rate of mutations. We investigate an optimal control model of carcinogenesis which includes cell division, death and mutations, and ask the following question: what (time dependent) mutation rate leads to most rapid cancer growth? We obtain the optimal mutation rate for the fastest time to cancer for different relations between mutation rate and the death rate of cells.

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MS42
Application of Discontinuous Galerkin Methods for Reaction-Diffusion Systems in Developmental Biology

Reaction-diffusion systems in modeling of regulatory network and tissue growth in developmental biology are usually highly stiff. They are typically considered on complex domains. We overcome computational challenges by combining discontinuous Galerkin methods with Strang operator splitting, on triangular meshes. Numerical solutions of the Schnakenberg model, and a system of skeletal pattern formation, are presented to demonstrate effects of domain geometries on the resulting patterns. (joint work with Jian-feng Zhu, Stuart Newman, Mark Alber.)

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MS43
Stimulus Competition Via Transition From Synchrony to Asynchrony

In networks of excitatory and inhibitory neurons, one can often find a parameter regime of synchronous, oscillatory activity immediately adjacent to a regime in which the inhibitory cells are active asynchronously, and the excitatory cells are suppressed altogether. We describe how to compute the boundary between the two regimes, which we call the suppression boundary, and show computations illustrating the often abrupt transition from one regime to the other. We also show computational simulations suggesting that experimentally observed phenomena concerning competition among visual stimuli and the attentional biasing of this competition may arise from toggling between the two regimes.

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MS43
Applications of Kinetic Theory to Neuronal Network Dynamics

Using kinetic theory is a common coarse-graining technique for integrate-and-fire neuronal networks. After reviewing the basics of this theory, this talk will concentrate on the kinetic theory for networks with fast and slow conductances driven by the same spike trains, and the Fokker-Planck limit of the kinetic equations. In the former, correlations due to the two types of conductances sharing some of the same input spikes will be discussed. In the latter, neuronal gain curves will be presented, and the limit of small fluctuations will be described.

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MS43
Coding in Neuronal Networks, Event-Chains, and Functional Connectivity

Networks of neurons respond to different stimuli in different ways, namely, distinct inputs generate reproducibly distinct activity profiles within the network. The talk will discuss certain coding properties of these systems, and illustrate these properties with numerical examples.

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MS44
Computational Methods for Understanding Flow Kinematics in Blood Vessels

Transport mechanisms, such as recirculation and stagnation, are thought to play important roles in disease progression and clot formation in blood vessels; however these mechanisms are not well understood. This is in part due to the challenging nature of characterizing unsteady fluid transport. We utilize the computation of Lagrangian coherent structures to better understand transport mechanisms occurring in realistic vascular flow models and discuss possible biological significance of these results.

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MS44
Multiscale Simulation for Bioimaging Informatics of Cells

Multiscale simulation is emerging as a new scientific field. The idea of multiscale modeling is straightforward: one computes information at a smaller (finer) scale and passes it to a model at a larger (coarser) scale by leaving out degrees of freedom as one moves from finer to coarser scales. The obvious goal of multiscale modeling is to predict macroscopic behavior from first principles (bottom-up approach). However, the emerging fields of biotechnology impose new challenges and opportunities. For example, the ability to predict and control phenomena with resolution approaching molecular scale while manipulating macroscopic scale variables can only be realized via multiscale simulation (top-down approach). In this talk, recent developments on coarse-grained Monte Carlo simulations will be discussed. Examples will be presented from the epidermal growth factor receptor (EGFR) spatiotemporal dynamics on the surface of plasma membranes of mammalian cells. The focus will be on diffusion (short times) and reaction (long times) leading to spatial self-organization of EGFR, whose signaling dysregulation is implicated in a number of cancers. Our work demonstrates that plasma membrane heterogeneity is central to signal transduction, especially for cancerous cells, and provides a means to bridge the length and time scale gap between various experimental techniques.

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MS44
A Multiscale Model of Thrombus Development

A multiscale model for studying formation of thrombus in
a blood vessel will be presented. This computational model involves components for modeling viscous, incompressible blood plasma; non-activated and activated platelets; blood cells; activating chemicals; fibrinogen; the vessel walls and their interactions. The macro scale dynamics of the blood flow is described by the continuum Navier-Stokes equations. The micro scale interactions between activated platelets, platelets and fibrin(ogen) and platelets and the vessel wall are described through a stochastic discrete Cellular Potts Model (CPM). Newly developed computational methods will be described for overcoming the difficulties posed by the coupling of events occurring at distinct spatial and temporal scales; by the non-linearity of the coupled governing equations; and by the geometry of the blood vessel. Simulation results predicted the development of an inhomogeneous internal structure of the thrombus and vortex blood flow behind the thrombus which were confirmed by the preliminary experimental data.

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MS45
Sound and Light Show Structure: Mathematics of Thermoacoustic Tomography II

Photoacoustic and thermoacoustic tomography are developing imaging technologies for biology and medicine. Via the thermoelastic effect, an imposed radiation field generates a pressure wave in the interior of a body which is then measured in the exterior. Associated inverse problems are to determine the absorption coefficient or the optical/acoustic properties of the medium. There has been substantial progress recently on several aspects of the mathematics, and this talk will survey our current understanding.

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MS45
Image Reconstruction in Optical Tomography II

The inverse problem of optical tomography is to reconstruct the optical properties of a highly-scattering medium from boundary measurements. I will review recent work on associated inverse scattering problems for the radiative transport equation. Our results will be illustrated by numerical simulations and experiments in model systems.

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MS45
Image Reconstruction in Optical Tomography I

The inverse problem of optical tomography is to reconstruct the optical properties of a highly-scattering medium from boundary measurements. I will review recent work on associated inverse scattering problems for the radiative transport equation. Our results will be illustrated by numerical simulations and experiments in model systems.

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MS46
Taylor Dispersion of Nano-Particles in Compliant Arterioles

A nanovector is a hollow or solid structure, with diameter in the 1-1000 nm range, which can be filled with anticancer drugs and detection agents. These nanovectors must reach with their payloads sites of inflammation, cancer lesions, and tumors via convective and diffusive transport through the vasculature. In arterioles and capillaries the flow conditions are those of Taylor dispersion when convective transport competes with molecular diffusion. In this flow regime G.I. Taylor derived effective equations that hold in tubes with FIXED walls, which can be used to describe effective diffusion of nano-particles in tubes with fixed walls. The resulting effective equations are of parabolic type. In this talk we present the results related to the study of Taylor dispersion in COMPLIANT tubes such as those of arterioles. We found a surprising result: effective equations describing concentration of nano-particles in compliant arterioles are of hyperbolic type. This means, in particular, that sharp fronts in nanoparticle concentration may arise due to the motion of the vessel walls! In particular, we found that in arterioles with porous vessel walls, such as those associated with neighbouring pathologies, the initial-boundary value problem is not well-posed (Goursat problem). This means that injecting nano-particles near the location of the tumor will give rise to the instabilities in the concentration distribution, not recommended for optimal drug delivery. Instead, nano-particles should be administered upstream from the location of the tumor, as is typically performed in intravascular cancer drug delivery.

Suncica Canic
MS46
A Kinematically Coupled Scheme for Fluid-Structure Interaction in Blood Flow

We will present a novel numerical strategy to solve the fluid-structure interaction in blood flow. The main difficulty of the problem lies in the strong interfacial coupling due to the fact that the ratio between the densities of the blood and the arterial wall is roughly equal to one. Traditionally, implicit schemes are employed to solve this strongly nonlinear problem. The novel algorithm that we will present is partitioned, has a modular architecture and, in contrast with other partitioned schemes, is stable in the blood flow regime.

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MS46
Modeling Viscoelasticity of the Arterial Wall

The mechanics of the arterial wall is complex, due to its material structure and load conditions, which influences hemodynamic properties as well as the growth and remodeling of the arterial network. In this study we analyze how elastic and viscoelastic wall properties differ across the large arteries and show how a viscoelastic model can be used to predict flow in the circle of Willis. Experimental data will be used to validate the model.

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MS47
Simulations of Blood Flow in a Compliant Vessel by the Immersed Boundary Method

We introduce a two-dimensional mathematical model which describes the interaction of blood flow with the aortic wall by the immersed boundary method. The mathematical model is validated by comparing with well-known solutions of the viscous incompressible Navier-Stokes equations in arteries. The hysteresis behavior in the pressure-diameter relation is observed when the viscoelastic material property of the arterial wall is taken into consideration.

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MS47
A Mathematical Model of Collagen Lattice Contraction

A mathematical model of fibroblast-collagen interaction is proposed which reproduces qualitative features of fibroblast-populated collagen lattice contraction. The model suggests two mechanisms for collagen contraction: collagen aggregates due to tension lines formed by the moving cells and collagen aggregates due to wrinkling of the collagen lattice.

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MS47
Kinetic Model for Lamellipodal Actin-Integrin Clutch Dynamics

In migrating cells, with especial prominence in lamellipodial protrusions at the cell front, highly dynamic connections are formed between the actin cytoskeleton and the extracellular matrix through linkages of integrin adhesion receptors to actin filaments via complexes of cytosolic connector proteins. Myosin-mediated contractile forces strongly influence the dynamic behavior of these adhesion complexes, apparently in two counter-acting ways: negatively as the cell-generated forces enhance complex dissociation, and at the same time positively as force-induced signaling can lead to strengthening of the linkage complexes. We obtained ranges of parameter value sets yielding behavior consistent with that observed experimentally for 3T3 cells and for CHO cells, respectively. Model simulations are able to produce results for the effects of paxillin mutations on the turnover rate of actin/integrin linkages in CHO cells, which are consistent with recent literature reports. Overall, although this current model is quite simple it provides a useful foundation for more detailed models extending upon it.

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MS47
An Elastic Continuum Model of Enterocyte Layer
Migration

We have developed a mathematical model of migration of enterocytes during experimental necrotizing enterocolitis, which is based on a novel assumption of elastic deformation of the cell layer and incorporates the following effects (i) mobility promoting force due to lamellipod formation, (ii) mobility impeding adhesion to the cell matrix, and (iii) enterocyte proliferation. We have recently extended the model to two-dimensions and using balance equations of continuum mechanics we obtained a second order PDE model with moving boundary. The models allows us to predict the time-dependent geometry of the wound edge.

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MS47
A Finite Element Model for Wound Healing with Coupling Wound Contraction and Neo-Vascularization

Wound healing proceeds by a number of (partially) overlapping steps: bleeding, blood clotting, removal of contaminants and bacteria, wound closure by cell mitosis and migration towards the wound center, repair of the vascular network, and wound contraction along lines of equal tension. We consider a model due to Adam [1] for the closure of a wound. The model is based on an epidermal growth factor that stimulates cell proliferation. Consequently, cell division, and hence also wound closure, takes place only if the epidermal growth factor exceeds a threshold value. The production of the growth factor is restricted to a strip of the tissue surrounding the wound, the so-called active layer. We assume that healing at a certain location of the wound edge takes place if and only if the growth factor concentration is not below a threshold concentration $c$. Furthermore, the rate of closure is assumed to depend on the local curvature of the wound edge. The model predicts no migration of the wound edge locally whenever the local growth factor concentration is less than the threshold value $c$. This implies the existence of a waiting time before wound closure sets in.

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MS48
The Dynamics and Control of Drinking: A Preliminary Study of the Role of Dispersal, Relapse and Social Dynamics

We introduce simple mathematical models in the study of the dynamics of drinking on homogeneous and heterogeneous mixing communities. The emphasis is on the role of relapse, mixing and dispersal on the dynamics and control of drinking behaviors at the population level. Tools from population dynamics and control theory are used to identify and highlight challenges and opportunities at the interface of the life, mathematical and social sciences.

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Impact of Vaccination and Screening of Chlamydia Trachomatis: A Mathematical Modeling Approach

Chlamydia trachomatis is the most frequently reported sexually transmitted disease in the United States, with an estimated 2.8 million Americans infected per year. The U.S. Preventive Services Task Force (USPSTF) recommends screening for Chlamydia infection for all sexually active non-pregnant young women aged 24 or younger and for older non-pregnant women who are at increased risk. Currently, researchers are also investigating potential vaccines for Chlamydia. Two mathematical models are formed to investigate the dynamic of the Chlamydia transmission. In a simple model, equilibriums and basic reproduction number $R_0$ are analyzed, as well as the uncertainty and sensitivity of $R_0$ with respect to various parameters. In a model with age structure, the transmission dynamic in the United State population and the effectiveness of various screening and vaccination strategies were investigated with numerical solutions of the model. The results of the analysis and simulation of the models expand our understanding of the disease transmission and effectiveness of various intervention strategies, develop more questions concerning the infection and transmission dynamic, as well as highlight the need for particular data for future field studies.

