IP1
Talk Title TBA - Reed

Abstract not available at time of publication.

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IP2
On Growth and Form: Geometry, Physics and Biology

The diversity of form in living beings led Darwin to state that it is "enough to drive the sanest man mad". How can we describe this variety? How can we predict it? Motivated by biological observations on different scales from molecules to tissues, I will show how a combination of physical experiments, mathematical models and simple computations allow us to begin to unravel the physical basis for morphogenesis.

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IP3
DNA Unknotting and Unlinking

Multiple cellular processes such as replication, recombination, and packing change the topology of DNA. Controlling these changes is key to ensuring stability inside the cell. The cell uses enzymes to simplify DNA topology. In Escherichia coli, DNA unlinking is typically mediated by the type II topoisomerase topoIV. In the absence of topo IV, the site-specific recombination system XerCD mediates sister chromosome unlinking. We here focus on DNA unknotting and unlinking by Xer recombination. We use topological methods, aided by computational tools, to unveil unlinking pathways and study the topological mechanism of action of these enzymes.

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IP4
Computational Physiology and the VPH/Physiome Project

Multi-scale models of organs and organ systems are being developed under the umbrella of the Physiome Project of the International Union of Physiological Sciences (IUPS) and the Virtual Physiological Human (VPH) project funded by the European Commission. These computational physiology models deal with multiple physical processes (coupled tissue mechanics, electrical activity, fluid flow, etc) and multiple spatial and temporal scales. They are intended both to help understand physiological function and to provide a basis for diagnosing and treating pathologies in a clinical setting. A long term goal of the project is to use computational modeling to analyze integrative biological function in terms of underlying structure and molecular mechanisms. It is also establishing web-accessible physiological databases dealing with model-related data at the cell, tissue, organ and organ system levels. This talk will provide an update on the current state of the standards, databases and software being developed to support robust and reproducible multi-scale models for the VPH/Physiome project. These standards include CellML and FieldML for encoding models and BioSignalML for encoding time-varying signal data, together with model repositories and software tools for creating, visualizing and executing the models based on these standards.

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IP5
Talk Title TBA - Taylor

Abstract not available at time of publication.

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IP6
Complex Systems in Health and their Breakdown with Aging and Disease

The output of human physiologic control systems, exemplified by the heartbeat at rest or during modest activity, shows complex dynamics, characterized by fractality, multiscale time irreversibility, nonstationarity and nonlinearity. In contrast, the frailty syndrome, and a wide variety of prevalent disease states, are associated with a loss of complexity. The collapse of complexity may serve as the basis of a new class of dynamical biomarkers, with potential applications to drug safety testing, disease detection and clinical monitoring, Restoration of complexity (incorporating multiscale plasticity and resilience) as a therapeutic goal invites consideration of new treatment modalities. Biologic complexity also poses challenges to those involved in efforts to create and test mathematical models of biologic dynamics in health and disease.

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IP7
Life at Stabilitys Edge: From the Fingertip to Seizure Onset

Mathematical models of bistability arise in discussions of seizure onset, balance control and decision making. In the presence of random perturbations and time delay, the unstable fixed point ('separatrix) that separates basins of attraction can have unexpected effects on dynamics, including transient stabilizations and oscillations not seen when the delay is zero. Thus when trajectories travel sufficiently close to the separatrix, the nervous system becomes vulnerable to the generation of novel dynamical behaviors not seen when the delay is zero. This mechanism may explain phenomena ranging from the increased risk of seizures as sleep stages change to the beneficial effects of vibration on human balance to the indecisiveness in decision making that occurs when athletes choke.

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IP8

Biological and Mathematical Perspectives on the Classification of Bursting Mechanisms

One of the success stories in mathematical physiology has been the classification of mechanisms for bursting oscillations, episodes of active spiking phases alternating with silent phases. This work has produced persuasive models for diverse neurons and endocrine cells. Further, bifurcation analysis has classified these mechanisms as exemplars of a broad family of systems based on the bifurcations that mediate switching between active and silent phases. This approach can, however, combine systems that are actually different. I will discuss classification based on unfolding of normal forms, learning from models of pituitary cells and pancreatic beta cells, as well as the duality of biology and mathematics: models corresponding to different cell types are related evolutionarily and developmentally, and different cell types sample nearby regions of parameter space.

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MS1

Model Reduction and Parameter Identifiability for Biochemical Reaction Networks

Chemical mechanisms for reaction network dynamics involve many highly reactive and short-lived species (intermediates), present in small concentration, in addition to the main reactants and products, present in larger concentration. Quasi-steady-state approximation (QSSA) is often used to eliminate the intermediates and remove the large rate constants that cannot be determined from concentration measurements of the reactants and products. We show that the program usually taught to students for applying the 100 year-old approach of classic QSSA model reduction cannot be carried out in many relevant kinetics problems. We also describe an algorithm that uses Gröbner bases and Galois theory to test a mechanism for solvability, and propose a new strategy for dealing with unsolvable systems, based on rescaling the reactive intermediate species. This is joint work with Casian Pantea and James Rawlings.

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MS1

Computing Linearly Conjugate Chemical Reaction Networks with Minimal Deficiency

Many important properties are known to hold for weakly reversible chemical reaction networks with low deficiency. In particular, the Deficiency Zero and Deficiency One Theorems guarantee strong regularity with regards to the number and stability of positive equilibrium states. In this talk, we propose a mixed-integer linear programming algorithm capable of determining reaction networks with a minimal deficiency which are linearly conjugate to a given network.

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MS1

New Results and Methods for Computing Dynamically Equivalent and Linearly Conjugate Reaction Network Structures

Dynamically equivalent and linearly conjugate reaction networks play a vital role in the realization theory of biochemical reaction networks where the task is to construct a network structure/parametrization with given dynamical properties. In this talk it is shown that the following problems can be solved in polynomial time: 1) deciding whether a dynamically equivalent weakly reversible realization exists, 2) determining a dense (weakly reversible) linearly conjugate realization. Biologically motivated examples illustrate the developed algorithms.

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MS1

Model Reduction and Elimination of Variables in Chemical Reaction Networks

Mathematical simplifications are necessary to study many biological systems. However, it is not clear how properties of simplified models relate to properties of more comprehensive models. In this talk I give a brief overview of techniques to eliminate variables in chemical reaction networks at steady state and how properties are transferable between models. I will end the talk by outlining some potential application areas of elimination procedures in relation to real data.

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MS2

Modelling Root Hair Initiation Via Non-Homogeneous Reaction Diffusion Equations in 1D and 2D

A simple mathematical model is developed of a key cellular-level process in plant morphogenesis, namely the biochemical process wich triggers outgrowth of a hair within a root hair cell of *Arabidopsis*. It involves the dynamics of the small G-proteins known as ROPs which bind to a specific location on the cell membrane, triggering cell wall softening

and subsequent hair growth. A reaction-diffusion model is taking into account where a catalytic effect, on a spatially dependent environment, of the hormone auxin is described. This hormone is experimentally known to play an important role in the location of the hair cell. Local analysis, numerical bifurcation analysis and numerical simulation in 1D and 2D are used to understand the dynamics of location point of the RH formation; moreover, "surviving" of emergent patches is studied via non local analysis.

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MS2

From Cell Polarity to Morphomics

We study pavement cells (PCs) to adress interdependencies between cell and tissue polarity. PCs resemble jigsaw puzzle pieces and interdigitate with neighbouring cells. We mathematically show that uniform activation of small GTPases triggers *intracellular partitioning*, due to mutual inhibition and membrane-cytosol switching. Interplay with auxin allows neighboring cells to coordinate their jigsaw-polarties, coined *indirect cell-cell coupling*. Finally, we use morphomics, which combines *in vivo* cell tracking with novel shape analysis, to understand PC formation dynamics.

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MS2

Crossroads: Interplay Between Modelling and Experiments to Unravel Stem Cell Division in Arabidopsis

Because plant cells cannot migrate, stem cell divisions must be confined to the appropriate spatial context. We investigate tissue-generating stem cell divisions within the Arabidopsis root. Mathematical modeling shows that those divisions are switched on through integration of radial and longitudinal information, determined by SHR and auxin distribution,respectively. Coupling of cell cycle progression to protein degradation resets the circuit, resulting in a 'flip flop' that constrains the cell divisions to the stem cell region.

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MS2

Nonlocal Eigenvalue Problems and the Stability of Localized Biological Patterns in Reaction-Diffusion Systems

In a singularly perturbed limit many reaction-diffusion systems admit solutions in the form of localized pulses. Examples of such systems include a reaction-diffusion model of urban crime, and a generalized Schnakenburg-type system modeling the dynamics of a certain plant protein believed to be responsible for root hair cell formation. We present a unified theoretical framework, based on the study of classes of nonlocal eigenvalue problems, for investigating the stability of quasi-equilibrium patterns of pulses in these systems. The spectral results typically provide an explicit formula for the minimum distance between neighboring pulses below which the pattern becomes unstable. The analytical theory is confirmed by full numerical results.

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MS3

Phenotypic Transition Maps of 3D Breast Acini Obtained by Image-Guided Agent-Based Modeling

We introduce an agent-based model of epithelial cell morphogenesis to explore the complex interplay between apoptosis, proliferation, and polarization. By varying the activity levels of these mechanisms, we derived phenotypic transition maps of normal and aberrant morphogenesis. These maps identify homeostatic ranges and morphologic stability conditions. The agent-based model was parameterized using experimental data. Simulations revealed apoptosis being necessary and sufficient for initiating lumen formation, but cell polarization being the pivotal mechanism for acini sphericity.

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MS3

A Novel, Patient-Specific Physical Pathology Approach for Prediction of Tumor Growth and Chemotherapy Outcome

Clinical outcome prognostication in oncology is a guiding principle in therapeutic choice. A wealth of qualitative empirical evidence links disease progression with tumor morphology, histopathology, invasion, and associatedmolecular phenomena. However, the quantitative contribution of each of the known parameters in this progression remains elusive. Mathematical modeling can provide the capability to quantify the connection between variables governing growth, prognosis, and treatment outcome. By quantifying the link between the tumor boundary morphology and the invasive phenotype, this work provides a quantitative tool for the study of tumor progression and diagnostic/prognostic applications. This establishes a framework for monitoring system perturbation towards development of therapeutic strategies and correlation to clinical outcome for prognosis.

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MS3

Optimizing Radiation Delivery Schedules for Gliomas

We have constructed a mathematical model to study the response of gliomas to radiation therapy. We consider two different cell populations: stem-like (i.e. Nestin +) cells that constitutes a small fraction of the tumor, and progenitor cells which comprise the tumor bulk. The stem-like cells display a larger extent of intrinsic resistance to radiation than the tumor bulk. In response to radiation, a fraction of the surviving progenitor cells revert to the stem like state. Based on these ideas a mathematical model is constructed to investigate the response of the tumor to arbitrary treatment schedules. This is done by combining a linear quadratic model of cell survival after radiation with a delay differential equation model of growth between treatments. We find that the response of the tumor is far more sensitive to the properties of progenitor cells than the properties of the stem like-cells, and identify optimal treatment strategies for a given parameter set via dynamic programming. When comparing the response under the optimal therapy to response under standard treatment, we find that the optimal strategy outperforms standard treatment schedules across a wide range of parameters.

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MS3

Dynamics in the Tissue State-Space: A Computational Environment

Mechanical interactions between cells and tissues are increasingly understood to be important in normal tissue function, with a number of new experimental techniques being developed to more accurately quantify the mechanical interactions of cells with their environment. We will report on a computational methodology to predict cell-tissue mechanics from first principles. We combine (1) projection methods to compute hydrodynamic forces, (2) reference maps for elasticity forces, and (3) Voronoi Implicit Interface methods for multiple cell junctions, to compute a host of biological problems, including mechanical properties of acini, motion of acini on liquid-collagen interfaces, rupture of basement membranes, and hydrodynamic and geometric influences on cellular structural stability.

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MS4

Cardiac Fluid-structure and Electro-mechanical Interaction

The heart is a coupled electro-mechanical system. Although the equations that describe cardiac mechanics and electrophysiology are different, we have developed a unified approach to describing both aspects of heart function. Specifically, we have extended the immersed boundary method for fluid-structure interaction to describe cardiac electrophysiology. This talk will describe this unified approach to fluid-structure and electro-mechanical interaction, which enables us to develop integrative models that couple descriptions of cardiac mechanics, fluid dynamics, and electrophysiology.

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MS4

Blood Flow Simulations in Coronary Artery Aneurysms in Children with Kawasaki Disease

Kawasaki disease (KD) is the leading cause of acquired heart disease in children, and can result in life-threatening coronary artery aneurysms in up to 25% of patients. Though clinical decisions are typically made using anatomy alone, we postulate that hemodynamic data could further risk stratify patients. Anatomic models were constructed from CT data and multiscale simulations were run to obtain hemodynamic parameters of interest. Future work aims to improve long-term management of KD patients.

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MS4

Multi-Scale Modeling of Electromechanics in the Failing Heart

We describe multiscale multiphysics models of coupled electromechanics in heart failure. Model geometry and fiber architecture are obtained using diffusion tensor MRI and discretized using Hermite finite elements. Systems models of signaling, ionic currents, calcium cycling, myofilament activation and crossbridge interactions are solved using operator splitting schemes within PDEs representing impulse propagation and wall stress equilibrium. We use genetically engineered mice to validate models. Patient-specific models are being developed to improve diagnosis and therapy.

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MS4

Electromechanical Pumping in the Embryonic Tubular Heart

Recent advancements in computational fluid dynamics have enabled researchers to efficiently explore problems such as blood flow through the aortic valve that involve moving elastic boundaries immersed in fluids. These advances have also made modeling the interaction between a fluid and an elastic model of an organ that includes some aspects of its physiology feasible. This presentation focuses on the development and implementation of coupled immersed boundary and electromechanical models of the embryonic heart tube.

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MS5

An Overview of Data Analysis in High-throughput High-content Flow Cytometry

The Flow Cytometry: Critical Assessment of Population Identification Methods project is providing the means to assess the current state of the art of automated analysis. Our results indicate that computational methods have reached a level of maturity and accuracy such that they are poised to replace manual gating for routine FCM data analysis. Further evidence of the utility of automated methods comes from their application to real datasets and several examples will be presented.

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MS5

Flowmatch: An Algorithm for Registering Cell Populations From high Throughput Flow Cytometry Data

We describe a hierarchical algorithm, **flowMatch**, that analyzes high throughput flow cytometry data and registers cell populations across samples, and then constructs a template of cell populations to describe each class of samples. **flowmatch** employs combinatorial algorithms and the concept of consistency from multiple sequence alignment. The algorithm successfully identified a phosphorylation shift in naive and memory T cells in human blood samples after stimulation with anti-CD3 monoclonal antibody.

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MS5

Quantitative Flow Cytometry Analysis using Domain Knowledge Constrained Spectral Unmixing

Flow cytometry (FC) measurement which involves acquisition of fluorescence from labels attached to biomarkers is traditionally represented as a linear mixture of pure signals contaminated by Gaussian noise. Herein a more rigorous approach is introduced following a physics-based model in

which the FC measurements are approximated by Poisson or Gamma processes and unmixing is performed using GLM framework. This approach allows recovery of true biomarker concentrations. Simulations and processing of real FC data are demonstrated.

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MS5

Fingerprinting, Pattern Discovery and Mining Flow Cytometry Data

In this talk we will introduce a relatively new method of analyzing flow cytometry (FC) data: Cytometric Fingerprinting (CF). CF provides a means to rapidly analyze high-dimensional, high-content flow cytometry data without investigator and system bias. CF breaks a multivariate distribution into a large number of non-overlapping regions (termed bins) that fully span the space. Given the set of bins, CF assigns each event to a bin, counts the number of events in each bin, and represents the full multivariate distribution for a sample as a flattened vector (called the fingerprint) of the number of events per bin. The multivariate probability distribution functions for multiple samples can be compared using straightforward statistical analysis methods. For example, one can search for bins that are significantly up- (or down-) regulated in one group of samples as compared with another group of samples using methods similar to those now routinely employed for the analysis of gene expression data. Therefore, the use of CF not only enables a datamining approach to the analysis of flow cytometric data, whereby disease- or treatment-related alterations of the multivariate distributions are discovered directly from the data, but also builds a bridge to integrative analysis with other -omics technologies. This stands in contrast to conventional analysis methods that rely on investigator-defined gates, which represent hypotheses of specific regions of multivariate space that might vary due to disease or treatment.

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MS6

The Role of Mutual Inhibition in Binocular Rivalry

Binocular rivalry is a phenomenon that occurs when ambiguous images are presented to each of the eyes. The observer generally perceives just one image at a time, with perceptual switches occurring every few seconds. A natural assumption is that this perceptual mutual exclusivity is achieved via mutual inhibition between populations of neurons that encode for either percept. Theoretical models that incorporate mutual inhibition have been largely successful at capturing experimental features of rivalry, including Levelt's propositions, which characterize perceptual dominance durations as a function of image contrasts. However, basic mutual inhibition models do not fully comply with Levelt's fourth proposition, which states that percepts alternate faster as the stimulus contrasts to both eyes are increased simultaneously. This theory-experiment discrepancy has been taken as evidence against the role of mutual inhibition for binocular rivalry. Here, I will show how various biophysically plausible modifications to mutual inhibition models can resolve this problem.

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MS6

Stochastic and Adaptive Switching in Competitive Neural Network Models of Perceptual Rivalry

Neural substrates of perceptual rivalry are often modeled by two pools of neurons, coupled with mutual inhibition, where dominance switches are induced by adaptation. We examine effects of fluctuations in a competitive neural field version of this paradigm with a finite number of neurons. Switching rates can be approximated with respect to inhibition, system size, and adaptation parameters. Predictions are also made for spatially extended neural fields, where percept dominance is represented as a bump.

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MS6

Explaining the Dynamics of Binocular Rivalry as Inference About Latent Images with Markov Chain Monte Carlo

Why do conflicting image interpretations in binocular rivalry yield stochastically alternating percepts? We argue that the visual system approximates probabilistic inference via Markov chain Monte Carlo (MCMC), yielding multistable mode switching is a direct consequence. We show that many binocular rivalry phenomena, including Gamma-like stochastic switching between interpretations, patchy percepts, fusion, and traveling wave mode transitions can be understood in terms of MCMC sampling over simple graphical models.

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MS6

Neural Field Model of Binocular Rivalry waves

We present a neural field model of binocular rivalry waves in visual cortex consisting of two mutually inhibitory networks. Slow adaptation is incorporated into the model by taking the network connections to exhibit synaptic depression. We derive an analytical expression for the speed of a binocular rivalry wave as a function of various neurophysiological parameters, and show how properties of the wave are consistent with the wave–like propagation of perceptual dominance observed in recent psychophysical experiments. In addition to providing an analytical framework for studying binocular rivalry waves, we show how neural field methods provide insights into the mechanisms

underlying the generation of the waves. In particular, we highlight the important role of slow adaptation in providing a "symmetry breaking mechanism' that allows waves to propagate.