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MS48
Evaluation of Hypothetical Mechanisms for the Changing Epidemiology of Pertussis Through Out the Developed World by Analysis of Natural Experiments in Sweden

In Sweden, county health officers included pertussis in their tjnstelkarrapporten early in the 20th Century, and laboratories began reporting culture-confirmed cases during the 1980s. Whole-cell pertussis vaccine was administered to Swedish infants from 1953 to 79, as have acellular vaccines (aP) since 1996. Pertussis became endemic among young children during the intervening 17 years, permitting several aP efficacy trials. Clinical and laboratory reporting have been mandatory since 1997. This tradition of reporting, together with pertussis resurgence during the hiatus in vaccination, enabled colleagues at the Swedish Institute for Infectious Disease Control to enhance routine passive surveillance, in which clinical course and vaccination status may be incomplete or lacking, and to ensure that sera from the 1997 national cross-sectional survey were tested for IgG antibodies against pertussis toxin. They have followed trial cohorts as well as children born since 1996, primarily to investigate long-term effectiveness of aP vaccines counties use one- to three-component products but also to study the possible need for booster doses. As 98+ percent of infants have been vaccinated at 3, 5, and 12 months of age since the hiatus, incidence has decreased an order of magnitude. But pertussis has not been eliminated. And Sweden now resembles other developed countries: reported cases occur mostly among older children and adults, with infants still at greatest risk of severe disease. The first natural experiment permits evaluation of four hypothetical explanations for the changing epidemiology: surveillance artifact, selection of vaccine-resistant antigenic variants, waning of increasingly vaccine-induced immunity absent boosting, and reduced transmission. By 2004, waning was apparent among vaccinated cohorts, as one hypothesis predicts. Accordingly, vaccinated children were offered aP with their DT boosters on attaining 10 years of age during fall of 2005, with boosters at 4-6 years beginning in 2007 and 14-16 years planned in 2017. We will estimate parameters of a mathematical model of our hypothesis from observations through 2000, identify deficiencies, if any, by comparing predictions to subsequent observations, remedy them, and use the validated model to ascertain the optimal number and timing of booster doses. The second natural experiment may permit county-level modeling with aP product-specific parameters.

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MS49
Synchronization in Oscillatory Networks

Recent research has revealed a rich and complicated network topology in the cortical connectivity of mammalian brains. A challenging task is to understand the implications of such network structures on the functional organization of the brain activities. This is studied here basing on dynamical complex networks. We investigate synchronization dynamics on the cortico-cortical network by modelling each node (cortical area) of the network with a sub-network of interacting excitable neurons. We find that the network displays clustered synchronization behaviour and the dynamical clusters coincide with the topological community structures observed in the anatomical network. Our results provide insights into the relationship between the global organization and the functional specialization of the brain cortex. These modelling results will be compared with the networks reconstructed from single EEGs measured during the performance of simple cognitive tasks. We compare different reconstruction methods based on partial phase coherence, symbolic dynamics and recurrence.

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MS49
Reconstructing Topology of Sparse Dynamical Networks

Methods are proposed for reconstructing the topology of a general dynamical network, given observations of node dynamics. We focus on networks where connections are sparse and data is limited. We find that for inferring network connections, true positive rates are optimized by using so-called compressed sensing techniques now common in signal processing.

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MS49
Kalman Filter Control of a Model of Spatiotemporal Cortical Dynamics

Recent advances in Kalman filtering to estimate system state and parameters in nonlinear systems has offered the
potential to apply such approaches to spatiotemporal non-linear systems. We here adapt the nonlinear method of unscented Kalman filtering to observe the state and estimate parameters in a computational spatiotemporal excitable system that serves as a model of cerebral cortex, to track spiral wave dynamics, and to use an observer system to calculate control signals through electrical fields.

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MS50
Integrating Numerical and Statistical Tools: Towards Understanding Brain Energetics

The debate over the primary fuel supporting the energetic needs of neuronal activity has been continuing for more than a decade, leading the experts to agree on the need for a mathematical model capable of offering a key to the sparse and indirect data. In this talk we show how by introducing a statistical framework it is possible to design a detailed yet tractable computational model of brain energy metabolism, in spite of the few data points available. The use of statistical tools can be extended to account for the variability of the model predictions, hence to quantify the reliability of the computed estimates. Finally posit a new hypothesis of brain energy metabolism suggested by the models predictions and show how it independently validates published experimental data.

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MS50
Predictive Models that Infer Structure and Dependencies: Modeling Tumor Progression

A modeling framework that allows for predictive models that simultaneously infer the geometry and statistical dependencies explanatory variables in high-dimensional (genomic) data is developed. This is then applied to the problem of modeling tumor progression. The talk will touch on manifold learning, dimension reduction, and inference of graphical models.

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MS50
Current and Future Roles of Statistics in Dynamical Biological Pathway Analysis

Computational biology contains distinctly different subspecialties. While statistics has played a crucial role in aspects of structure and function prediction, molecular simulations, and the analysis of static networks, it is not typically associated with, or applied to, dynamic pathway analyses, which are seen as firmly embedded in the field of differential equations. Well-known long-term exceptions have included Kolmogorov differential equations, which result from stochastic processes, and Monte Carlo simulations. In this presentation I will discuss a few less typical topics where biological pathway analysis and statistics meet. From among topics that have been addressed in the past I will discuss the dynamics of populations with distributed features and the amplification or attenuation of distributed input signals in dynamical systems. I will furthermore present topics of biological pathway analysis that would benefit from the help of statisticians.

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MS50
A Model for Cross-Species Co-Expression Analysis: An Application to Aging Transcription Programs

Systems biology is a relatively new integrative discipline that focuses on the systematic study of complex interactions in biological systems, thus using a new perspective (integration instead of reduction) to study them. Comparative analysis is a fundamental tool in systems biology. The focus of comparison is to identify either conservation or differences. For examples, conservation of expression values among species often indicates the functional importance of a gene, while differences of gene expression are critical markers of cell types. A work-in-progress project on comparative analysis of gene expression will be reported in this talk. It aims to develop a probabilistic model for identification of co-expressed genes that are conserved across species. Different from previous clustering efforts, the goal here is to simultaneously 1) cluster genes in each species and 2) arrange as many orthologous genes into conserved clusters as possible. Our current treatment combines a finite mixture model for modeling gene expression in each species and a logistic regression model to the counts of genes in corresponding clusters across species. Results in synthetic data show that this model outperforms the k-means clustering performed in each species, even by traditional measures. Applying this model to an analysis of human and fruit fly aging data, we find that dietary restriction, the practice of limiting dietary energy intake, strongly influences three conserved gene clusters. This result offers an interpretation at molecular level to the repeated observations of correlation between dietary restriction and increase life span in various species. It pinpoints the core regulatory pathways that are modulated by food intake throughout the evolution of at least 600 million years. Work in collaboration with Jun Cai, Zhewen Fan and John Marden.

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MS51
Intracellular Mechanisms of Regulation of Muscle Metabolism During Exercise

Skeletal muscle can maintain intracellular [ATP] constant during the transition from rest to exercise, while reaction rates may increase significantly. Among the key regulatory factors, the dynamics of cytosolic and mitochondrial NADH and NAD+ during exercise have not been characterized. To determine the extent of regulation exerted by these intracellular metabolic signals on skeletal muscle metabolism at the onset of exercise, a computational model was developed. In this model, transport and metabolic fluxes in distinct capillary, cytosolic, and mitochondrial domains are integrated. We hypothesized that during the transition from rest to exercise (60% VO2max), the dynamics of lactate concentration [Lac] in exercising muscle is independent of mitochondrial redox state. We tested this hypothesis by simulating the metabolic responses of
skeletal muscle to exercise, while altering the transport rate of reducing equivalents from cytosol to mitochondria and muscle glycogen content. Simulation with optimal parameter estimates showed good agreement with experimental data from muscle biopsies in human subjects. Compared with the optimal values, a 20% increase (decrease) in NADH transport coefficient led to an 85% decrease (7-fold increase) in cytosolic redox state, and ~50% decrease (~85% increase) in muscle [Lac]. Doubling (halving) glycogen concentration resulted in a 30% increase (20% decrease) in cytosolic redox state, and ~10% increase (~25% decrease) in [Lac]. In both cases, mitochondrial redox states had minor changes. In conclusion, simulations suggest that the regulation of lactate production at the onset of exercise (~60% VO2max) is primarily dependent on the dynamics of cytosolic redox state and independent of mitochondrial redox state.

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**MS51**

**Modeling the Cardiovascular Closed-Loop Baro-Reflex**

In cardiac physiology, a strong interconnection exists between all scales: normal function at a given level (e.g. tissue) depends on the underlying synergy of sublevels (myocytes) but also on higher levels, when considering feedback mechanisms. Hence, we propose a comprehensive model of the cardiovascular system that includes a finite element model of ventricular mechanics with passive and active material properties, the circulation, and the baro-reflex which feeds back to heart rate and beta-adrenergic stimulation of the cardiac myocytes.

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**MS51**

**Geometric and Fluid Flow Coupling Between Macro and Micro Scales in Respiration Simulation**

We present several components of a semi-automated subject-specific end-to-end medical image through CFD analysis capability for the human respiratory system. The particular model components emphasized here are related to the macro-through-micro scale coupling of geometry and flow physics. Specifically, in the area of geometric modeling, four elements are summarized: i) semi-automated processing of medical image data to derive upper airway and lobe geometries, ii) partitioning and truncation algorithms, iii) automated unstructured 3D gridding of the trachea through generation 5-8, and iv) interfacing this upper bronchi and lobe geometry with a volume filling algorithm for the subresolved bronchi. In the area of flow modeling, algorithm components related to 3D through quasi-1D transition, loss modeling, and boundary conditions are presented. Particular emphasis here is placed on the issues and models related to interfacing the macro and micro scales. The overall model is demonstrated through application to unsteady respiration simulation of a live subject.

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**MS55**

**Multiscale Simulation of Gas Flow in Subject-Specific Models of the Human Lung**

This presentation describes a comprehensive computational fluid dynamics (CFD) framework for pulmonary gas flow that utilizes multidetector-row computed tomography (MDCT)-based subject-specific airway geometries, spans multiple scales, and employs a data-driven approach to simulate flow in a breathing lung. The framework is based upon MDCT imaging, geometric modeling of airway trees, three-dimensional (3D) and one-dimensional (1D) coupled mesh generation, 3D and 1D CFD methods, image-based physiological boundary conditions, and a novel moving mesh technique. At a local level, the fluid-structure interaction and acinar flow simulations are employed for regional wall-shear stress in compliant airways and mixing in alveolar sacs. Some applications of the multiscale technique will be presented.

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**MS52**

**Quantitative Reconstruction in PhotoAcoustic Tomography**

PhotoAcoustic Tomography (PAT) uses light to create sound sources (by heat generated on optical absorption) and image reconstruction consists of an inverse acoustic source reconstruction, which can be done using conventional ultrasound methods. In order to quantify the optical properties underlying the sound generation it is necessary to couple models for optical and acoustic propagation. In this talk I present some of our recent work on this problem, utilising a non-linear algorithm for recovering optical absorption coefficient.

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**MS52**

**Conductivity Imaging Using Electrical Impedance Tomography and Elastic Deformation**

Electrical impedance tomography (EIT) is an imaging technique that uses Cauchy data to reconstruct the conductivity in a domain. On the practical point of view the task is difficult. A new imaging technique that combines boundary electrical measurements and elastic deformation inside the domain is under investigation (Ammari et al., to appear). A small spherical deformation is induced by ultrasound around a point x in the domain. Using asymptotic estimates, the electrical power in a small domain around the point x is recovered from the variation of the boundary measures. This modality provides more information than classical EIT, since measures are available inside the domain and not only on the boundary. An algorithm is proposed to reconstruct the conductivity, assuming the measured data is the energy density at each point of the domain. The cost-function is the L2 distance between the measured and the predicted energy density. The direct and adjoint derivatives of the energy density with respect
to the conductivity distribution are calculated. The reconstruction algorithm uses a multigrid approach: at a coarse level the Jacobian of the cost function is assembled. At a fine level a matrix-free Gauss-Newton optimization is implemented, using direct and adjoint differentiation. We also present numerical results on synthetical data in 2D and 3D.

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MS52
Modelling of Wave Equations Obeying Frequency Dependent Attenuation Laws for Thermoacoustic Tomography

It is reasonable that the resolution in Computed Thermoacoustic Tomography can be improved by taking the attenuation of the pressure waves inside the tissue into account. Loosely spoken the classical attenuation law states that a frequency component of a pressure wave is exponentially damped with an exponent that is proportional to some fractional power $\gamma$ of the absolute value of the frequency and to the distance from the origin. For some fractional powers $\gamma$ the solutions of the common models have causality problems which indicate the incompleteness of these models. In this talk we discuss these causality problems and present a new class of pressure wave equations obeying frequency dependent attenuation that guarantees causal solutions.

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MS52
Thermoacoustic Tomography with Integrating Transducers

Thermoacoustic imaging is a promising new modality for nondestructive evaluation. So far mainly point measurement data for thermoacoustic imaging are used. In this talk we review using setups with large detectors. Imaging algorithm based on the Radon transform are presented to cope with the measurements produced by the large detectors. We present numerical simulations for simulated and real data.