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MS7

Progress and Ongoing Challenges in Protein-Solvent Modeling

This talk will introduce the challenging problem of implicit-solvent models in molecular biophysics, and a brief overview of progress and emerging trends. Recent years have seen exciting advances and I will present the necessary context for a general audience to appreciate the challenges and the contributions made by the speakers in this minisymposium. I will emphasize the need for more mathematical analysis of new models, and in particular the advantages of identifying a common analytical framework. First of all, mathematics provides a meaningful (rigorous) language to test and compare models. Just as importantly, a unified theoretical framework allows experts in high-performance computing (HPC) to develop massively parallel algorithms that are suitable for broad classes of solvent models, rather than just one or two.

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MS7

Multi-scale Modeling of pH Dependent Viral Capsid Dynamics

Viral capids are comprised of multiple copies of a few proteins organized as icosahedral shells. These shells undergo significant changes in shape and size during the virus life cycle as they assemble, mature and ultimately release their genetic material. Often these transformations are dependent on changes in the pH of the environment. One such system, HK97, undergoes changes in shape and size in response to changes in pH and provides a model for such processes in other virus systems. We will describe our efforts to understand the nature of this pH-mediated transition using constant pH molecular dynamics methods combined with multi- scale approaches to explore the physical properties that characterize the capsids ability to respond to its environment. We will discuss recent results aimed to characterize the material properties of vial capsids in terms of elastic moduli for bending and expansion. These will be connected to both elasticity theory and viral shape transitions and recent single molecule AFM measurements of capsid elasticity.

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MS7

Continuum Electrostatics with Ionic Size Effects and Variational Solvation

Electrostatic interactions contribute significantly to the structure, dynamics, and functions of biomolecules in an aqueous solution. Continuum models of electrostatics are efficient descriptions of such interactions. This talk reports the recent progress of studies on two related topics on continuum electrostatics in biomolecular systems. One is the development of a theory and method for electrostatic interactions with ionic size effects. The other is the role of dielectric boundary force in the variational framework of solvation of biomolecules. Both analytical and numerical results are presented to demonstrate the initial success of the theory and method.

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MS7

Structured Continuum Free Energy Calculations

Continuum solvation models are particularly useful to for scanning many, large, complex systems where a full atomic model of the solvent and cosolvent components is too computationally expensive to use. Among the most costly evaluations by simulation are solvation free energy calculations. In this contribution a fast way to calculate electrostatic solvation free energy while retaining much of the accuracy of explicit solvent free energy simulation is given. The basis of our method is to treat the solvent not as a structureless dielectric continuum, but as a structured medium by making use of universal proximal radial distribution functions to reconstruct the solvation shells. Using a deca-alanine peptide as a test case, we compare the use of our theory with free energy simulations and traditional continuum estimates of the electrostatic solvation free energy. The method is rapid and accurate.

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MS8

Switching in Multisite Phosphorylation Networks

Multisite phosphorylation networks are an integral part of mathematical models describing important biochemical processes. Here we study a system consisting of two such networks coupled by transport reactions. First each network is studied in isolation and the multistationarity region is parameterized. Numerical analysis shows that values from this region can lead to bistability. Coupling the networks then allows to study the effect of bistability on the overall system.

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MS8

Preclusion of Switch Behavior in a Large Class of Reaction Networks

I will open the minisymposium with an overview of the

problem of determining whether a reaction network can exhibit switch behavior. I will proceed to discuss a criterion to preclude the existence of multistationarity within any stoichiometric class, based on the injectivity of the species formation rate function. The criterion, which is easily implemented, applies to any network endowed with any kinetics fulfilling certain monotone conditions. The results will be illustrated with examples mainly from gene regulation and cell signaling.

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MS8

An Approach to Multistationarity via Elimination

Structure in the steady state ideal of a mass–action chemical reaction system facilitates the analysis for multistationarity. When the ideal is binomial, by analyzing certain linear inequalities, we can determine if there are multiple steady states. When such a clear structure is missing, there is still some algebraic analysis that can be done. We recover existing results from well–known systems via algebraic elimination. This is joint work with Carsten Conradi, Alicia Dickenstein and Anne Shiu.

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MS8

Steady States of Multisite Phosphorylation Systems

Chemical reaction networks taken with mass-action kinetics are dynamical systems governed by polynomial differential equations that arise in systems biology. This talk concerns the biochemical reaction networks networks that describe the multisite phosphorylation of a protein by a kinase/phosphatase pair in a sequential and distributive mechanism. We focus on the capacity of these systems to exhibit multiple steady states. By using techniques from real algebraic geometry, including real root classification for parametrized systems of polynomials, we extend work of Wang and Sontag (2008).

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MS9

Exploring the Dynamics of Stem Cell Maintenance in the Stem Cell Niche through Models of Inter and Intracellular Feedback Regulation

A fascinating question is what are the mechanisms by which stem cells are maintained within a growing stem cell niche, while being a source of differentiated cells which are required for the development of the organism. Focusing upon the plant Arabidopsis thaliana, I will discuss computational models of gene regulation and intra/intercellular communication in cells acting through a system of feedback loops which provides the current paradigm for the homeostatic maintenance of stem cell numbers.

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MS9

Numerical Bifurcation Analysis of Pattern Formed in a Leaf Growth Model

We examine the pattern formation in transport models of growth hormones in a one dimensional domain. We search for the stationary solutions as a function of the model parameters by using numerical continuation methods and bifurcation analysis. We show results for the model of Smith et al (2006). We identify 2 generic bifurcation scenarios and investigate the difference with other hormone transport models.

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MS9

Recent Developments in VirtualLeaf, a Framework for Cell-based Plant Tissue Simulations

VirtualLeaf is an open-source framework that gives plant modelers the opportunity to develop and study cell-based plant tissue models. It uses straightforward C++ classes to represent relevant biological structures and their mechanical and chemical interactions. This talk gives an overview of the recent developments in VirtualLeaf that aim to provide additional flexibility towards the study of new models and scalability to leverage the power of state-of-the-art numerical solvers for simulation of large-scale systems.

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MS9

Cell-based Modeling of Plant Tissue Growth and

Phytohormone Transport using VirtualLeaf

Abstract not available at time of publication.

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MS10

Hypoxia Inducible Factors Mediate the Inhibition of Cancer by Gm-Csf: A Mathematical Model

Under hypoxia, tumor cells and tumor-associated macrophages produce VEGF that induces angiogenesis. The same macrophages, when treated with GM-CSF, produce sVEGFR-1 that binds with VEGF and inactivates it. The production of VEGF is regulated by hypoxia inducible factor HIF-1α, and the production of sVEGFR-1 is mediated by HIF-2α. We developed a mathematical model based on a system of partial differential equations to present recent experiments , which were conducted to measure the effect of inhibiting tumor growth by GM-CSF treatment in mice with HIF-1α-deficient macrophages or HIF-2α-deficient macrophages. The model can then be used to suggest strategies for inhibiting tumor growth. For example, the model quantifies the extent to which GM-CSF treatment in combination with a small molecule inhibitor that stabilizes HIF-2α will reduce tumor volume and angiogenesis.

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MS10

Temporal Dynamics of Cancer Recurrence

Mutation-induced drug resistance in cancer often causes the failure of therapies and cancer recurrence, despite an initial tumor reduction. The timing of such cancer recurrence is governed by a balance between several factors such as initial tumor size, mutation rates, and growth kinetics of drug-sensitive and resistance cells. To study this phenomenon we characterize the dynamics of escape from extinction of a subcritical branching process, where the establishment of escape mutants can lead to total population growth after the initial decline. We derive uniform in time approximations for the paths of the escape process and its components, in the limit as the initial population size tends to infinity and the mutation rate tends to zero. We use these approximations to characterize the distribution of the 'turnaround time', the time that the total population size switches from subcritical to supercritical. This represents the time at which progression of disease is clinically observed through serial tumor scans or bloodwork (in leukemias). In addition, we characterize the 'crossover time' at which mutant populations first reach threshold frequencies the tumor population. Estimates of crossover times are useful in making informed decisions on the optimal time to switch to another therapy and thus 'target' a different subpopulation of cells within the tumor.

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MS10

Guiding Ovarian Cancer Treatment with Mathematical Modeling

A biochemically motivated model of the treatment of ovarian cancers that accounts for cell cycle arrest and cell death induced by chemotherapy is presented. The actions of carboplatin (a platinum-based drug), and ABT-737 (a small molecule inhibitor of Bcl-2/xL), are simulated in order to investigate the molecular basis of synergy between the two drugs. This information is then used to optimize treatment protocols, and to investigate treatment options targeting the emergence of resistance to carboplatin.

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MS10

Energy Metabolism and Evolution of the Angiogenic Switch in Cancer: Novel Targets for Antiangiogenic Therapy

In cancer, angiogenic clones are vulnerable to "cheater" lineages that shunt energy from angiogenesis to proliferation. Here I show that clone-level selection on angiogenesis also acts on cell energetics, which secondarily drives evolution of the angiogenic switch. Hydrolysis of ATP for angiogenesis can increase total ATP and, secondarily, proliferative potential. This dynamic, coupled with increased vascularization, leads to runaway selection for extreme vascular hypo- or hyperplasia, suggesting potential antiangiogenesis treatment strategies that target energy metabolism.

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MS11

ATP, Adenosine and Coronary Regulation in Ischemia and Hypoxia

Myocardial underperfusion or hypoxia induce release of ATP and adenosine eliciting coronary arteriolar smooth muscle relaxation. With repeated underperfusion the adenosine released diminishes; phosphorylation potential is better maintained. The explanation appears to be down-regulation of AMP hydrolysis, as revealed by a multicellular model including cardiomyocytes, endothelial cells and smooth muscle cells, of mitochondrial energetics, membrane transport and exchange, and receptor activation. Switch-like kinetics are explained by competition for substrate along pathways for adenosine diffusion.

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MS11

Multiscale Blood Flow Regulation Models Incorporating Cellular Function of the Vessel Wall

Determinants of blood flow regulation act at multiple scales across the microvasculature and are known to involve cellular, vessel and vascular network function. However, a single effector integrates these regulatory stimuli: circumferentially oriented vascular smooth muscle (VSM) cells, which contract or relax to constrict or dilate the vessel lumen. Examples of multiscale computational models describing how these stimuli are integrated to determine blood flow regulation at the single vessel and network level will be presented.

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MS11

Modeling Firing of the Baroreceptor Nerves

Understanding the cardiovascular control system is crucial for gaining more insight into the physiology not only for the healthy individuals, but also to detect pathologies. An important contributor to the cardiovascular control is the baroreflex (or baroreceptor reflex), which uses specialized neurons called baroreceptors, that are activated using mechano-sensitive sensors located in the aortic arch and carotid sinuses. These neurons are stimulated by changes in blood pressure and contribute to short-term regulation of vascular efferents including: heart rate, cardiac contractility, and vascular tone. Baroreceptor dynamics have been studied since 1950s. Unfortunately most models are of little or no biological motivation. In this presentation, we will review various mathematical techniques and approaches used in the past to describe baroreceptors. Finally, we propose a new biologically motivated model, which reflects all known static and dynamic properties of the baroreceptors including: saturation, threshold, PED (post-excitatory depression), adaptation and rectification.

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MS11

Theoretical Models for Regulation of Blood Flow in the Microcirculation

Local control of blood flow is achieved by contraction and dilation of smooth muscle in arterioles. In the myogenic response, increased wall tension causes contraction. In the shear-dependent response, increased wall shear stress causes dilation. In metabolic regulation, metabolic status is sensed in capillaries and venules, and information is transmitted upstream along vessel walls. Theoretical models have been used to understand how these mechanisms combine to achieve coordination of blood flow with local tissue needs.

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MS12

A Dynamical Systems Perspective of Cytokine Signaling Responses by Human T Cells

Effective immune responses rely on the recognition of and response to antigens through precise dynamic coordination of cytokines secreted by activated T cells. We employ computational strategies to investigate the temporal and multifunctional evolution of specific cytokine responses that are indicative of a healthy response. Resolving the regulatory networks that govern T cell responses enables the identification of productive cytokine signatures, offering insight toward more effective control of immune function and personalized treatment strategies.

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MS12

Interconnecting biochemical modules: propagation of oscillations as a case study

Synthetic biology is leaving its exploratory stage: artificial biological circuits are becoming more and more complex networks of modules. Unfortunately, molecular devices characterized in isolation may lose their dynamic properties once interconnected. I will illustrate this challenge with a case study: we used an in vitro synthetic clock to drive conformational changes in a molecular nanomachine, called "DNA tweezers". Mathematical models and experiments show that mass conservation introduces undesired interactions that perturb the oscillator trajectories. These disturbances are proportional to the total amount of tweezers "load". To overcome this problem, we used a genetic switch acting as a buffer amplifier, achieving signal propagation, and reducing at the same time the perturbations on the source of signal. Understanding how to design effective interconnections between subsystems is critical to develop scalable synthetic biology.

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MS12

Sparse-grid-based Adaptive Model Predictive Control of HL60 Cellular Differentiation

This work develops a sparse-grid-based adaptive model predictive control strategy to direct HL60 cellular differentiation. Sparse grid sampling and interpolation support a computationally efficient adaptive model predictive control scheme in which multiple data-consistent regions of the model parameter space are identified and used to calculate a control compromise. The algorithm is evaluated *in silico* with structural model mismatch. Furthermore, the controller is evaluated *in vitro* to differentiate HL60 cells in both normal and perturbed environments.

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MS12

Quantification of the Interplay Between Growth and Stress Responses Using Automated Flow Cytometry

Determination of the physiological state of a population of cells that is changes in cell size, growth rate and gene transcription across time, environmental conditions and genetic backgrounds presents challenges in terms of accuracy and throughput. We have developed an automated robotic setup for monitoring of complex phenotypes using flow cytometry. We describe novel strategy that for straightforward measurement of stimulus-response experiments for cell populations and the estimation of transient gene expression and growth dynamics.

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MS13

Emergence of Nonuniform Connectivity in Spiking Neuronal Networks and Dynamical Consequences

We study the dynamics and variability of neuronal networks with clustered connections. Clustering introduces high spike time variability and long timescale firing rate fluctuations due to bistability in the cluster firing rate dynamics. The configuration of high firing rate clusters can be manipulated by a stimulus, thereby reducing firing rate variability.

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MS13

Reliability of Spike Times in Sparsely Connected Networks

If the same sensory stimulus is presented multiple times to a neuronal network, how similar are the spike trains that it evokes? This question of the reproducibility, or reliability, of stimulus-induced spike times has a long history in neuroscience. Here, we study features constraining reliability of spiking networks, where neurons are modeled as phase variables with sparse, random connectivity and balanced excitation and inhibition. We show that a given network can behave reliably or not, depending on attributes of a driving signal perturbing the network dynamics.

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MS13

Asynchronous States between Neural Populations

Correlations are key to how the brain encodes information it receives from the world. We present a deceptively symmetric system of stochastically driven differential equations that model the dynamics of two reciprocally coupled neuronal populations. We show how the cross-correlation between the population responses depends on the density of the inhibitory population, and explore the origins of the zero-correlation state. We show asynchronous states occur only in asymmetrical systems where one population outnumbers the other.

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MS13

A Linear Response Theory of Correlations in Neuronal Networks

I will present recent work utilizing linear response theory which allows for an explicit approximation of cross-correlations in recurrent neuronal networks of integrate-and-fire neurons. The correlations are expressed in terms of the response properties of individual cells and synaptic architecture. Cortical connectivity rules may differ significantly from an Erdős-Rényi description. As an application of the linear response theory, I will show how certain second-order motifs may directly influence average correlation in neuronal networks.

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MS14
On Wilson's Generalized Rivalry Network

Wilson has proposed a neuronal network for generalized rivalry that consist of n attribute columns and m intensity levels for each attribute. We use coupled cell systems theory and symmetry to analyze this network. This talk focuses on the case of rivalry between two learned patterns in the network and shows how the mn-node network can reduce to one of 2 or 3 nodes, depending on whether the patterns have attribute levels in common. The 2-cell reduction is equivalent to recent models of binocular rivalry. Notably, these reductions lead to large recurrent excitation in the reduced network even though the individual nodes in the original network may have none.

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MS14
Organizing Centers for Two Patterns and Preliminary Results for Multiple Patterns

A general class of networks in which rivalry can occur between two patterns can be reduced to a network consisting of either 2 or 3 cells. I will show how much of the behavior of such networks can be understood in terms of a two dimensional system. The cells in the networks are typically modeled by two dimensional ODEs, so this represents a reduction from 4 or 6 dimensions to 2. The dynamics of the planar system is organized by a codimension 2 symmetry-breaking bifurcation known as the Takens-Bodganov bifurcation. The situation for networks supporting more than two patterns is not so nice. I will present some preliminary results and indicate some possible directions for future research.

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MS14
Percept Strength and Reaction Time at the Onset of Bistable Perception

Most theoretical and experimental studies of bistable perception have been focused on its long term dynamics. We consider the transitional stage of bistable perception, right after the introduction of the stimulus for binocular rivalry, ambiguous plaid motion, and bistable depth ordering phenomena. The probability for a particular percept to be the first one to dominate is compared with its probability to dominate during the sustained presentation of the stimulus (percept?s ?strength?), both in experiments and with the simulations of the neuronal competition models. The results of the simulations are consistent with the recent observation that the models must operate within a balance between the noise and adaptation in order to reproduce experimentally observed statistics of bistable perception. Reaction time to a particular percept depends on the percept's strength. The simulations of models with input strength normalization are consistent with experimental results for reaction times.

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MS14
Generalized Rivalry and Neural Decisions

The two eyes normally receive slightly different views of the environment, and the brain uses these differences to compute stereoscopic depth. When the two monocular views are radically different, the brain cannot compute depth, and binocular rivalry ensues. Generalizations of rivalry to 3-4 partially overlapping neural patterns will be discussed, and it will be argued that these provide insight into the neural nature of decisions based on ambiguous data.

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MS15
Multiscale Modeling of Ion-protein Interactions with Density Functional Theory of Liquids

Theories like Poisson-Boltzmann model ions as point charges. However, when ions are near highly-charged binding sites on proteins or inside ion channels, the size of the ions produces first-order effects because the ions concen-

trations are very large. Density Functional Theory (DFT) of electrolytes is a thermodynamically-derived theory that includes the effects of ion size in confining geometries. 1D DFT gives steady-state continuum results with sub-Angstrom resolution in systems up to microns in size.

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MS15

Energetic Variational Approaches: General Diffusion, Stochastic Differential Equations and Optimal Transport

I will discuss Onsager's Maximum Dissipation Principle and its applications in ionic solutions and ion channels. Also, we will look at it relations to generalized diffusion, optimal transport and stochastic integrations.