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MS53
Cardiovascular Control: The Importance of the Pulse Pressure

Low pulse pressure (i.e., the difference between systolic and diastolic pressure) has been shown to be an independent predictor of mortality in heart failure patients. However, underlying mechanisms have not been discussed in detail. Applying a pulsatile and a non-pulsatile mathematical model of the cardiovascular system we investigate the information content of the pulse pressure and its role in the cardiovascular control loop during orthostatic stress based on experimental data. Sensitivities to physiological parameters provide a quantification of the developed concepts.

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MS53
Development of a Comprehensive Cardiopulmonary Model

We developed a comprehensive cardiopulmonary model that takes into account the mutual interactions between the cardiovascular and the respiratory systems along with their short-term regulatory mechanisms. The model includes the systemic and pulmonary circulation, lung mechanics, gas exchange and metabolism, and the action of several regulatory factors (baroreflex, chemoreflex, pulmonary mechanoreceptors, local peripheral control). It can represent a valid tool for clinical practice and medical research, providing an alternative way to experience-based clinical decisions.

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MS53
Subset Selection and Reduced-Order Parameter Estimation

Large-scale physiological models have become commonplace in medicine and engineering. Identifying model parameters from experimental data is a challenging task, however, as the high level of modeling detail usually stands in contrast to relatively few data streams available for identification. We present a subset-selection approach to assess which parameters of a given model are the ones to tune in order robustly to match the model to a particular set of experimental signals.

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MS53
Modelling Feedback Mechanisms Regulating the
Cardiovascular System

The overall function of the baroreceptor feedback mechanism is known. However, the underlying biochemical mechanistic processes are not fully understood and they are not easily investigated in vivo. By a methodology called the mathematical microscope a mathematical model is developed making the invisible visible and the inaccessible accessible, via an in silico investigation of the feedback mechanisms. In this talk, I will illustrate how to access inaccessible features of the baroreceptor feedback chain regulating heart rate.

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Spread of Disease

In this joint work with Hsieh and van den Driessche, we propose a multi-patch model to study the impact of travel on the spatial spread of disease between patches with different level of disease prevalence. The basic reproduction number for each patch in isolation is obtained along with the basic reproduction number of the system of patches. Inequalities describing the relationship between these numbers are also given. For a two-patch model with one high prevalence patch and one low prevalence patch, results pertaining to the dependence of the basic reproduction number on the travel rates between the two patches are obtained. For parameter values relevant for influenza, these results show that, while banning travel of infectives from the low to the high prevalence patch always contributes to disease control, banning travel of symptomatic travelers only from the high to the low prevalence patch could adversely affect the containment of the outbreak under certain ranges of parameter values. Moreover, banning all travel of infected individuals from the high to the low prevalence patch could result in the low prevalence patch becoming disease-free, while the high prevalence patch becomes even more disease-prevalent, with the resulting number of infectives in this patch alone exceeding the combined number of infectives in both patches without border control. Under the set of parameter values used, our results demonstrate that if border control is properly implemented, then it could contribute to stopping the spatial spread of disease between patches.

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MS54

Modeling the Effects of Latently Infected Cell Activation on Low-Level Viral Persistence, Slow Decay of the Latent Reservoir, and Intermittent Viral Blips in HIV-Infected Patients Under Drug Treatment

Current HAART regimens cannot eradicate HIV-1 from infected individuals. Although the potent combination antiretroviral therapy is usually able to suppress plasma viral loads to below the limit of detection of conventional clinical assays, a low level of viremia can be detected to persist in plasma by more sensitive assays. Moreover, a number of patients experience transient episodes of viremia above the detection limit, termed HIV-1 blips, even with highly suppressive therapy for many years. A major known obstacle to viral eradication is the persistence of the latent reservoir for HIV-1 in resting memory CD4+ T cells. These cells decay slowly, with a half-life up to 44 months, but are ready to produce new virus when they encounter their relevant antigens and are reactivated. The mechanisms underlying low viral load persistence, slow decay of the latent reservoir, and intermittent viral blips are not fully characterized. The quantitative contributions of residual viral replication to the viral and latent reservoir persistence remain unclear. In this talk, I will address these issues by developing a mathematical model that considers latently infected cell activation in response to stochastic antigenic stimulation. The model provides a quantitative and integrated prospective into the dynamics of virus and the latent reservoir in the setting of HAART and may have significant treatment implications in clinical practice.

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Impact of Travel Between Patches for Spatial

In this project, we marry the mathematical modelling to surveillance data from South Ontario to show that the non-crow family birds which are susceptible to West Nile virus...
are one of the key factors to make the virus become an endemic disease and the density of dead crow is not an accurate indicator for the virus after the virus sustain in a region, while the density of mosquito in an area can give us the signal of the risk level of the virus.

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MS55

Systems Identification and Functional Analysis of Genetic Switching Networks

Developing a quantitative understanding of switching behaviour in genetic networks is a challenging and multifaceted problem. This talk focuses on two aspects of this problem: the generation of unbiased network models from experimental observations and the computational analysis of network models to gain insights into the network design features. I will present our efforts to development of a systematic gene perturbation algorithm (SGPA) that can be used to infer causalities within genetic networks by combining high-throughput characterization of network input-output relationships and systems identification methods. Additionally, I will discuss our work on using computational tools to develop new insights into the organization of genes within the embryonic stem cell switch and how different network features contribute to the functional robustness of this switch.

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MS55

Time Evolution of Gene Expression Distributions in Bacterial Populations

We use a highly simplified construct to express a fluorescent protein from plasmids in bacterial cells, and observe the distribution of gene expression levels across the population in this case. We disturb the population in two ways: by diluting it into fresh medium after a period of growth, and by using a cell-sorter to select out the brightest 10 percent of the population. The distribution of protein expression levels is tracked over six to twelve hours, and I will discuss the resulting dynamics in the two cases. The diluted population shows a transient response in both mean and variance, and never settles to a simple steady state: values continue changing for the full twelve hours observed. The sorted population shows different behaviors in two plasmid types: a tightly regulated (medium-copy) plasmid relaxes rapidly back to the initial distribution; while an unregulated (high-copy) plasmid takes many hours to return to the original state. We have had some preliminary success at modeling these effects.

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MS55

Modeling Drosophila Development at the Molecular, Promoter, and Pattern-Formation Levels

The segmentation network of Drosophila melanogaster is well-known for its role in embryo patterning. We present modeling efforts and methodological advances that improve our understanding of this system at three different levels: at the phenomenological level of pattern formation, at a level relating phenomenological regulatory parameters to promoter sequence composition, and at the individual molecule level, where we estimate absolute protein copy numbers and noise based on fluctuations of fluorescence in expression images.

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MS55

Quantifying and Predicting Gene Regulation in Single Cells

The quantitative relation between transcription factor concentrations and the rate of protein production from downstream genes is central to the function of genetic networks. I will describe a technique to measure this relation, the gene regulation function, in individual living cells. The gene regulation function is often a sigmoidal function, and I will show that, by interpreting genetic networks as inference modules, we can make predictions about why this sigmoidal function has different characteristics for different genetic networks. Our results should provide a basis for both understanding cellular decision-making and for designing synthetic genetic circuits.

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MS56

Inferring Effective Connectivity in Networks of Spiking Neurons Recorded with Hundreds of Electrodes

To probe effective connectivity in cortical slice networks, we recorded spontaneous activity with a 512 electrode array for periods > 1 hr in five cultured networks. We used transfer entropy to infer effective connections between neurons. Transfer entropy correctly identified true connections in simple model networks. The resulting networks from the data displayed large fluctuations in topology around a small but highly connected central core.

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MS56
Analyzing Brain Networks with Granger Causality

Multielectrode neurophysiological recordings produce massive quantities of data. Multivariate time series analysis provides the basic framework for analyzing the patterns of neural interactions in these data. It has long been recognized that neural interactions are directional. Being able to assess the directionality of neuronal interactions is thus a highly desired capability for understanding the cooperative nature of neural processing. Research over the last few years has shown that Granger causality is a key technique to furnish this capability. In this talk, I will discuss the concept of Granger causality and present results from applications of this technique to multichannel local field potential recordings from monkeys performing cognitive tasks.

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MS56
Estimating Neuronal Network Connectivity Despite Hidden Nodes

Determining the connectivity structure of neuronal networks from measurements of spike times is hindered by one’s inability to simultaneously measure the activity of all neurons. Many unmeasured neurons could be interacting with the small set of measured neurons and corrupting estimates of connectivity in unknown ways. For example, a common connection from an unmeasured neuron could introduce correlations among two measured neurons, which might lead one to erroneously infer a connection between the measured neurons. We present a model-based approach to control for such effects of unmeasured neurons. We demonstrate the promise of this approach via simulations of small networks of neurons driven by a visual stimulus.

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MS56
Modeling and Decoding Multineuronal Responses in the Primate Retina

A key challenge in neuroscience is to understand how large networks of neurons collectively encode information. It has recently become possible to record simultaneously from complete mosaics of 100 ON and OFF parasol cells over a 4x8 degree region of peripheral retina, providing the opportunity to better understand the message the eye sends the brain. We present a new generalized linear multivariate point process model of the visual response properties of networks of these retinal ganglion cells. We discuss model fitting and validation (challenging due to the high dimensionality of the data, but computationally tractable due to the concavity of the loglikelihood), demonstrate the model’s accuracy in predicting retinal responses to novel visual stimuli, and describe Bayesian techniques for decoding the network responses. With J. Pillow, E. J. Chichilnisky, E. Simoncelli, and J. Shlens.

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MS57

The intrinsic mechanisms underlying burst generation in vitro are generally well understood. However, how these mechanisms are implemented under in vivo conditions is still not clear. ELL pyramidal cells have a well defined burst mechanism in vitro but in vivo data shows a very different burst mechanism. This talk will explore, through a combination of experimental and modeling approaches, how the conditions found in vivo affect a well characterized burst mechanism found in vitro.

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MS57
Bursts and the Detection of Transient Electrosensory Signals.

Electric fish rely on their electro-sense to localize preys and communicate with one another. We show that in different hindbrain regions, bursts encode different behaviourally relevant signals. In particular synchronized bursting is triggered by transient communication signals in a region of the hindbrain believed to be important for communication. We argue that bursting in electric fish, as in other systems, is a conspicuous neural code signalling the occurrence of transient and behaviourally relevant sensory events.

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MS57
Bugs, Bats and Bursts: Behaviorally Relevant Bursting in an Insect Auditory System

Bursts of action potentials have been proposed, in many systems, to detect salient stimulus features but have rarely been shown to influence behavior. Spike bursts of an identified auditory interneuron of crickets accurately detect large increases in stimulus amplitude and sound location whereas non-burst spikes do so poorly. Comparison of spike trains and behavioral responses shows that only bursts elicit behavioral responses, thus demonstrating that bursts are indeed behaviorally relevant.

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MS57
The Role of Thalamus in Cortical Function: Not Just a Simple Relay

For thalamic relay cells, the recent history of membrane voltage determines which of two firing modes, tonic or burst, prevails. Burst firing occurs when the cell is relatively hyperpolarized, and tonic firing, when relatively depolarized. These modes have significant consequences for the thalamocortical relay. We have begun studies of another cell showing burst firing, the layer 5 corticthalamic cell, and the consequences of bursting are similar in these thalamic and cortical cells.

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MS58
Control of Macro-Scale Mixing and Transport in the Small Intestine: A Lattice-Boltzmann Model

The primary function of the small intestine is the absorption of nutrients through the epithelial surface into the blood stream. Two basic motility patterns are responsible for the transport: peristaltic contractions for axial transport, and repetitive segmental contractions of short sections of the gut for radial transport. We evaluate the relative contributions of peristaltic and segmental contractions to the absorption process using a two-dimensional model of flow and mixing of passive scalar using a lattice-Boltzmann model of small intestine motility with second-order moving boundary conditions for velocity and scalar. Mixes of segmental and peristaltic contractions are parameterized with magnetic resonance imaging (MRI) data from the rat intestine and nutrient uptake was quantified as surface scalar transport. We find that any level of peristaltic contribution degrades uptake, explaining radiologic observations where peristalsis is absent during the initial digestive period and appears only periodically later to transport chyme.

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MS58
Triple-Decker: Interfacing Atomistic-Mesoscopic-Continuum Flow Regimes in Biological Fluids

Multiscale flow phenomena in microfluidic and biomedical applications require the use of heterogeneous modeling approaches. We present a hybrid method based on coupling the Molecular Dynamics (MD) method, the Dissipative Particle Dynamics (DPD) method, and the incompressible Navier-Stokes (NS) equations. MD, DPD, and NS are formulated in separate sub-domains and are coupled via an overlapping region by communicating state information at the sub-domain boundaries. Imposition of boundary conditions in the MD and DPD systems involves particle insertion and deletion, specular wall reflection and body force terms. The latter includes a boundary pressure force in order to minimize near-boundary density fluctuations, and an adaptive shear force which enforces the tangential velocity component of boundary conditions. The triple-decker algorithm is verified for prototype flows, including simple and multi-layer fluids (Couette, Poiseuille, and lid-driven cavity), using highly accurate reference solutions. A zero-thickness interface is also possible if it is aligned with the flow streamlines.

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MS58
Multiscale Simulation of the Musculoskeletal System using Surrogate Models of Tissue Behavior

The primary tools of computational biomechanics include multi-body dynamics at the body level and finite element methods at the organ level. The multi-body technique lacks the complexity to accurately capture tissue behavior and finite element models are typically too computationally intensive for body level simulations. Presented here is the use of computationally efficient surrogate models of tissue within a multi-body framework. The input-output relations of the surrogate models are derived from finite element solutions.

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MS58
Understanding the Functionality of Myosins, the Motive Forces of Living Systems

Molecular motors play crucial roles in diverse biological processes ranging from gene replication to muscle contraction to cell division. They convert chemical energy such as ATP hydrolysis into mechanical work. Myosins belong to one important family of molecular motors moving on actin filaments and performing various mechanical functions within living cells. Recent studies have shown that myosin VI is correlated with ovarian and prostate cancers, but the detailed molecular mechanism remains unknown. We describe work focused on understanding myosin VI, the effect of molecular mutations and its similarity to other myosins, which have been extensively studied. We have used computational approaches to guide the design of chimeric myosins and predict the step size and the directionality of each designed myosin. We then expressed these molecules and used in vitro motility assays to test their dynamic behavior. One remarkable difference between myosin VI and other myosins is that it moves in the reverse direction as compared to other myosins. We were able to engineer myosins moving toward the opposite ends of actin filaments with a change of only 18 amino acids.
MS58
Microstructure and Composition Based Constitutive Relationships for Meniscus/Cartilage

Objectives: To develop stress-strain relationship for modelling the deformation behavior of soft tissues, such as knee meniscus and cartilage, based upon their microstructure and composition. Methods: The knee meniscus and cartilage is considered to be composed of hydrated collagen fiber network, hydrated proteoglycan (PG) gel and free water. Consequently, we seek constitutive relationships of the type used in fluid saturated porous medium. The effective stress in this poroelastic constitutive law is obtained from a simple volume average of the stress on the non-fibrillar PG gel and the stress on the fibrillar network. The stress on the non-fibrillar PG gel is estimated using a modified neo-Hookean model. The stress tensor of the fibrillar network is obtained by considering the fiber orientations and fiber loading condition. The fiber network is considered to be under pre-tension that results from the swelling pressure caused by the PG gel hydration under a given ion concentration. At present, the pre-tension stress is estimated using the Donnan osmotic pressure model. Finally, we make the kinematic assumption that the strain in the non-fibrillar PG gel and the fibrillar network are the same. The resultant stress-strain relationship is used to perform parametric study of overall tissue behavior under various loading conditions. Using this approach we are able to obtain closed form expressions for overall stress-strain behavior under uniaxial compression and tension. For multiaxial loading cases, the stress-strain behaviors are evaluated numerically. Results: Stress-strain behavior under strain controlled uniaxial compression is found to be significantly affected by the fiber content, fiber network pre-tension and fiber stiffness. For large pre-tension, the overall behavior can show softening at intermediate strain-levels. For small pre-tension and fiber stiffness, the overall behavior is dominated by the non-fibrillar part.

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MS58
euHeartL: Multi-Scale Computational Models of the Heart

Mathematical models of the heart are arguably some of the most advanced examples of integrating multiple data sets into a consistent biophysical framework for quantitative prediction of function. The philosophy underpinning a large number of these models is one of providing a framework within which to encapsulate physiological understanding. That this is now becoming a reality is demonstrated by the increasing number of studies which now use or extend previously developed modelling frameworks. Such component reuse and knowledge capture within modelling frameworks is an enormously powerful feature of Systems Biology approaches. Component reuse is also a central philosophy within exciting global initiatives such as the Physiome and Virtual Physiological Human (VPH) Projects which aim to develop integrated multi-scale models of physiological systems. We argue that the application of model reuse requires methods for analysing model structure to maintain transparent links with experimental and clinical data. To meet this need we propose tools for the analysis of cardiac models. We argue that these approaches are important for providing the confidence in model results which will in turn enable the translation of research into clinical environments to meet the objectives of several new European Union funded projects.

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MS58
A Multiscale Lattice-Boltzmann Model of Macroto-Micro Scale Couplings in the Small Intestine

Nutrient and pharmaceutical absorption in the small intestine involve coupled multiscale transport and mixing processes that span several orders of magnitude. We have hypothesized that muscle-induced villi motions generate and control a "micro-mixing layer" that couples with macroscale mixing to enhance molecular transport to and from the epithelium. To test this hypothesis, we developed a 2-D numerical method based on a multigrid strategy within the lattice-Boltzmann framework. Emphasis is placed on the treatment of moving boundaries with arbitrary curvatures for flow and scalar. We model a macro-scale cavity flow with microscale finger-like "villi" in pendular motion on the lower surface and evaluate the coupling between macro and micro-scale fluid motions, scalar mixing, and uptake of passive scalar at the villi surface. Results show that the moving villi can be effective mixers at the micro scale, especially when groups of villi move in a coordinated out-of-phase fashion. A time-evolving series of flow recirculation eddies are generated over the villi, which form a micro mixing layer. These eddies increase the transport of scalar from the macro eddy to the surface of villi by advection. Higher frequency of villi motions enhances scalar absorption. This enhancement of absorption is lower with smaller villous length.

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PP1
Monolithically Coupled Fluid-Structure Interaction for Blood Flow in Arteries

We develop a scalable parallel finite element solver for the simulation of blood flow in compliant arteries. Monolithic coupling of the incompressible Navier-Stokes equations with a linear elastic structure model for the artery walls ensures stability, and an unstructured dynamic mesh in the arbitrary Lagrangian-Eulerian frame allows for complicated geometry and large grid deformation. The resulting algorithm features good parallel performance and scalability and is robust to changes in timestep, Reynolds number, and other physical parameters.

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PP1
Bifurcation Theory for a Model of the Oculomotor
Neural Integrator

The oculomotor neural integrator converts sensory signals proportional to eye velocity into eye position commands. We analyze neural network models of the integrator. Our analysis shows that, to function normally, the system must operate in a region where small perturbations can push it into regions of instability or oscillation. Our model will also simulate a class of eye movement disorders known as "congenital nystagmus". Both normal and abnormal behavior depend crucially on the non-normality of the system.

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PP1
IMAG: Multi-Scale Modeling of the Heart in Metabolic Syndrome and Cardiovascular Disease

Our work to date on this project has focused on capturing the physiological state of the heart specifically the integrated components of energy metabolism, electrophysiology, and coronary transport in a computer model at the appropriate level of detail upon which metabolic dysfunction in cardiovascular disease can be naturally imposed. Several important outcomes have emerged from our analysis of the physiological system. The first concerns the mechanism of maintaining metabolic stability in the heart in response to changes in work rate. The mechanism of metabolic control has eluded explanation for three decades because it has been assumed that the substrates for oxidative phosphorylation (ADP and Pi) do not vary enough for feedback to significantly contribute to metabolic control in vivo. However, by analyzing data from 31P-magnetic resonance spectroscopy (31P-MRS) we have determined that feedback-driven control is sufficient to explain the observed data. Our detailed mechanistic model of integrated oxygen transport and oxidative metabolism not only explains the observed data, but also predicts that the maximal work rate of the heart is an emergent property and is limited not simply by the maximal rate of ATP synthesis, but by the maximal rate at which ATP can be synthesized at a potential at which it can be utilized. Novel predictions associated with this finding are validated based on independent data obtained during acute ischemia and recovery. In sum, our mass-, charge-, and energy-balanced model of oxygen transport and energy metabolism in the heart provides a unique and deeply validated platform for modeling of oxygen transport and energy metabolism not only explains the important outcomes have emerged from our analysis of the physiological system. The first concerns the mechanism of maintaining metabolic stability in the heart in response to changes in work rate. 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In sum, our mass-, charge-, and energy-balanced model of oxygen transport and energy metabolism in the heart provides a unique and deeply validated platform for modeling of oxygen transport and energy metabolism not only explains the important outcomes have emerged from our analysis of the physiological system. The first concerns the mechanism of maintaining metabolic stability in the heart in response to changes in work rate. The mechanism of metabolic control has eluded explanation for three decades because it has been assumed that the substrates for oxidative phosphorylation (ADP and Pi) do not vary enough for feedback to significantly contribute to metabolic control in vivo. However, by analyzing data from 31P-magnetic resonance spectroscopy (31P-MRS) we have determined that feedback-driven control is sufficient to explain the observed data. Our detailed mechanistic model of integrated oxygen transport and oxidative metabolism not only explains the observed data, but also predicts that the maximal work rate of the heart is an emergent property and is limited not simply by the maximal rate of ATP synthesis, but by the maximal rate at which ATP can be synthesized at a potential at which it can be utilized. Novel predictions associated with this finding are validated based on independent data obtained during acute ischemia and recovery. In sum, our mass-, charge-, and energy-balanced model of oxygen transport and energy metabolism in the heart provides a unique and deeply validated platform for modeling of oxygen transport and energy metabolism not only explains the important outcomes have emerged from our analysis of the physiological system. The first concerns the mechanism of maintaining metabolic stability in the heart in response to changes in work rate. The mechanism of metabolic control has eluded explanation for three decades because it has been assumed that the substrates for oxidative phosphorylation (ADP and Pi) do not vary enough for feedback to significantly contribute to metabolic control in vivo. However, by analyzing data from 31P-magnetic resonance spectroscopy (31P-MRS) we have determined that feedback-driven control is sufficient to explain the observed data. Our detailed mechanistic model of integrated oxygen transport and oxidative metabolism not only explains the observed data, but also predicts that the maximal work rate of the heart is an emergent property and is limited not simply by the maximal rate of ATP synthesis, but by the maximal rate at which ATP can be synthesized at a potential at which it can be utilized. Novel predictions associated with this finding are validated based on independent data obtained during acute ischemia and recovery. In sum, our mass-, charge-, and energy-balanced model of oxygen transport and energy metabolism in the heart provides a unique and deeply validated platform for further investigations into roles of metabolism and mitochondrial function and dysfunction in cardiac health and disease.

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PP1
Analysis of a Drug-Drug Interaction Problem from Pharmacokinetic

A two drug interaction is usually predicted by individu-
PP1
Computational Modeling and Simulation Lead to the Development of MM-121, a Human Monoclonal Antibody ErbB3 Antagonist

The epidermal growth factor receptor and ErbB2 have been heavily targeted by therapeutic agents, with some success. Understanding the relative importance of the ErbB receptors for inducing activation of downstream signaling cascades is complicated for a number of reasons: the ErbB receptors homo and heterodimerize to become activated, are expressed to differing degrees in different cancer types, and undergo ligand-specific trafficking. Hence, we have taken a systems approach to the problem and developed a computational model of the ErbB signaling network for the purpose of developing more efficacious ErbB targeted therapeutics. The computational model describes the dynamics of all four ErbB receptors in response to ligands that bind to EGFR (Betacellulin) or ErbB3 (Heregulin). Ligand-induced dimerization, receptor internalization, degradation and downstream signaling of the PI3K-Akt cascade are included. To train the model the activation status of all ErbB receptors and pAkt, an important regulator of cell proliferation and survival, were measured after stimulation with each ligand in ADRr cells: 12 time points ranging up to 2 hours post stimulation and 8 ligand concentrations spanning three orders of magnitude. This dataset constrained the dynamic behavior of the model for parameter estimation and the model was then tested using DU145 and ACHN cell lines. Sensitivity analysis was performed of the system to determine the key proteins in the network for activating pAkt over a diverse range of heterogeneous ErbB receptor profiles. ErbB3 was found to be an ultra-sensitive inhibition point in response to either Betacellulin or Heregulin. This prediction was verified by developing and testing a novel anti-ErbB3 antibody, MM121, in cell based assays. MM-121 was also found to be more effective at inhibiting Heregulin-induced pErbB3 and pAkt than other therapeutic agents targeting the ErbB pathway further supporting the findings. The kinetic parameters of MM-121 were also used to build an in silico version of the inhibitor. The model was then used to predict the IC50 values of pAkt and pErbB3 in response to MM121 in a number of cell lines stimulated with Heregulin or Betacellulin and these predictions were experimentally verified. These in vitro findings were further validated in vivo using multiple xenograft models. In summary, we describe 1) how a systems approach to drug discovery has suggested a potentially better mechanism of inhibiting the ErbB pathway and 2) the ability of our computational model to accurately simulate the effect of an anti-ErbB3 monoclonal antibody on signaling in a variety of cancer cell type.