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MS15

Conjunction of MD and DFT for Rapid Prediction of Solvation Free Energy with Atomic Details

We present an atomistic density functional theory (ADFT) as an alternative to molecular simulation for rapid and accurate computation of solvation free energies in water. The free-energy functional is formulated within the framework of the reference interaction site model (RISM) with a closure that accounts for multi-body correction effects based on the hypothesis of the universality of the bridge functional. With the site-site direct correlation functions of the pure water obtained from molecular simulation and the bridge functional derived from the modified fundamental measurement theory, ADFT enables rapid prediction of the solvation free energies from the atomic density profiles of the solvent molecules around the solute obtained from molecular simulation or from direct free-energy minimization. The new computational procedure is fully compatible with conventional force fields and can be easily integrated with standard simulation packages.

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MS15

Advances in Nonlocal Dielectric Modeling for Protein in Ionic Solvent

The nonlocal dielectric approach can significantly enhance the classic Poisson dielectric model by considering the polarization correlations among water molecules. However, current studies on the approach are mostly restricted to the water solvent, due to modeling and algorithmic complications that arise in the case of ionic solvents. In this talk, one new nonlocal continuum electrostatic model will be presented for protein in ionic solvent, along with the corresponding fast numerical solvers. It will be shown to significantly improve the accuracy of electrostatic potential calculations in comparison to the classic Poisson-Boltzmann equation. This project is a joined work with Prof. L. Ridgway Scott at the University of Chicago. It is supported in part by NSF grant #DMS-0921004.

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MS16

Computational Methods for Stochastic Models Arising in the Biosciences

I will discuss computational methods for the most common stochastic models that arise in the life sciences. I will show how different methods can be developed and analyzed by utilizing different representations for the processes. In particular, I will discuss methods that are orders of magnitude faster than using a straightforward implementation of Gillespie's algorithm, or other common computational techniques. The hour-long mini-tutorial on stochastic simulation will provide a more in-depth introduction to the basic algorithms, whereas this talk will focus on the newer methods.

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MS16

Markov Chain Aggregation, with Application to Protein-protein Interaction

We consider a continuous-time Markov chain (CTMC) whose state space is partitioned into aggregates, and each aggregate is assigned a probability measure. We give a sufficient condition for defining a CTMC over the aggregates, which is an 'exact reduction' of the original one. Moreover, we characterize sufficient conditions for 'de-aggregation', that is, when the measure over the original process can be recovered from that of the aggregated one. We show how the applicability of de-aggregation depends on the initial distribution. Our methods illustrate novel ways of reducing the complexity of stochastic models for biochemical reaction networks, particularly, in connection to protein-protein interaction.

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MS16

Stochastic Reaction-drift-diffusion Methods for Studying the Influence of Subcellular Structure on Biochemical Processes

We will describe our recent work constructing numerical methods for solving stochastic reaction-drift-diffusion models. The methods we develop will then be applied to the study of how volume exclusion due to cellular substructure influences the dynamics of gene regulation and signal transduction. Our detailed three-dimensional simulations will be constructed using several different types of high-resolution imaging of the ultrastructure within mammalian cells.

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MS16

Numerical Methods for Stochastic Bio-chemical Reacting Networks with Multiple Time Scales

Multiscale and stochastic approaches play a crucial role in faithfully capturing the dynamical features and making insightful predictions of cellular reacting systems involving gene expression. Despite their accuracy, the standard stochastic simulation algorithms are necessarily inefficient for most of the realistic problems with a multiscale nature characterized by multiple time scales induced by widely disparate reactions rates. In this talk, I will discuss some recent progress on using asymptotic techniques for probability theory to simplify the complex networks and help to design efficient numerical schemes.

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MS17

Quantitative Analysis of Actin Dynamics during Clathrin-mediated Endocytosis

We used quantitative confocal microscopy to measure the absolute numbers of cytoskeletal proteins assembling and disassembling from the site of clathrin-mediated endocytosis. From these data we built a mathematical model to infer the molecular mechanisms of actin dynamics and to make experimentally testable predictions. The two main results showed that the Arp2/3 complex is more active in vivo than in vitro and ADF/cofilin releases chunks of the actin patches into the cytoplasm.

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MS17

Steady State Patterning and Remodeling Dynamics of Actin Asters

We model cortical actin (CA) as a collection of active contractile polar filaments on a 2D substrate, using a continuum description in the presence of athermal noise. The model exhibits complex phase behaviour including steady states of different arrangements of inward pointing asters, remodelling of asters with a noise dependent lifetime distribution and anomalous concentration fluctuations. The theory is tested in the lab by probing fluorescently labelled membrane molecules that bind to CA.

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MS17

Formation of Regular Actin Bundle Networks Driven by Entropic Forces

Using an experimental bottom-up system we study the formation of confined actin networks by entropic forces. Experiments based on molecular crowding and counterion condensation are complemented by coarse-grained modeling. We find a very general tendency of isotropic, homogeneous filament solutions to aggregate into regular actin bundle networks connected by aster-like centers even in the absence of motor proteins. Additional anisotropies and perturbations further result in drastic changes of the network architecture.

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MS17

Role of the SCAR/WAVE-mediated, Dendritic F-actin Polymerization in the Chemotactic Migration of Amoeboid Cells

We present detailed characterization of the traction stresses phenotypes of the wild-type cells and various mutant cell lines, providing new insights into the role that F-actin polymerization plays in regulating cell substratum interactions and traction stresses required for amoeboid cell motility. We compare the traction stresses exerted by cells lacking theSCAR/WAVE complex proteins PIR121 (pirA-) and SCAR (scrA-) with those of wild-type cells while migrating on flat elastic substrates.

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MS18

Assessing Breast Tumor Aggressiveness Using Histopathology-based Computational Modeling

Tumor microenvironment influences not only tumor development but also delivery and efficacy of anticancer treatments. We present a methodology towards building data-driven computational models of tumor microenvironment influences. Our methodology utilizes systematic mining of the histopathology images across multiple scales at subcellular, cell and cellular-network levels using graph theoretical and classification methods. We demonstrate our approach on a computational model for assessing breast tumor aggressiveness.

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MS18

How Does miR451 (microRNA) Regulate the Proliferation and Migration of Glioblastoma Cells: A Mathematical Model

Glioblastoma is a highly invasive brain tumor with survival rate of less than a year. Cell mechanics in tumor microenvironment plays an important role in the active migration. A thorough understanding of the microenvironment would provide a foundation to generate new strategies in therapeutic drug development. Cancer is a complex, multiscale process, in which genetic mutations occurring at a sub-cellular level manifest themselves as functional changes at the cellular and tissue scale. We developed a mathematical model to better understand the role of miR-451 (microRNA) and cell mechanics in creating different growth/invasion patterns. We analyze intracellular dynamics of miR-451/CAB39/AMPK signaling pathways

and role of these pathways in controlling proliferative and migratory phases of glioblastoma cells in response to fluctuating glucose levels. Cell mechanics plays a key role in predicting correct invasion patterns in response to various glucose levels via this intracellular dynamics. The hybrid model generate several hypotheses for developing therapeutic strategies that need to be experimentally validated in future work.

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MS18

Impact of Improved Intracellular Fluid and Calcification Dynamics on Patient-Calibrated Simulation of Dcis and Comedonecrosis

In recent work, we showed that the rate of ductal carcinoma in situ (DCIS) growth critically depends upon the biomechanics of the necrotic core, which, in turn, varies with short- and long-timescale volume changes in necrotic cells. We now extend the work with improved models of intracellular fluid transport and calcification, and we investigate the impact of these dynamics on virtual pathology and mammography in patient-calibrated simulations, with quantitative validation against clinical data.

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MS18

The Role of Tissue Architecture in Anticancer Drug Penetration and Efficacy

With 90% of drugs failing during the Phase II of clinical trials it seems that the process of drug penetration into the tumor tissue is still not understood. In this talk we address the role of tumor tissue architecture, ECM structure and interstitial fluid flow on the transport and distribution of therapeutic agents. By integrating tumor histopathology images with biophysical properties of therapeutic compounds our computational model can provide explanation for ineffective drug efficacy.

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MS19

Theoretical Models of Blood Flow Autoregulation in Skeletal Muscle and the Retina

The autoregulation of blood flow, the maintenance of relatively constant blood flow despite variations in pressure, is characteristic of many tissue types. Here, a theoretical model is used to analyze the contributions of pressure, shear stress, and metabolic-dependent vasoactive responses to autoregulation in skeletal muscle and retina. Conducted responses are shown to be crucial for autoregulation, and the response to lactate production in small arterioles and capillaries is predicted to be significant in the retina.

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MS19

Control of the Cardiovascular System on the Basis of the Arterial CO2 Concentration.

Optimal control theory has been successfully used in order to determine feedback controls for the reaction of the CVS to a constant ergonometric workload. This approach fails in cases of time varying workloads where the CVS is not approaching a new equilibrium. We present an approach which is based on the fact that for a rather wide range of dynamic regimes the arterial CO_2 partial pressure is kept closely to approximately 40 mmHg.

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MS19

Neural and Cardiovascular Alterations During Changes in Posture: A Dynamic Example of Physiological Regulation

Assumption of the upright posture changes the hydrostatic pressure levels in the body causing displacement of blood volume from the upper to the lower parts. If unopposed, this would lead to a critical drop in cerebral perfusion and hence to loss of consciousness. Baroreceptors sense the

pressure fall and relate the alteration to the cardiovascular brain centres through afferent autonomic nerves. The cardiovascular centres adjust vascular resistance and compliance as well as heart rate and cardiac contractility through the efferent autonomic nerves thus counteracting the acute volume changes. Neuroendocrine signals provide a similar but long term adaptation to the upright posture.