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PP1
IMAG: Time Course of Metabolic Adaptations during Loading and Unloading

Skeletal muscle can maintain intracellular [ATP] constant during the transition from rest to exercise, while reaction rates may increase significantly. Among the key regulatory factors, the dynamics of cytosolic and mitochondrial NADH and NAD+ during exercise have not been characterized. To determine the extent of regulation exerted by these intracellular metabolic signals on skeletal muscle metabolism at the onset of exercise, a computational model was developed. In this model, transport and metabolic fluxes in distinct capillary, cytosolic, and mitochondrial domains are integrated. We hypothesized that during the transition from rest to exercise (60% VO2max), the dynamics of lactate concentration [Lac] in exercising muscle is independent of mitochondrial redox state. We tested this hypothesis by simulating the metabolic responses of skeletal muscle to exercise, while altering the transport rate of reducing equivalents from cytosol to mitochondria and muscle glycogen content. Simulation with optimal parameter estimates showed good agreement with experimental data from muscle biopsies in human subjects. Compared with the optimal values, a 20% increase (decrease) in NADH transport coefficient led to an 85% decrease (7-fold increase) in cytosolic redox state, and ∼50% decrease (∼85% increase) in muscle [Lac]. Doubling (halving) glycogen concentration resulted in a 30% increase (20% decrease) in cytosolic redox state, and ∼10% increase (∼25% decrease) in [Lac]. In both cases, mitochondrial redox states had minor changes. In conclusion, simulations suggest that the regulation of lactate production at the onset of exercise (∼60% VO2max) is primarily dependent on the dynamics of cytosolic redox state and independent of mitochondrial redox state.

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PP1
A Novel Method for Error Regulation in Biological Systems

We propose a novel, versatile way for cells to regulate the error rates of biochemical reactions. This mechanism provides a thermodynamic basis for the theory of “kinetic checkpoints” and shows how it is coupled to energy input from the cell. Though we focus primarily on DNA replication, our model and mechanism are applicable to a wide range of biochemical processes, including actin binding and motor proteins.

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PP1
Singular Limits of Reaction Diffusion Equations of Fisher Type in An Infinite Cylinder.

The limit of a scaled reaction diffusion equation of monostable type on an infinite cylinder is analyzed. The equation is scaled with two small parameters. The scaling provides the equation with a large and small diffusion coefficients in the cross sectional and longitudinal coordinates of the cylinder respectively. The reaction term of this equation has two equilibrium states, one stable and the other unstable. We show that the solutions of the scaled equation converge locally uniformly to piecewise constant function that attains the equilibrium of the equation, as the parameters approach zero.

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PP1
Recurrence of Epidemic Human Influenza: Insights From Simple Models

Abstract not available at time of publication.

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PP1
Complex Temporal Patterns of Spontaneous Initiation and Termination of Reentry in a Loop of Cardiac Tissue

A model is developed consisting of a discrete loop of cardiac cells that circulates action potentials as well as a pacing mechanisms. The dynamics of circulating pulses and the pacer’s action are regulated by threshold relations. Patterns of spontaneous initiations and terminations of reentry generated by this system are studied. These patterns can be regular or irregular; causes of irregularities are identified as threshold bistability of reentrant circulation and phase-resetting interactions with the pacer.

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PP1
The Difference of Synchronization Between Bipolar Patients and Normal Subjects in the Prefrontal Cortex

Bipolar Disorder (BD) is a severe mental disorder characterized by recurrent episodes of alternating elated and depressed mood states interposed by remission periods. We recruited ten normal controls and ten patients with bipolar I disorder during euthymic phase (five males and five females, mean age=32.5 +10.3 y/o, range=21:53). For each subject, 2-minutes eye-closed resting MEG data of 1 kHz sampling rate were recorded with a whole-head 306-channel neuromagnetometer (Vectorview; Elekta-NeuroNag, Helsinki, Finland ). We observed increased delta synchronization, decreased alpha and beta synchronization in the frontal regions of bipolar patient.

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PP1
The Dynamics of Macrophage Activation

The ability of an individual macrophage to change its activation state is an unresolved immunological question with enormous significance. The proper activation state determines if the host will effectively eliminate pathogens and appropriately heal wounded tissue. Our ode model describes the signaling cascade and associated substrate-enzyme dynamics of competing activation states within an individual macrophage and demonstrates that individual macrophages can switch their activation state under certain environmental conditions.

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PP1
IMAG: Multi-Scale Imaging, Analysis, and Integration of Brain Networks

The mammalian nervous system exhibits intricate structural (anatomical) organization at multiple scales, subsuming specific functional roles. In this project, we investigated such structural organizations and their relationships in the mouse brain at three levels of detail: nanoscale (tens of nanometers), microscale (several micrometers), and macroscale (hundreds of micrometers up to several millimeters). The use of innovative volume microscopy techniques has played a key role in this respect. We employed data from the Serial Block-Face Scanning Electron Microscopy (nanoscale), Array Tomography (nanoscale and microscale), Knife-Edge Scanning Microscopy (KESM, microscale), and Magnetic Resonance Microscopy (MRM, macroscale) to obtain an accurate structural reconstruction of mouse brain circuits and analyze their functions. A major part of the project focused on developing the microscopy techniques (KESM and Array Tomography) and
fully automating them, and another part focused on efficient 3D reconstruction algorithms, structural analysis algorithms, and data organization and dissemination methods for data and model sharing. We expect our extensive data and dissemination framework to enable major discoveries, both by us and other neuroscience researchers.

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PP1
Monte Carlo Simulations of the Signaling Scaffold Formation Linking ErbB1 and Ras

Experimental evidence reveals heterogeneities of protein clustering within the cell membrane. Two proteins observed in these clusters are ErbB1 and Ras which are key regulators of the MAPK pathway and often dysregulated in many cancers. When ErbB1 becomes activated proteins within the cytosol are recruited to the membrane establishing a signaling scaffold which leads to the guanine nucleotide exchange from Ras-GDP to Ras-GTP. Interestingly both ErbB1 which is a transmembrane protein and Ras which is tethered to the cytosolic membrane are seen clustered. Although much work has been done to model these proteins very little work has been done to understand the spatial establishment of this signaling scaffold. Here we have developed a lattice based framework using a spatial Monte Carlo algorithm which couples two lattice based models with a non-spatial stochastic model. This provides a pseudo 3D framework for understanding formation of a signaling scaffold.

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PP1
Low Red Cell Production May Protect Against Severe Anemia During a Malaria Infection - Insights From Modeling.

The malaria parasite causes lysis of red blood cells, resulting in anemia, a major cause of mortality and morbidity. Intuitively, one would expect the production of red blood cells to increase in order to compensate for this loss. However, it has been observed that this response is weaker than would be expected. Furthermore iron supplementation for iron deficient children in malaria endemic regions can paradoxically adversely affect the clinical outcome of malaria infection. A possible explanation may lie in the preference that some malaria parasites show for infecting immature red blood cells (reticulocytes). In the presence of a parasite preference for immature red cells, a rise in red cell production can fuel the fire of infection by increasing the availability of the parasites preferred target cell. We present a mathematical model of red blood cell production and infection in order to explore this hypothesis. We assess the effect of varying the reticulocyte replacement rate and preference of the parasite for reticulocytes on four key outcome measures assessing anemia and parasitemia. For a given level of parasite preference for reticulocytes we uncover an optimal erythropoietic response which minimizes disease severity. Increasing red blood cell production much above this optimum confers no benefit to the patient, and in fact can increase the degree of anemia and parasitemia. These conclusions are consistent with epidemiological studies demonstrating that both iron deficiency and anemia are protective against severe malaria, whilst iron supplementation in malaria endemic regions is with an increased number of malaria related adverse effects. Thus, suppression of red blood cell production, rather than being an unfortunate side effect of inflammation, may be a host protective effect against severe malarial anemia.

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PP1
Some Bifurcation Conditions via Stoichiometric Network Analysis

Using notions from stoichiometric network analysis (SNA) and algebraic geometry, we will present some sufficient conditions for polynomial chemical reaction networks to dis-
play specific bifurcations that are often associated with model oscillations and multistationarity. Advantage of SNA is that it can successfully deal with two common modeling issues in systems biology: parameter uncertainty and network size.

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PP1
Models of Drug Therapy During Hepatitis Delta Virus Infection

Hepatitis Delta Virus (HDV) is a subviral satellite that replicates only with assistance from Hepatitis B Virus (HBV). Its close relationship with HBV makes it difficult to target with virus-specific therapeutic treatments, and complicates any effort to model its interaction with the host hepatocyte population. We use the results of HBV drug trials in HDV patients to develop and refine a model of this viral system, and evaluate the likely efficacy of differing antiviral strategies.

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PP1
Cell Metabolism, Parkinson's Disease and Therapy

Parkinson's patients who are being treated with levodopa (L-Dopa) have significant elevations of plasma homocysteine, probably due to an alteration of homocysteine metabolism secondary to catechol-O-methyltransferase (COMT) mediated metabolism of L-Dopa. It has also been stated that the extent to which homocysteine is elevated above normal is dependent upon the B-vitamin status, as plasma homocysteine is inversely correlated with folate and vitamin B12 in L-Dopa treated patients. To better understand the impact of the L-Dopa treatment on the health of the Parkinson's patients we develop a mathematical model for the methionine, folate and dopamine metabolism. The ODE model reproduces the observed effects of L-Dopa treatment on cell metabolism, under both normal and folic acid/B-vitamin deficient conditions. These results suggest that cost-efficient computational experiments based on our model can be used to further explore the complex metabolic pathways relevant to Parkinson's disease.

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PP1
Simulating Cell Internal Structure Using Delaunay Technique

We develop an agent-based model for a cell where the cell is modeled as a set of discrete interacting particles. We use a Delaunay triangulation [Meyer-Hermann, M.: Delaunay-Object-Dynamics: Cell mechanics with a 3D kinetic and dynamic weighted Delaunay-triangulation, Curr. Top. Dev. Biol., 81 (2007) 373-399] to obtain the neighborhood relations between the sub-cellular particles, and a set of interaction potentials to differentiate the types of particles and define their role inside the cell. We believe that the model can help us to better understand the relations between cell internal restructuring and its consequences on cell shape and movement.

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PP1
A Quasi Newton Method for Constrained Molecular Dynamics Simulation

MD simulation can be used to study various dynamic properties of proteins, but a long sequence of iterations has to be carried out even for small protein motions due to the small time step (10e-15sec) required. The bonding forces are among those causing fast protein vibrations that require small time steps to integrate, but they may be replaced by a set of bond length constraints, to increase the step size and hence the simulation speed. Lagrange multiplier methods have been developed for constrained dynamics simulation. However, the multipliers have to be determined in every step to satisfy the constraints through the solution of a nonlinear system of equations. The Newton method is used in molecular dynamic simulation to solve such constrained problems. But, this process is computationally expensive since Newton method is required to calculate Hessian matrix every step. Alternatively, the penalty function method is easy to implement and costs less than a Lagrange multiplier method, which requires the solution of a nonlinear system of equations in every step. We propose a Quasi-Newton method for constrained dynamics. The simulation with the Quasi-Newton Method can be done by using approximation to Hessian matrix. The Quasi-Newton method is easily implemented on Newton method and costs less than a Lagrange multiplier method, which requires the solution of a nonlinear system of equations in every step. We implemented the Quasi Newton method in CHARMM and applied it to protein Bovine Pancreatic Trypsin Inhibitor (BPTI). We compared the simulation results with Verlet, Shake and Penalty function. We describe the Quasi Newton method and its implementation details, discuss our results and the issues to be resolved, show the
advantages as well as the disadvantages of the method, and demonstrate the potential of using the method for general constrained molecular dynamics and energy minimization.

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PP1
Network Activity Coupled By Gap Junctions
We study the network activity of excitable cells coupled by gap junctions. We investigate how the voltage response of two gap junctionally coupled cables depends on cable diameter. Specifically, we show that there exists an optimal diameter for which the signal can be transmitted most effectively and the propagation time also can be minimized at the optimal diameter. We find that diameter regulation allows neurons to selectively transmit action potentials in gap junctionally connected networks.

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PP1
Structural Dynamics of Tree Trunks and the Effects of Carbon Dioxide Levels on the Natural Frequency of Trees.
Studies suggest plants often uproot or snap when forced at their natural frequencies by winds or waves because mechanical stresses along the root-shoot system are greatest during resonance. CO₂ exposure may alter plants' natural frequencies. Nonlinear changes in elastic modulus of plant stems are investigated. A forced Duffing oscillator model is used to study effects of nonlinear stiffness on resonant behavior. Model results are compared to experimental mechanical measurements at various levels of CO₂ exposure.

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PP1
Be Still My Beating Heart: Cardiovascular Modeling of Mammalian Hibernation
Hibernating mammals are able to survive extreme physiological changes as their core body temperature falls to as low as -3 C. The heart rate can fall from 300 beats per minute to as low as 2 bpm, and respiration and oxygen consumption plummet as well. A simple model of the cardiovascular system of a typical mammalian hibernator will be presented.