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MS19

Modeling Blood Pressure Dynamics during Head-up Tilt

Physiological realistic models of the controlled cardiovascular system are constructed and validated against clinical data. Special attention is paid to the control of blood pressure, cerebral blood flow velocity, and heart rate during postural challenges. We address patient specific models, including how sensitivity analysis and nonlinear optimization methods can be used to predict patient specific characteristics using experimental data. Finally, we discuss how to use modeling to identify biomarkers.

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MS20

Effective Stochastic Equations and Fluctuations in Neural Networks

Neural networks are high dimensional dynamical systems which are difficult to simulate and analyze and which possess far more degrees of freedom than are experimentally accessible. With the advent of multi-neuron recordings it is of increasing importance to establish a theory of correlations in these high dimensional models. Here we present a general framework for analyzing the fluctuations in neural network models, applicable to both stochastic neurons as well as deterministic neurons in heterogeneous networks.

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MS20

Associative Memory in Bump Attractor Networks

The hippocampus is often thought of as a "Swiss knife" of the brain. While some hippocampal functions, such as spatial navigation, can be performed by "bump attractor" networks, other functions such as associative memory appear to require a different synaptic organization. Can the different functions of the hippocampus coexist on the same recurrent network? I will describe a framework where associative memories can be encoded in a network via perturbations of a bump attractor network.

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MS20

A Model for the Origin and Properties of Flicker-induced Geometric Phosphenes

We present a model for flicker phosphenes, the spontaneous appearance of geometric patterns in the visual field when a subject is exposed to diffuse flickering light. We suggest that the phenomenon results from interaction of cortical lateral inhibition with resonant periodic stimuli. Both the quantitative and qualitative aspects of the patterns change with frequency of stimulation and provide an explanation for these differences.

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MS21

Coarse-graining and Simplification of the Dynamics Seen in Bursting Neurons

A system of bursting neurons often exhibits complex dynamics which consist of multiple states and chaotic behavior. However, in certain applications, the exact details of this dynamics may not be important. For example, the respiratory muscle contracts when it is excited by spiking neurons whether the spiking is chaotic or not (provided the spikes are dense enough). We will discuss ideas, based on Equation Free techniques, to simplify the neural network while maintaining important dynamical features.

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MS21

Analysis of Soft Thresholds and the Consequences for Parameter Estimation in Spiking Dynamics

Recent computational work on the Hodgkin-Huxley model of neural excitability identifies major dynamic features of the changing nullclines in 2D phase plane projections during spike initiation. Such analysis provides a greater understanding of the meaning of the "soft threshold' in voltage and current. Additionally, the measured features of the

nullclines can be used to effectively guide certain parameter estimation tasks using a combination of local gradient information and global sampling.

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MS21

A Dynamical Systems Analysis of a Neuromechanical Locomotor System: Model Reduction and Extensions

In a previously published system, locomotion is modeled by coupling a central pattern generator to a mechanical limb. Activating drive establishes a rhythm, and limb feedback helps control phase switching and stabilization. Using dynamical systems analysis, we elucidate general principles of phase/frequency control in this model and derive a reduced representation that can be studied rigorously. We continue this analysis by considering various model extensions including implementing treadmill forcing and backward walking.

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MS21

Contributions of the Two Negative Feedback Variables in the Hodgkin-Huxley Model

The Hodgkin-Huxley model for action potentials in excitable membrane incorporates two negative feedback variables (n, activation of the outward current and h, inactivation of the inward current). These two variables usually act together to terminate an action potential and, during the interspike interval, relax to allow the next action potential. In this talk, we will describe a measure of the contribution of each variable to terminating the action potential and initiating the next spike.

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MS22

Adapting Computational Protein Design Algorithms to Define the Space of Functional Protein Sequences

Studying mutational effects on protein fitness can help us understand the possible reasons for protein sequence conservation. We present a computational protocol that involves modifying computational protein design algorithms to efficiently search protein sequence and conformational spaces, and an analytical approach in interpreting mutational sensitivity based on energetic and structural data. This allows us to study how mutations influence protein function, focusing on the abilities to properly fold and bind to an appropriate partner.

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MS22

Boundary-Integral Formulations for Fast Solutions of the Poisson-Boltzmann Equation in Ligand Optimization

Abstract not available at time of publication.

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MS22

Understanding the Designability of Proteins with Generalized Models

Abstract not available at time of publication.

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MS23

Connection between Microscopic Stochastic and Macroscopic Nonlinear Diffusion Models of Reversing Bacteria

Periodic reversals in the direction of motion in systems of self-propelled rod-shaped bacteria enable them to effectively resolve traffic jams formed during swarming and maximize the swarming rate of the colony. In this talk, a connection will be described between a microscopic one-dimensional cell-based stochastic model of reversing non overlapping bacteria and a macroscopic nonlinear diffusion equation describing the dynamics of cellular density. Stochastic dynamics averaged over an ensemble will be shown to be in very good agreement with the numerical solutions of the newly derived nonlinear diffusion equation.

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MS23

Stochastic Limits for Molecular Motor-Cargo Complexes

We describe a system of stochastic differential equations

(SDEs) which model the interaction between processive molecular motors, such as kinesin and dynein, and the biomolecular cargo they tow as part of microtubule-based intracellular transport. We show that the classical experimental environment fits within a parameter regime which is qualitatively distinct from conditions one expects to find in living cells. Through an asymptotic analysis of our system of SDEs, we develop a means for applying in vitro observations of the nonlinear response by motors to forces induced on the attached cargo to make analytical predictions for two parameter regimes that have thus far eluded direct experimental observation: 1) highly viscous in vivo transport and 2) dynamics when multiple identical motors are attached to the cargo and microtubule. Time permitting, we will discuss the connections between the stochastic model described and those at the single motor level.

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MS23

Stochastic Limit Cycles for Conductance-Based Neural Models: A Master Equation Approach

In deterministic dynamics, a stable limit cycle is a closed, isolated periodic orbit. Points in its basin of attraction may be disambiguated by their asympototic phase. In stochastic systems with approximately periodic trajectories, asymptotic phase is no longer well defined, because all initial densities typically converge to the same stationary measure. We explore circumstances under which one may nevertheless define a flow-invariant foliation analogous to the "asymptotic phase" of a deterministic system.

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MS23

Noise Induced Stochastic Cell Fate Determination in Engineered Gene Networks

Bistable systems are very common modules in natural biological systems. In this work, well-characterized biological components are used to construct a gene network in S. cerevisiae through mutual inhibition. Mathematical modeling is combined with molecular biology to design and construct the genetic toggle switch. We show that, guided by modeling predictions, we can achieve bistability by tuning the system. At the end, I will illustrate the artificial "cell differentiation", both experimentally and mathematically. This work demonstrates the use of synthetic gene networks to uncover general regulatory mechanisms in natural biological systems.

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MS24

The Nonlinear Dynamics of F-actin at Cell Membranes

Cytoskeletal dynamics are crucially impacted by reciprocal interactions between F-actin and the cell membrane. Membrane-bound agents activate actin polymerization, and F-actin in turn exerts feedback effects on these agents. We explore the effects of such interactions by simulating three-dimensional actin network growth at a cell membrane. We find dynamic behaviors consistent with experimental observations, including spontaneously traveling patches and waves. The relevance of these effects to symmetry-breaking cell polarization will be discussed.

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MS24

Understanding Actomyosin Contractions with Simulations, and Continuum Analysis

Actomyosin contractions are a pulsed gathering of actin filaments and myosin motors in the cortical layer of cells and are responsible for cell shape change and motility. In order to understand the forces generated by these contractions, we used Monte Carlo simulations, and a Kuramoto-type continuum analysis. We found that the principle components affecting the organization of the actomyosin network were myosin contractility and actin polymerization rates.

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MS24

Coupling Actin Flow, Adhesion, and Morphology in a Computational Cell Motility Model

Cell migration is a pervasive process in many biology systems and involves both internal forces and forces between the cell and the substrate. Here we describe a computational model for cell motion that includes a reaction-diffusion model for the actin-myosin machinery and discrete adhesion sites. It integrates the adhesion dynamics with the dynamics of the actin filaments, modeled as a viscous network. The model is able to reproduce recent experimental results using keratocytes.

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MS24

A Model of Excitable Actin Dynamics Underlying Leading Edge Protrusion and Retraction in XTC Cells

We have observed periodic patterns of protrusion and retraction along the leading edge of fully spread XTC cells,

including traveling waves of protrusion. In this talk I will present a phenomenological model of the actin polymerization dynamics that underlie these periodic fluctuations. We apply non-linear reaction-diffusion equations to generate excitable actin dynamics, which are in turn coupled to a mechanical model of the moving cell membrane. We reproduce experimentally observed membrane motions.

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MS25

Multiscale Modeling of Breast Cancer Angiogenesis with Therapeutic Applications

Angiogenesis, the formation of new capillaries from preexisting microvasculature, is required for tumor growth and metastasis. VEGF is a potent modulator of angiogenesis that has been identified as a target in anti-angiogenic cancer therapies. We present results from our computational model of VEGF distribution and interactions at multiple scales of biological organization, explore the regulatory mechanisms underlying the complex process of VEGF-mediated angiogenesis, and investigate the effect of various therapies that target VEGF.