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PP1
Simulation of the Reaction-Diffusion Master Equation on Unstructured Meshes in Molecular Cell Biology
We generate trajectories of the reaction-diffusion master equation on a triangulated, unstructured mesh. The discrete, stochastic treatment is very computationally demanding, but necessary when the number of molecules is small, as is the case in many models from molecular cell biology. Using ideas from a hybrid method for the chemical master equation, we can simulate some species deterministically in some regions in space, and stochastically in others, reducing the work substantially in two biological examples.

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PP1
Locally Dispersing Populations on Dynamic Spatiotemporally Structured Heterogeneous Landscapes
Previous models have shown two opposite results: static spatially clustered habitat heterogeneity increases equilibrium density of locally-dispersing populations, while spatially correlated disturbances simultaneously affecting many contiguous sites reduces equilibrium density. Here, both effects are combined within one model on dynamic landscapes with specified spatial and temporal autocorrelations, via large-scale disturbances leaving sites temporarily unsuitable. Depending on relative rates of landscape versus population dynamics, increasing the spatial scale of disturbances may help or hinder the population.

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PP1
A Phase Space Approximation Method for the Efficient Solution of Cardiac Membrane Models

The reaction-diffusion system characterizing cardiac electrical behavior requires the solution of a large number of nonlinear equations describing cell membrane behavior. We have developed a method to reduce the computational effort. Our method dynamically enumerates the phase space of the membrane equations and uses the revealed geometry to reduce the total number of computations. In this presentation we will describe the method and show its application to problems in cardiac electrophysiology.

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PP1
NMDA Receptor Antagonist Induced Rhythm Switches in the Entorhinal Cortex

The medial entorhinal cortex participates in theta (4-12Hz), beta (15-25Hz), and gamma (30-80Hz) frequency rhythms. Recent findings from slice preparations have shown that NMDAR antagonists cause a decrease in gamma activity in the presence of kainate and an increase in gamma in its absence. We investigate the mechanisms for these results and interactions of the different frequency bands with a model consisting of populations of pyramidal cells, fast-spiking interneurons, theta-producing interneurons, and stellate cells.

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PP1
Modeling the Flow Cytometric Measurement of the Coverage of Bacteria

Surface coverage by host proteins is the beach head of host defense against invasive bacteria. We propose a low-dimensional ODE model to characterize the dynamics of surface opsonization of the bacteria. The extent of coverage by fluorescently labeled proteins can be measured using a flow cytometer, providing a distribution of size and fluorescence values. We present efforts with model identification and parameter estimation in the presence of Gaussian noise in the observations.

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PP1
IMAG: Multi-Scale Analysis of Cellular Force Transmission and Biochemical Activation

Mechanical force plays an important role in numerous cellular processes such as migration, adhesion and apoptosis. The dynamic framework of the cytoskeleton provides a cell with structural integrity and transmits the physical cues to the targets that respond to the external force. We have studied the structure and mechanical properties of the cytoskeleton using computational models and experimental measurements. In the computational studies, we have developed a rigorous three-dimensional computational model of the cytoskeleton based on Brownian dynamics and used it to investigate cytoskeletal morphology and rheology. Through a parametric study, we found that the morphological properties of the cytoskeleton are effectively captured by a relatively small number of parameters. The developed model demonstrates how the actin cytoskeleton responds to external force exhibiting power-law rheology, strain-stiffening, and stress relaxation. In the experiments, interactions between actin filaments and actin binding proteins (ABPs) were probed at both molecular and network scales using optical tweezers. Unbinding and unfolding force of ABPs were measured by pulling one of actin filaments in the ABP/F-actin complex. Mechanical deformation of an actin network cross-linked with ABPs under external shear was visualized by confocal microscopy and the network elasticity was characterized by both passive and active methods using optical tweezers. We have also developed a two-dimensional coarse-grained membrane/cortex model with dynamic protein associations for human erythrocytes or other cell types to elucidate the roles of shear stress, specific chemical agents, and thermal fluctuations in cortex remodeling. The human erythrocyte demonstrates extraordinary ability to undergo reversible large deformations and fluidity. Such mechanical responses cannot be consistently rationalized on the basis of fixed connectivity of the spectrin network tethered to the phospholipid membrane. In this study, we have demonstrated a clear solid-to-fluid transition depending on the metabolic energy influx. The solid networks plastic deformation also manifests creep and yield regimes depending on the strain...
rate. This cytoskeletal dynamics model offers a means to resolve long-standing questions regarding the reference state used in red blood cell elasticity theory for determining the equilibrium shape and deformation response.

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**PP1**

A Low-Dimensional, Morphologically Accurate, Quasi-Active Integrate-and-Fire Model

Realistic compartmental models of active neurons yield nonlinear dynamical systems with thousands of equations. We linearize such systems and build their balanced truncations where $B$ permits synaptic input into each compartment and $C$ observes only the soma potential. Using true morphologies with a broad class of synaptic inputs, we find that the full quasi-active somatic dynamics can be approximated to nearly 10 digits by reduced systems of dimension two orders of magnitude smaller.

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**PP1**

Stable Identification of Lamé Parameters in Linear Elasticity

This talk will focus on the problem of identifying Lamé parameters in linear elasticity. This inverse problem has found interesting applications in elasticity imaging (in locating cancerous tissues, and other abnormalities). The main emphasis of the talk will be on a comparison of the numerical efficiency of various methods that can be used to solve the inverse elasticity problem. Adaptive finite element methods will be used.

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**PP1**

Traveling Pulses and Wave Propagation Failure in Inhomogeneous Neural Media

We use averaging and homogenization theory to study traveling pulses in an inhomogeneous neural network.Spatially periodic modulations of homogeneous synaptic connections reduces the speed of the pulse. For large amplitude modulations, the pulse becomes a multibump solution, where individual bumps are nonpropagating and transient, and propagation corresponds to the appearance (disappearance) of bumps at the leading (trailing) edge. Wave propagation failure occurs when bumps cease to form at the leading edge.

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**PP1**

IMAG: A Multi-Scale Approach for Understanding Antigen Presentation in Immunity

The immune system and the process of antigen presentation in particular encompass events that occur at multiple length and time scales. Despite a wealth of information in the biological literature regarding each of these scales, no single representation synthesizing this information into a model of the overall immune response as it depends on antigen presentation is available. In the work supported by this grant, we outline an approach for integrating information over relevant biological and temporal scales to generate such a representation for MHC class II-mediated antigen presentation. In addition, we begin to address how such models can be used to answer questions about mechanisms of infection and new strategies for treatment and vaccines.

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**PP1**

T Cell Differentiation and Aging

We report on the derivation and analysis of a model for tracking the distribution of T cell populations as a function of antigen experience gained through interactions with dendritic cells in lymph nodes during the activation phase of an immune response. This model is motivated by the heterogeneity of specific T cell lineages which have been observed from early stages in an immune response with different characteristics including the capacity to become short lived effector cells or memory cells. Linear reaction-hyperbolic systems of partial differential equations in one space dimension arise in the model formulation similar to models developed for describing axonal transport in nerve cells. We derive a closed form approximate solution for an initial-boundary value problem of such a system. The approximate solution obtained is a translating solution of a heat equation.

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PP1
Stochastic Optimization of the Transition Pathways Between Protein Conformations

Protein structures often reveal distinct conformational states with different functional roles, but the connecting pathways of conformational change have to be explored by computational modeling. We use the trajectory swarm approach to compute the dynamics of protein conformations in discrete intermediate states. Based on these data we perform computational interpolation between the states, and use Markov process machinery to optimize the overall probability of the pathway. The resultant path is compared to the output of the string method for several sample systems.

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PP1
Modeling β Amyloid Clearance in Alzheimer's Disease

Alzheimer's disease (AD) is one of the most prevalent neurodegenerative disorders affecting elderly populations today. The increased concentration of amyloid β protein is thought to be an important contributor to AD pathogenesis. A mathematical model of amyloid β production and clearance both by intracellular and extracellular mechanisms has been developed to study what clearance mechanisms and rate constants may play a role in the pathogenesis of AD and the onset of plaque formation.

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PP1
Global Bifurcations and the Appearance of a One-Dimensional Spiral Wave in Excitable Media

Excitable media can support a “fast” stable traveling pulse, which appears through a saddle-node bifurcation accompanied by a “slow” unstable traveling pulse. Furthermore, the uniform rest state is stable. We provide numerical evidence that, near the saddle-node bifurcation, the threshold between the rest state and fast pulse consists of the stable manifold of the slow pulse. However, further away from the saddle-node bifurcation, the threshold involves an unstable periodic solution sometimes referred to as a 1D spiral wave.

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PP1
Deciphering Cell Migration Mechanics: Novel Approaches to Understanding Chemical Signaling and Morphological Responses During Epithelial Wound Repair

A migrating cell is regulated by a complex network of signaling molecules that act on dynamic mechanical structures known as the cytoskeleton. Utilizing biological and computational tools, we have examined in parallel the activity of signaling molecules with local changes in cytoskeleton dynamics in edge cells undergoing wound repair. By combining high-resolution speckle microscopy with data analysis programs that examine multivariate behavior, we have gained new insights into complex mechanical processes that govern cell motility.

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PP1
IMAG: Multi-Scale Simulation of Gas Flow Distribution in the Human Lung

This poster describes the methodologies and technologies developed for multi-scale simulations of subject-specific pulmonary air flow. Variation in individual airway geometry makes subject-specific models essential for the study of pulmonary air flow and drug delivery. Recent evidence also suggests that early exposure to environmental pollutants has chronic, adverse effects on lung development in children from the age of 10 to 18 years. Thus, the capability of predicting air flow and particle deposition in the subject-specific human lungs is essential in understanding the correlation between structure and function, and for assessing individual differences in vulnerability to airborne pollutants. This project aims to develop a comprehensive computational fluid dynamics (CFD) model for pulmonary 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. This effort brings together expertise in medical imaging, geometric modeling, high-performance computing, and physiology and medicine. The potential applications of the model include optimizing pharmaceutical aerosol drug delivery, advancing xenon or helium enhanced CT/MRI imaging, and predicting subject-specific regional ventilation for diagnosis of patterns related to pathologic changes in airway geometry and parenchyma.

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PP1
Integrating Factor Methods for High Spatial Dimensions

The dominant cost for integration factor (IF) or exponential time differencing (ETD) methods is the repeated vector-matrix multiplications involving exponentials of discretization matrices of differential operators. Although the standard discretization matrices usually are sparse, their exponentials are not, unless the discretization matrices are diagonal. For example, a two-dimensional system of $N \times N$ spatial points, the exponential matrix is of a size $N^2 \times N^2$, and the cost of vector-matrix multiplication is of order $N^4$. The storage and computations associated with such vector-matrix multiplication are usually prohibitive even for moderate size of $N$. In this paper, we introduce
a compact representation of the discretization of the differential operators for the IF and ETD methods in both two and three dimensions. In the approach, both required memory and computational cost are magnitudely reduced for both IF and ETD methods. For the case of the two-dimensional system, the required storage is reduced to an order of $N \times N$, and the computational cost is reduced to an order of $N^3$. The improvement on three-dimensional systems is even more significant. In this paper, we analyze and apply this technique to a class of semi-implicit integration factor method recently developed for stiff reaction-diffusion equations. Direct simulations on test equations along with applications to a morphogen system in two dimensions and an intra-cellular signaling system in three dimensions demonstrate an excellent efficiency of the new approach.

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PP1  
Spike Train Statistics and Dynamics with Synaptic Input from Any Renewal Process

In the population density approach to neural network modeling, a common simplifying assumption is that the arrival times of input events are governed by a Poisson process. This model does not capture temporal correlations in the input. We formally extend these methods to allow inputs from any temporally modulating renewal process. We study how the regularity of the inputs affect the output statistics (i.e., spike rate, interspike interval distribution, autocorrelation, and coefficient of variation). This is work with Dan Tranchina.

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PP1  
The Total Quasi-Steady-State Approximation for the Mitogen-Activated-Protein Kinase Cascade

The total quasi-steady-state approximation (tQSSA) for Michaelis-Menten enzyme kinetics involves a simple change of variable in the conventional QSSA and has the benefit of being valid over a wider parameter range, and more complicated networks of coupled enzymatic reactions have been treated (Ciliberto et al., PLoS Computational Biology, 2007). We generalize the tQSSA to discrete and stochastic models of biochemical kinetics, via the chemical master equation, with application to the mitogen-activated-protein kinase cascade.

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PP1  
Estimating Underlying Biological Dynamics From Sequence Data Using Graph Theoretic Measures of Clonal Trees

Mutating birth-death processes (MBDP) are a fundamental component of biology at many different time scales, ranging from evolution of species, through epidemiological evolution of bacteria and other pathogens, to within-host mutation of viruses such as HIV. A special case is somatic hypermutation of B cells, which is a main focus of this paper. However, the methods that we develop can be applied to many MBDP. Despite the significance of mutating birth-death processes, methods to estimate the underlying parameters from available data are lacking in many cases. We consider systems with constant mutation rate over time and between populations and with discrete generations. The basic biological parameters of the MBDP that we study are the mutation rate, the frequency of lethal mutations, and the rate and type of selection. We use graph theory measures (further denoted as tree shapes) on genetic trees to estimates these parameters. Individual trees typically cannot provide information on the underlying dynamics, because of the significant under-sampling. However, by looking at the collective properties of a set of trees from the same generative process, maximum likelihood methods can be used to compute the most probable set of biological parameters. The ML estimates are based on a comparison between the expected joint distribution of multiple tree shapes based on one numerical simulations or analytical formulae, and the observed tree shapes. We use synthetic data sets to measure the precision of the maximum likelihood estimates for different numbers of trees, and show that our methods work even with realistic amounts of experimental data.

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PP1
Transitions Between Bursting and Spiking in Conditional Respiratory Pacemaker Networks With Excitatory Synaptic Coupling

In mammals, the respiratory rhythm is maintained under a wide range of conditions, depending on age, metabolic demand, and environmental factors. This rhythm is driven by a pacemaker system in the brainstem. Hence, a central question is, how does this pacemaker system generate such robust, adaptable rhythms? In this work, we focus on a component of the respiratory pacemaker system called the pre-Botzinger complex (pBC), a collection of neurons that can exhibit bursts of activity under appropriate conditions and that are coupled with synaptic excitation. We derive a map representation for small model networks of synaptically coupled pBC cells and use this to determine conditions on parameters for the transition between spiking and bursting activity in the network and for the instability of spike synchrony. These results help show how synaptic coupling promotes bursting in a network of conditional oscillators such as may be relevant in driving respiration.

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PP1
A Combined Model for Biofilm Development and Biocorrosion

We propose a combined model investigating the interplay between a growing biofilm on a metallic surface and environmental supported stress corrosion. The biofilm model incorporates both substrate diffusion, bacteria metabolism and biofilm development, making it possible to estimate the pH at the metallic surface. The biocorrosion model is based on strain driven dissolution. The final model iterates between biofilm development that changes the pH at the surface and biocorrosion that changes the geometry of the substratum.

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PP1
Regression and Path Analysis for Wheat Characterizes in Dry Land Condition

In this study, effect of different density (250, 300, 400 and 450 seed per m² and 3 row space: 15, 25, 40 cm) of wheat (Kohdasht cultivar) on some morphological, physiological and biochemical properties in dry land farming by use regression and path analysis evaluated. The experiment was arranged as randomized complete block design. The results of path analysis and regression showed leaf area, stem length, seed per spike, protein accumulation, water-soluble carbohydrates were effected and decreased by increase in density. Multiple regression and path analysis indicated that maximum yield showed in 400 seed per m². The coefficient of correlation between harvest index and density was negative and significant and correlation between root and shoot dry weight was positive. Therefore on basis of this data and compare with normal condition we can conclude this cultivar in dry land farming is sensitive cultivar

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PP1
IMAG: Multi-Scale Modeling of the Mouse Heart: From Genotype to Phenotype

The goal of this project is to develop mechanistic multiscale models that can predict the electromechanical function of the failing heart in genetically engineered mouse models with defects in genes responsible for the regulation of cardiac contraction. We have studied several different mouse models and are currently focusing on mice harboring mutations in MLC2v which render the regulatory light chain of myosin non-phosphorylatable. The multi-scale models span the following scales protein states in the regulatory unit, regulatory network, whole cell, multi-cellular, tissue, whole organ, and circulatory system. This poster will show new results especially in relation to: Markov model of the regulation of thin filament activation and the role of cooperative interactions between adjacent regulatory units; Whole cell systems models of the myocyte excitation contraction coupling; Microstructural modeling of murine ventricular myocardium fiber and sheet architecture; Whole organ continuum modeling of ventricular electromechanics and the influence of regional heterogeneities in protein expression. Much of this work uses the multi-scale modeling package Continuity, developed with support
of a MSM grant from NSF and the National Biomedical Computation Resource, an NIH P41 grant.

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**PP1**  
**Quantitative Inference of Cellular Parameters from Microfluidic Cell Culture Systems**

Measurements in microfluidic cell culture systems can yield quantitative information on cellular biophysical parameters in a more physiological environment. We demonstrate the application of a mathematical nutrient transport model in inferring cellular oxygen uptake rates from the measurements of oxygen concentrations in an oxygen permeable poly(dimethylsiloxane) micro-bioreactor. Our results are significant for the development of novel assays to quantitatively characterize cell response, and for the design, and optimization of efficient in-vitro systems for tissue engineering.

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**PP1**  
**All-Atom Multiscale Analysis (ama) Theory and Application to Virology**

Viruses and other biomanosystems undergo structural processes across multiple time and length scales. We introduce order parameters generated with orthogonal polynomials to capture their slowly-varying nanoscale dynamics and derive a stochastic (Fokker-Planck or Smoluchowski) equation for the order parameters through a multiscale analysis of the N-atom Liouville equation. The AMA theory justifies a Molecular Dynamics/Order Parameter eXtrapolation (MD/OPX) approach for simulating large biomanosystems. It greatly accelerates MD code and is demonstrated on vi-
is a peak in oscillation irregularity (maximal incoherence) for intermediate input currents $I$, with relatively coherent oscillations occurring for small and large currents. An analytic formulation of the system as a stochastic escape problem establishes that the underlying mechanism is distinct from standard forms of coherence resonance. Our results are used to explain recent data concerning variations in the oscillation regularity of the Pre-Bötzinger Complex, which is a population of neurons responsible for generating the mammalian inspiratory breathing rhythm.

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PP1
Exact Solutions in Population Dynamics: Logistic Equation with Periodic Harvesting and a Model from Epidemiology

We transform a logistic equation with periodic harvesting into a classic Mathieu equation. The latter is known to have exact solutions (eigenfunctions) for certain values of parameters. We give explicit expressions for corresponding solutions of the original problem in terms of special functions. We also introduce a new version of the classic Taylor method for nonlinear, non-polynomial ODEs and demonstrate its application to a Kermack McKendric epidemic model. Possible applications of the classic methods to other population dynamics models will be discussed.

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PP1
A General Model for Steroid Receptor-Mediated Gene Expression

Steroid hormones are important in regulating development, differentiation, and homeostasis in a concentration-dependent manner. Experimentally, it has been found that the gene activity (Amax) induced by steroids precisely follows a Michaelis-Menten (MM) curve. The classic explanation was that receptor-steroid binding was the rate-limiting step in steroid receptor-mediated gene expression. However, this was refuted when it was found that various cofactors affected the sensitivity (EC50) as well as the Amax for the same receptor-steroid pair. Considering a mass-action model of transcription that involves the building of increasingly large complexes of transcription factors and associated proteins, we derive the most general form of the equilibrium concentrations and mass-conservation equations that preserve MM kinetics between the steroid concentration and final product. The form dictates that individual reactions in the steps leading to transcription dissociate from downstream reactions, implying that complexes are weakly bound and only exist transiently. The model predicts that there exists a final rate- or concentration-limiting step beyond which the concentration of downstream complexes depends linearly on the concentration of upstream products. The model also predicts that receptor dimerization is not required for steroid gene regulation and suggests that steps both before and after the concentrating-limiting step are crucial in regulating the ultimate amount of gene expression. Applying the model to the cofactor ubiquitin-conjugating enzyme 9 (Ubc9) suggests that at least two catalytic steps are necessary to explain the ability of Ubc9 to modulate gene expression.

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PP1
IMAG: Bifurcation and Self-Organized Cellular Structure and Dynamics: Intercellular Genomics of Subsurface Microbial Colonies

Key steps in the bacterial life cycle are modeled using complementary approaches. A Langevin model is used to discover the forces for chromosome segregation following replication. The dynamics of E. Coli chromosome segregation is simulated with an energy-driven string model. The results demonstrate the possibility of self-organized chromosome segregation that does not involve cytoskeletal guidance or an advanced apparatus in E. Coli. A 3-D reaction-diffusion model is used to uncover dynamical attractors accompanying cell division. Simulated normal and abnormal patterns of intracellular Min protein distribution and consequent cell division irregularities are predicted. The model accounts for Min protein adsorption/desorption at the membrane, reaction and transport along the surface and in the interior of E. Coli. A novel reaction network, involving the role of Min protein dimers and other complexes, is introduced and cast as chemical reactions and associated rate laws. A third model coupling metabolic reactions and the membrane potential is used to predict the properties of bacterial fuel cells and to serve as a computer-aided tool for optimizing current output. Bifurcation theory is used to understand mechanisms of stem cell differentiation/proliferation and cancer using an extensive database of transcriptional, translational, post-translational processes in human cells, and concepts of self-organization and symmetry-breaking instability. Implications for energy, environment and health will be discussed.

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PP1
Mitochondrial Calcium Trafficking: Sequestrator, Excitability, Oscillations, Waves and Untimely Demise

In the study of calcium waves, the endoplasmic reticulum (ER) and its IP3 mediated calcium induced calcium release (CICR) mechanism has dominated the spotlight. However, more than the ER can display this type of excitability. The oft-times overlooked (in regards to signaling) mitochondrial calcium ($\text{Ca}^{2+}$) is a peak in oscillation irregularity (maximal incoherence) for intermediate input currents $I$, with relatively coherent oscillations occurring for small and large currents. An analytic formulation of the system as a stochastic escape problem establishes that the underlying mechanism is distinct from standard forms of coherence resonance. Our results are used to explain recent data concerning variations in the oscillation regularity of the Pre-Bötzinger Complex, which is a population of neurons responsible for generating the mammalian inspiratory breathing rhythm.

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the cytosol, and the mitochondria to include dynamics due to the PTP. Three key components come into play: non-steady state mitochondrial proton concentration, the permeability transition pore, and a weak-acid term that is essential for robust mitochondrial homeostasis. We show that, with these simple additions, the model exhibits mitochondrial CICR (mCICR). Furthermore, we extend the model from a single point to a spatially extended system and find traveling waves of both calcium and potential, as found by Ichas et al. in 1997. In addition, the model also captures the pore “popping” event whereby the pore opens to and remains in a high-conductance state, which ultimately leads to apoptosis (or oncosis) due to calcium cytotoxicity.

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PP1
IMAG: All-atom Multiscale Analysis (AMA) Theory and Application to Virology

Viruses and other bionanosystems undergo structural processes across multiple time and length scales. We introduce order parameters generated with orthogonal polynomials to capture their slowly-varying nanoscale dynamics and derive a stochastic (Fokker-Planck or Smoluchowski) equation for the order parameters through a multiscale analysis of the N-atom Liouville equation. The AMA theory justifies a Molecular Dynamics/Order Parameter eXtrapolation (MD/OPX) approach for simulating large bionanosystems. It greatly accelerates MD code and is demonstrated on viral structural transitions

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PP1
Immune Response to Influenza A

In mammals, Influenza A virus first triggers innate immunity and then adaptive immunity. This project seeks to model the immune response, and identify methods of preventing lung failure and improving recovery. The model expands upon existing models of adaptive immune response, adding an innate immune response; it is then calibrated to a greatly expanded data set. Mathematical techniques explore solutions to the inverse problem and address uncertainties in data in a fully stochastic framework.

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PP1
Bifurcation and Self-Organized Intra-Bacterial Structure

Key steps in the bacterial life cycle are modeled using complementary approaches. A Langevin model is used to discover the arriving forces for chromosome segregation following replication. A 3-D reaction-diffusion model is used to uncover dynamical attractions accompanying the dividing of the division plane. A third model coupling metabolic reactions and the membrane potential is used to predict the properties of bacterial fuel cells and to serve as a computer-aided tool for optimizing current output. Bifurcation theory is used to understand mechanism of stem cell differentiation/proliferation and cancer using an extensive database of transcriptional, translation, post-translational processes in human cells, and concepts of self-organization and symmetry-breaking instability.

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PP1
A Coalescent Theory Analysis of the Population Structure Statistic $F_{st}$

Populations are often divided into subpopulations. $F_{st}$ is a statistic used to experimentally test for population subdivision. We consider a stochastic model of evolution for subdivided populations. We analyze $F_{st}$ under different scaling limits for parameters of this model. We show that the distribution of $F_{st}$ depends on mutation rate. Our results are the first to characterize the distribution of $F_{st}$ and demonstrate its dependence on mutation rate. We use a coalescent approach to derive our results.

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PP1
Nasal Airflow Distribution in Human Subjects

Differences in nasal anatomy among human subjects may
cause significant differences in respiratory airflow patterns and subsequent dosimetry of inhaled gases and particles in the respiratory tract. This study used computational fluid dynamics (CFD) to study inter-individual differences in nasal airflow. Steady-state inspiratory laminar airflow at 15 L/min was calculated using commercial CFD software. Streamline patterns, velocity and helicity were compared.