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MS25

Using Mathematical Models to Plan Dendritic Cell Vaccine Strategies

An increasing number of medical researchers have begun to recognize the importance of harnessing a patient's immune system to combat cancer, and there is a wide array of immune therapies currently under investigation. One promising immune therapy is dendritic cell (DC) treatment: the FDA has just approved the first DC vaccine for prostate cancer. Dendritic cell treatment consists of injecting primed DCs into the patient to trigger an improved immune response to an existing tumor. An open question in DC treatment is what impact the choice of injection site has on the efficacy of the therapy. In this mathematical model, we describe the trafficking and interactions of DCs and other immune cells in the body. Data from murine studies of the effect of DC injections are used to calibrate the model. The model allows us to investigate various cancer responses to treatment as DC injection sites and doses are varied.

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MS25

Microtubule Bundling as an Indicator of Cancer Cell Response to Chemotherapy

Inspired by the microtubule bundling observed in circulating tumor cells which are responsive to the taxane-based therapy, we designed a computational model that consists of growing microtubules inside a cell boundary. We studied microtubules behavior in response to the tubulin stabilization under various cytoskeletal and morphological conditions to identify the mechanism of microtubule bundling. Furthermore, it is intended to establish a direct relationship between microtubule reorganization and taxane-based therapy as a diagnostic and prognostic tool.

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MS25

Patient-specific Spatial and Temporal Variation of Treatment Resistance Mechanisms in Radiation Therapy

Glioblastoma is a highly invasive primary brain tumor that has poor prognosis despite aggressive treatment, which almost always includes radiation therapy. A hallmark of these tumors is their diffuse invasion of the surrounding brain. Response to treatment is difficult to quantify, and is intimately linked to baseline growth kinetics. Spatial and temporal variation of hypoxia, a known resistance mechanism to ionizing radiation, impacts response and varies across patients, as shown with a patient-specific mathematical model.

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MS26

Coronary Morphology Quantification for Bifurcating Stent Design

Challenges with treating lesions at coronary bifurcations suggest that stent design should reflect a thorough understanding of bifurcation morphology. We designed a patient-specific image-based workflow that quantifies geometric indices for three left coronary bifurcation sites across a heterogeneous patient data set. Statistical methods were applied to quantify differences in indices between and amongst bifurcation sites and vessels. Results may provide a foundation for bifurcating stent design that helps minimize the growth of coronary lesions.

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MS26

A Mathematical Model for Intimal Thickening

Atherosclerosis is an inflammatory disease of the artery characterized by an expansion of the intima. We present a model of intimal thickening, posed as a free boundary problem. By coupling a boundary value problem for cytokine concentration to an evolution law for the intimal area, we derive a nonlinear differential equation for the vessel radius. We perform a bifurcation analysis and compare model solutions to data from rabbits whose arteries are subject to balloon pullback injury. Our main finding is that chemotaxis in atherosclerosis is about 100 times weaker than in dermal wounds. This cell behavior is indicative of a weak, chronic inflammatory response which is typical in atherosclerosis.

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MS26

Parameter Identification for Atherosclerotic Plaques from its Material Spectrum gained by Intravascular Ultrasound Imaging

An inverse spectral method is developed for recovering a spatially inhomogeneous shear modulus for arterial wall. The study is motivated by a novel use of the intravascular ultrasound technique to image arteries for possible atherosclerotic plaques. Boundary value problems are formulated to reflect the arterial response due to imposed blood pressure and intravascular ultrasound interrogation via an asymptotic construction. Shear modulus is then reconstructed through a nonlinear inverse spectral technique.

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MS26

On the Mechanical Stability of Growing Arteries

Arteries are modeled, within the framework of nonlinear elasticity, as incompressible two-layer cylindrical structures that are residually stressed through differential growth. These structures are loaded by an axial force, internal pressure and have nonlinear, anistropic, hyperelastic response to stresses. Parameters for this model are directly related to experimental observations. The possible role of axial residual stress in regulating stress in arteries and preventing buckling instabilities is investigated. It is shown that axial residual stress lower the critical internal pressure leading to buckling and that a reduction of axial loading may lead to a buckling instability which may eventually lead to arterial tortuosity.

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MS27

Simulating Elastic Filaments with Bend and Twist by the Generalized Immersed Boundary Method

A general version of the immersed boundary (IB) method combined with the unconstrained Kirchhoff rod theory has been developed to study biological fluid mechanics in the filamentous structure such as bacterial flagella and DNA strand. A thin elastic filament (rod) in the Kirchhoff model that resists bending and twisting can be modeled as a "three-dimensional space curve' together with an orthonormal triad (material frame) at each point of the rod. The triad indicates how much the filament bends or twists or shears. This is a well-established theory in the statics and dynamics of thin elastic filaments without fluid. Combining Kirchhoff rod theory with the standard models of viscous incompressible fluids will allow us to study the complicated hydrodynamics of bacterial swimming or DNA supercoiling.

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MS27

Helices, Waves, and Kinks: Geometric Optimization of Prokaryotic and Eukaryotic Flagella

Many microorganisms swim by passing waves along slender flagella. We will discuss polymorphism in bacterial flagella, and show by examination of experimental data and numerical simulation that fluid mechanical forces may have played a role in the evolution of the flagellum. For eukaryotic flagella, we will see how the optimal waveform is degenerate under the most common efficiency measure, and how that solution is regularized when energetic costs of bending and axonemal sliding are considered

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MS27

An Overview of Modeling Thin Filaments in Fluid

In the past forty years, there has been an ever-increasing interest in thin filament dynamics in applications to biology, in particular with regard to the shape, dynamics, or biomaterial parameters, flagellated swimming organisms, and filament growth. In many of these applications, hydrodynamic interactions have been of the utmost importance. We will bring together a diverse group of mathematicians and physicists whose work has included the modeling of thin biological structures coupled to a fluid environment, each having different approaches. This minisymposium will disseminate recent advances and help bridge the gap between disparate perspectives on the modeling of thin filaments in fluids.

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MS27

The Morphology and Motility of the Lyme Disease Spirochete

The mechanisms that determine bacterial shape are in many ways poorly understood. The mechanisms by which flagellated bacteria swim is better understood; however, in the spirochetes, shape and motility are coupled, as the flagella are encased within the periplasmic space and serve both skeletal and motility functions. In addition, many spirochetes are pathogenic and live at least part of their life in the tissue of a host. Presumably, the unique shape and motility of the spirochetes enables them to be such successful and dangerous pathogens. A prime example is the Lyme disease spirochete, Borrelia burgdorferi, which cycles between a tick vector and a mammalian host. For this bacterium, motility is believed to be crucial for navigating into and out of both of these hosts. B. burgdorferi has a striking flat-wave morphology, which is produced by coupling its helical flagella to its rod-shaped cell body. Rotation of these flagella inside the periplasmic space leads to traveling wave undulations that propel the bacterium. Here, I describe a mathematical model that accounts for the creation and maintenance of the flat-wave morphology, and show that this unique shape is in fact a natural consequence of the geometrical and material properties of the components. With this model as a starting point, we can begin to develop a full model for the biophysical mechanisms that allow the bacterium to navigate host tissue. I will describe a number of recent observations of the motility of B. burgdorferi in the tick and the mammal. In an effort to bridge our understanding of in vitro motility with these new observations, we examine quantitatively the motility of Borrelia in gelatin matrices. As Borrelia can bind collagen, swimming through gelatin is vastly different than swimming in standard in vitro assays and closer resembles the behavior of the bacterium in the host.

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MS28

Front Propagation in Stochastic Neural Fields

We analyse the effects of extrinsic multiplicative noise on front propagation in a scalar neural field. Using a separation of time scales, we represent the fluctuating front in terms of a diffusive–like displacement (wandering) of the front position at long time scales, and fluctuations in the front profile at short time scales. One major result is to show that fronts locked to a moving stimulus are much more robust to noise than freely propagating fronts, since the variance in front position saturates in the long time limit rather than increasing linearly with time. Finally, we consider a stochastic neural field that supports a pulled front, and show that the wandering of the front is now subdiffusive.

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MS28

Bifurcations of Smooth and Lurching Waves in a One-dimensional Thalamic Neuronal Network

We consider a two-layer, one-dimensional lattice of neurons; one layer consists of excitatory thalamocortical neurons, while the other is comprised of inhibitory reticular thalamic neurons. Such networks are known to support lurching waves, for which propagation does not appear smooth, but rather progresses in a saltatory fashion; these waves can be characterized by different spatial widths (different numbers of neurons active at the same time). We show that these lurching waves are fixed points of appropriately defined Poincare maps, and follow these fixed points as parameters are varied. In this way we are able to explain observed transitions in behavior, and, in particular, to show how branches with different spatial widths are linked with each other.

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MS28

Observing and Controlling Spatiotemporal Brain Dynamics

The observation of spatiotemporal dynamics from brain can be performed with computational models reflecting the underlying network architecture and dynamics. Furthermore, fusion of experimental measurements from electrical or optical imaging data from active neuronal networks can

be used in such data assimilation paradigms. I will discuss the background for such model-based observation of spatiotemporal dynamics, and demonstrate new calculations on the formal observability of neural field ordinary differential equation models with and without inhibitory neurons.

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MS28

Dynamics of Transitions Between Depth Perception and Binocular Rivalry

When the two eyes are presented with radically different images (eg. horizontal versus vertical lines), the brain cannot compute binocular depth, and binocular rivalry oscillations ensue. This talk will explore the transition between depth perception and rivalry, which has been shown to involve hysteresis. A neural network will be developed to explain this hysteresis, and the role of rivalry circuitry in normal stereoscopic vision will be discussed.