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PP1
Modelling Isolation Strategy for Controlling Tuberculosis

In the aim to reduce the incidence of the tuberculosis, we develop a mathematical model incorporating isolation of smear positive pulmonary tuberculosis individuals to explore the potential of such intervention to control tuberculosis on global scale. The dynamic of the model is governed by ordinary differential equations; we therefore present the analysis of the disease free equilibrium and the endemic equilibrium and give conditions for local and global stability of these points.

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PP1
Epidemics on Adaptive Networks: The Effects of Seasonal Forcing

During an epidemic, individuals may modify their behavior to avoid exposure to the disease. We consider an SIRS model in which the contact network rewire so that non-infected individuals avoid contact with infectives. In the absence of any periodic forcing, mean field bifurcation analysis reveals a homoclinic orbit. We include a seasonally varying spreading rate and explore the interaction between the intrinsic dynamics and the forcing in both mean field and the full stochastic network.

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PP1
Distinguishing Between Directed and Undirected Cell Motility Within An Invading Cell Population

Cell invasion is central to several biological systems including developmental morphogenesis and disease progression. The details of whether cell motility is directed or undirected within the invasive population of cells cannot be determined using continuum models that focus on population-level data. This is a major impendiment limiting our ability to interpret experimental data. We overcome this difficulty using individual-level data and discrete models. This approach can be used to interpret and design time-lapse experiments.

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PP1
On the Population Dynamics Problem With Child Care

Many species of animals produce a small number of offsprings and take care of them. This phenomenon is natural for many species of mammals and birds and forms the main difference between the behavior of a population taking care of their offspring and that of a population without maternal (or parental) duties. Mammals and birds feed, warm, and defend their young offsprings from enemies. If one of these native duties is not realized, young offsprings die, and the population vanishes. For many species of mammals only females take care of their young offsprings. Some species of mammals and birds care of their offsprings in couples. In last years, to describe the population dynamics with child care some models were proposed and examined [2],[7],[7].

The existence and uniqueness theorem, separable solutions, and the asymptotic behavior of the solution with the initial distribution of the general type to a one-sex age-structured population dynamics model [7] will be discussed taking into account a discrete set of offsprings, their care, and environmental pressure. All individuals have pre-reproductive, reproductive and post-reproductive age intervals. Individuals of pre-reproductive age are divided into young (under maternal care) and juvenile (who can live without maternal care but cannot reproduce offsprings) groups. Individuals of reproductive age are divided into the single and taking child care classes. The model consists of integro-partial differential equations subject to conditions of integral type. The number of these equations depends on the biologically possible maximal newborns number of the same generation produced by an individual. Both non-dispersing and migrating population cases will be considered an numerical results will be exhibited.

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PP1
The Effect of Diffusion on Calcium Oscillations

Ordinary differential equation models are widely used to study IP3-mediated calcium oscillations. There, a cell is taken as a well-mixed compartment, but experiments often show spatial inhomogeneity in intracellular [Ca]. Using a spatially extended model, we study how diffusion affects calcium release. It lowers the [Ca] at a particular release site while increasing the concentration at neighboring sites. Varying the diffusion coefficient can significantly change
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PP1
Optimal Control of the Keller-Segel Chemotaxis Model

This talk proposes and analyzes an optimal control problem associated to the Keller-Segel chemotaxis model which describes the movement of an organism / group of cells toward or away from a chemical or sensory stimulus. The convective part of this convection-diffusion system is of mixed hyperbolic-elliptic type, which may cause severe instabilities when solved by straightforward numerical methods. The optimal solution is obtained by the use of a gradient type algorithm, involving discontinuous Galerkin methods and Runge-Kutta methods for the fully discrete optimality system.

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Imag:

DaplDs:
A Dynamically Adaptive Protein-Ligand Docking System Based on Multi-Scale Modeling

The DAPLDS project, aims to build a computational environment to assist scientists in understanding the atomic details of protein-ligand interactions. High-throughput, protein-ligand docking simulations are performed on a computational environment that deploys a large number of volunteer computers (donated compute cycles) connected to the Internet. The scales proposed in DAPLDS are not the traditional scales currently used in the life sciences. We deal with computational rather than experimental multiscales. Our multi-scale approach comprises three spanning scales (dimensions) of docking assumptions: protein-ligand representation, solvent representation, and sampling strategy. Within a scale, different scale values require different models and different algorithms to represent the models. In such a scenario, the two most critical challenges in dealing with multiple scales computationally are: (1) the ability to model biological systems with algorithms that dynamically adapt to the most appropriate value of each scale and (2) the ability to assure that the algorithms can, indeed, be executed in the required amount of time using large numbers of distributed volunteer computing systems. The latter point refers to having the necessary computational resources (CPU cycles, memory, network, etc.). The nature of these challenges requires collaboration among computational biophysicists, computational scientists, computer scientists, and system architects. These challenges and our main achievements are presented in this poster.

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PP1
Reduction Properties and Synchronization in Lotka-Volterra Systems with Adaptive Competition

A general N-species Lotka-Volterra system is considered for which, in absence of interactions, each species is governed by a logistic equation. Interactions take place in the form of competition, which also includes adaptive abilities through a (short term) memory effect. As a consequence the dynamics of the model is governed by a system of NxN nonlinear ordinary differential equations. The existence of classes of invariant subspaces, related to symmetries, allows the introduction of reduced models, where N appears as a parameter, which give full account of existence and stability for the equilibria. Reduced models are found effective also in describing time-dependent regimes, both in the form of periodic oscillations and chaotic behavior and with remarkable properties of synchronization.

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PP1
Cgmd Simulation Method for the Interaction Between Influenza Ha-Fusion Peptides and a Lipid Bilayer Membrane

Fusion of viral enveloped and cellular membranes is a crucial step for any successful viral infections. We use a Coarse-Grained Molecular Dynamics (CGMD) simulation method to study the interaction between influenza hemagglutinin(HA) fusion peptides and a phospholipid bilayer membrane. With CGMD, we have been able to simulate a relatively large piece of membrane for a sufficiently long time period and with more than one peptide embedded in the membrane, which is necessary for the detail understanding of the fusion process. We obtained the kink-shaped conformation of the peptide with the kink at the...
level of phosphate group, consistent with NMR study. The N-terminal segment of the peptide inserts more deeply into the membrane bilayer, compared to the C-terminal segment. The presence of fusion peptides inside a membrane may cause instability to the bilayer thickness. We also present the effect of the peptide-membrane interaction on other important properties such as helix tilt angle, order parameters for one and multiple peptides.

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PP1
Shape Transformations to Sickling in the Red Cell

We intend to find a transformation that will take the bi-concave shape of the red blood cell and map it into the parabolic-type sickle cell shape. Red blood cells change their shapes due to reorganization of their hemoglobin and usually this shape change is not reversible in sickle cell anemia. We would presume that such a shape change will preserve volume and exhibit no tearing or stretching of the cell wall. This idea has been presented in the classic paper of Y.C.B. Fung and P. Tong concerning the spherical of the normal red blood cell.

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PP1
IMAG: Mapping and Modeling ErbB Receptor Membrane Topography

Our goal is to understand the topographical regulation of ErbB signaling in breast and endometrial cancers, where amplification of ErbB1 (the EGFR) or 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. In work that is now in press, we report on first electron microscopy images mapping distributions of ErbB receptors on SKBR3 breast cancer cell membranes. We found the most abundant receptor, ErbB2, is phosphorylated, clustered and active. Kinase inhibitors ablate ErbB2 phosphorylation without dispersing clusters. Modest coclustering of ErbB2 and EGFR, even after EGF treatment, suggests that both are predominantly involved in homointeractions. This observation, in particular, suggests that previous mathematical models overestimate heterodimerization. We also show some usual topographic distributions for receptors and associated signaling molecules. For example, Heregulin leads to dramatic clusters surrounded by PI 3-kinase. Other docking proteins, Shc and STAT5, respond differently to receptor activation. Levels of Shc at the membrane increase 2-5 fold with EGF while preassociated STAT5 becomes strongly phosphorylated. These data suggest that the distinct topography of receptors and their docking partners modulates signaling activities. We are using several mathematical modeling approaches to evaluate these data and to build predictive models of signal transduction during carcinogenesis and response to therapy. We report on novel use of Markov Random Field modeling to simulate relative locations of receptors and signaling molecules, revealing hidden states or associations. We also report on results using an agent-based, stochastic model designed to simulate receptor diffusion, clustering, dimerization and signal propagation in a spatially realistic manner.

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PP1
A Systematic Model of Bacterial Chemotaxis: from Signal Transduction to Cell Motility in Escherichia Coli

The movement of bacteria in response to environmental changes of specific metabolites and signaling molecules is called bacterial chemotaxis. Chemotaxis in Escherichia coli (E. coli) is a best studied system. The authors will present a systematic model of E. coli chemotaxis that can capture many features of the system and reproduce a full range of experimental data from signaling (high sensitivity, wide dynamic range, excitation, perfect adaptation, and robustness) to motor behavior and cellular motility.

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PP1
A Fluid-Structure Interaction Computation of Cellular Blebbing

Eukaryotic cells are composed of cytoplasm, a cytoskeleton and a plasma membrane. Blebs are protrusions of the membrane formed when the membrane separates from the underlying actin filament network, and is pushed outward by pressure-driven cytoplasm. We present a mathematical model to probe this phenomenon. This model includes the motion of the actin filaments and the membrane (modeled by elasticity equations), the cytoplasm (modeled by the unsteady Stokes equation), and the interactions of these
structures.

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PP1
From Inverse Problems in Mathematical Physiology to Quantitative Differential Diagnoses

BACKGROUND: The improved capacity to acquire quantitative data in a clinical setting has generally failed to improve outcomes in acutely ill patients, suggesting a need for advances in computer supported data interpretation and decision making. Mathematical models as quantitative descriptions of physiological mechanisms could help to improve this situation by augmenting the interpretation of quantitative, patient-specific information, and could eventually be used to improve therapy by predicting future developments and effects of interventions. An obstacle to achieving this aim lies in the fact that realistic mathematical models of pathophysiology are complex and nonlinear, which may prevent the identification of unique parameters and states of the model that best represent available data; that is, the inverse problem of parameter identification is usually ill posed, limiting the usefulness of classical parameter estimation techniques such as nonlinear least squares.

METHODOLOGY/PRINCIPAL FINDINGS: Hypothesizing that the non-uniqueness of the solution to the inverse problem may in fact reflect useful information, we implemented a simplified simulation of a common differential diagnostic process (based on hypotension observed in an acute care setting), using a combination of a mathematical model of the cardiovascular system, a stochastic measurement model, and Bayesian inference techniques to quantify parameter and state uncertainty. We used Monte Carlo integration to generate prior densities for model parameters and states, and we approximated the posterior densities on a uniformly spaced grid. For subsequent inference steps, these were smoothed using standard kernel density estimation techniques. The output of this procedure was a probability density function on the space of model parameters and initial conditions for a particular simulated patient, based on prior population information together with patient-specific clinical observations. We show that even from unimodal, uninformative priors, multi-modal posterior probability density functions arise naturally. The peaks of these densities correspond to clinically relevant differential diagnoses and can, in the simplified simulation setting, be constrained to a single diagnosis by assimilating additional observations from dynamical interventions (e.g., fluid challenge). By modifying parameters of the stochastic measurement model, we also illustrate how several inaccurate observations, while essentially useless on their own, can cumulatively serve to discriminate between possible hypotheses about physiological state, represented by peaks in the posterior densities obtained.

CONCLUSIONS/SIGNIFICANCE: We conclude that the ill-posedness of the inverse problem in quantitative physiology is not merely a technical obstacle, but rather reflects clinical reality and, when addressed adequately in the solution process, provides a novel link between mathematically described physiological knowledge and the clinical concept of differential diagnoses. The discriminatory power of the physical examination performed by a physician, which consists of a number of observations that by themselves are relatively inaccurate, is reflected in the refinement of density functions through accumulated low-accuracy measurements in the proposed theoretical framework. We outline possible steps towards translating this hybrid approach to the bedside, to supplement today’s evidence-based medicine with a quantitatively founded model-based medicine combining dynamical systems with statistical techniques, to integrate mechanistic knowledge with patient-specific and population-level information.

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PP1
Geometric and Analytic Analysis of the Role of the A-Current on the Transient and Long-Term Behavior of a Neuron Receiving Inhibitory Input

The transient potassium (A-) current plays a critical role in determining the post-inhibitory rebound activity phase of neurons receiving rhythmic inhibition. We use geometric dynamics to analyze how the A-current parameters determine the transient behavior of such a neuron. We then derive iterative equations to predict the long term behavior. Our analysis shows that the interaction of the A-current and other intrinsic parameters, such as the h-current, can lead to distinct periodic or chaotic solutions. Support: NSF 0615168 (AB); NIH MH-60605 (FN).

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