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MS29

When transitions between bursting modes induce network synchrony

We study synchronization of bursting neurons with excitatory and inhibitory connections. Fast inhibition is known to promote pairwise asynchrony in inhibitory bursting networks. We show that the addition of such repulsive inhibition to excitatory networks induces bursting synchrony, in contrast to one's expectations. Through stability and geometrical analysis, we reveal the mechanism underlying this purely synergetic phenomenon and show that it originates from the transition between bursting of different types caused by excitatory-inhibitory synaptic coupling.

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MS29

Torus Canards in the Transitions from Spiking to Bursting

Computational models of neural systems often exhibit complex bifurcation structure in the transition from spiking to bursting. In this talk, we describe how one type of bifurcation - a torus canard explosion - appears in a broad array of well-known computational neuronal models. We consider three different classes of bursting dynamics: sub-Hopf/fold cycle bursting, circle/fold cycle bursting, and fold/fold cycle bursting. The essential features that these models share are multiple time scales leading naturally to decomposition into slow and fast systems, a saddle-node of periodic orbits in the fast system, and a torus bifurcation in the full system. We show that the transition from spiking to bursting in each model system is given by an explosion of torus canards. Based on these examples, as well as on emerging theory, we propose that torus canards are a common dynamic phenomenon separating the regimes of spiking and bursting activity.

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MS29

Isochron Portraits at Transitions between Bursting and Spiking Modes

The two main modes of neuronal behavior – spiking and bursting – are inherently multiple time-scale dynamical phenomena. We have found that the phase response properties of neuronal models also depend heavily on specific characteristics of their fast and slow subsystems which are changing as the neurons move between activity regimes. Computation of isochrons, manifolds of equivalent asymptotic phase, gives a global portrait of a system's intrinsic phase response properties (i.e. for weak and strong perturbations). Here we present isochron portraits for neuronal models in spiking and bursting regimes and in transitional regions between activity modes. In our analysis, we link isochronal curvature, phase response sensitivity, and timescale separation.

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MS29

Dynamics in Models of Individual and Networked Neurons

We performed a thorough bifurcation analysis of elliptic burster models, using a computer-assisted reduction to equationless, one-dimensional Poincare mappings for a voltage interval. We were able to examine in detail the bifurcations of not only stable fixed points but also unstable limit solutions of the system, including periodic, homoclinic and heteroclinic orbits that underlie the complex activity transitions between: tonic spiking and bursting, bursting and mixed-mode oscillations, and finally mixed-mode oscillations and quiescence in the FitzHugh-Nagumo-Rinzel model. We illustrate the wealth of information, qualitative and quantitative, that was derived from the Poincare mappings, for the neuronal models and for similar

(electro)chemical systems. Using such interval mappings we can compute various quantitative characteristics such as topological entropy and kneading invariants for examinations of global bifurcations in the neuron model.

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MS30

Ion Channels: Nanovalves that use Atomic Structures to Control Macroscopic Flows

Simulations of ion channels so far have been unhelpful because they are not calibrated and do not compute biological phenomena. Intermediate scale models like engineering device equations are needed. Such models exist because the survival of life depends on their robustness. The theory of inverse problems is the appropriate mathematics to determine such models and their parameters. This approach has been successful in dealing with complex properties of calcium, sodium, and RyR channels.

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MS30

Energetic Variational Approaches for Ionic Fluids: Diffusion and Transport

I will discuss Onsager's Maximum Dissipation Principle and its applications in ionic solutions and ion channels. Also, we will look at it relations to generalized diffusion, optimal transport and stochastic integrations.

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MS30

Pump-Leak Models of Cell Volume Control and Electrolyte Balance

Abstract not available at time of publication.

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MS30

Binding Kinetics of Proteins with Small-Molecule Ligands and Macromolecular Targets: Influence of Conformational Switch

Abstract not available at time of publication.

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MS31

Some Results on Chemical Reaction Networks without the Assumption of Mass Action

We review some approaches to studying the asymptotic behaviour of chemical reaction networks (CRNs) given only weak assumptions on the chemical kinetics. The classical theory of monotone dynamical systems, along with nontrivial extensions, has proved useful for proving that certain chemical systems have strong convergence properties. Examples of families of CRNs to which such theory can be applied will be presented.

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MS31

Oscillatory Patterns in Cell Signaling Networks

Interactions of complex networks of genes, proteins and enzymes play a central role in modern cellular biology. Since these networks are very complex, it is useful to understand dynamics of important sub-network structure. We will consider the sub-networks known as feedback loops and we will discuss the relation between topology and interesting dynamical features. In particular we discuss necessary conditions for existence of multistability and oscillations.

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MS31

Turing-Hopf Instability in Biochemical Reaction Networks

A biochemical reaction network with any number of species and one moving species is represented by a simple digraph, and is modeled by a reaction-diffusion system with non-mass action kinetics. A novel graph-theoretic condition for potential Turing-Hopf instability that requires the existence of a pair of subnetworks, each containing an even number of positive cycles is obtained. The technique is illustrated with a double-cycle Goodwin type model.

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MS31

Ultrasensitivity for Graded Multisite Activation Networks

Multisite protein modification is widely recognized as an essential feature of many switch-like dose responses. It is usually assumed that cooperativity is involved, i.e. the ability of one modified site to alter the rate of modification of its neighbors. We make a very different set of assumptions to obtain ultrasensitive behavior, namely that the individual sites are identical and independent of each other, and that

the protein activity is an arbitrary increasing function of the number of modified sites. Under these assumptions we provide theoretical estimates of the Hill coefficient of the dose response. Examples are provided along with numerical simulations for biochemical reaction network models of bacterial chemotaxis and the yeast pheromone pathway.

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MS32

Dynamical Systems Tools for the Investigation of Cell Signalling

Computer-assisted studies of cell signalling have greatly benefited from theory and numerical methods for dynamical systems. Conversely, particularly the development of theory and methods for dynamical systems with multiple time scales has been motivated by biological applications. This presentation gives an overview of recent developments showcasing the tools from dynamical systems as well as their use in biological applications.

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MS32

Negative Feedback for Oscillations, Negative Feedback for Robustness

Slow negative feedback both contributes to oscillations and limits their frequency (adaptation). Ermentrout showed that adaptation is expected near a SNIC bifurcation, where the unadapted frequency-current (FI) curve has infinite slope. We show that a SNIC is neither necessary nor sufficient for adaptation; more fundamental is some mechanism to stretch the steep region near threshold. Sufficient adaptive conductance can overcome the steepness of the FI curve whether oscillations begin at SNIC or Hopf bifurcations.

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MS32

Modelling Electrical Activity and Calcium Signalling in Developing Inner Hair Cells

Inner Hair Cells (IHCs) organise sound transduction in mammals, which generates a receptor potential whose amplitude and phase drive auditory nerve firing. I will present a mathematical model of electrical activity and calcium dynamics that reproduces experimentally-observed patterns in immature IHCs, such as spiking and pseudo-plateau bursting electrical activity. A numerical bifurcation analysis reveals the existence of a complex but structured set of periodic attractors with multiple-spike solutions.

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MS32

Effects of Multiple Time Scales in Cell Dynamics

An important feature of most physiological systems is that they evolve on multiple time-scales. It is the interplay of the dynamics on these different scales that creates complicated rhythms and patterns. Geometric singular perturbation theory provides us with tools to understand some of these complex intrinsic patterns known as mixed-mode oscillations via canard theory. In this talk, I will show how canards are also able to explain 'unexpected' transient dynamics observed in some multiple time-scale systems.

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MS33

Signaling Regulated Endocytosis and Exocytosis Lead to Mating Pheromone Concentration Dependent Morphologies in Yeast

Polarized cell morphogenesis requires actin cytoskeleton rearrangement for polarized transport of proteins, organelles and secretory vesicles, which fundamentally underlies cell differentiation and behavior. During yeast mating, S. cerevisiae respond to extracellular pheromone gradients by extending polarized projections, which are likely maintained through vesicle transport to and from the membrane. In this talk, we will present the experimental results which demonstrate that projection morphology is pheromone concentration dependent, and propose underlying mechanism elucidation through mathematical modeling.

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MS33

Changes in Domain Thickness Halt Par Protein Travelling Wave Solutions in a Model of the Early C. Elegans Embryo

Shortly after fertilization, embryos of the nematode worm *Caenorhabditis elegans* polarize by segregating specific components to opposite ends of the cell. The boundary

between these distinct domains is reliably positioned in wild type animals, although the mechanism is not yet understood. We use numerical simulations of a biologically based model and asymptotic solutions to the Allen Cahn equation to show that changes in domain geometry may help to position the boundary between polarized domains.

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MS33

Adaptation in a Eukaryotic Pathway: Combining Experiments with Modeling

Adaptation in signaling systems, during which the output returns to a fixed base-amount following a change in the input, often involves negative feedback loops and plays a crucial role in eukaryotic chemotaxis. In experiments, we determined the dynamical response of a eukaryotic chemotaxis pathway immediately downstream from G protein-coupled receptors following a uniform change in chemoattractant concentration. This response showed near perfect adaptation and we attempted to fit these results using mathematical models for the two possible simple network topologies that can provide perfect adaptation. Only one, the incoherent feedforward network, was able to accurately describe the experimental results. This analysis revealed that adaptation in this Ras pathway is achieved through the proportional activation of upstream components and not through negative feedback loops. Preliminary results which further probe the system will also be presented.

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MS33

The Conflicting Influence of Spatial Stochastic Dynamics on Cell Polarity

In this talk, I will describe our analysis of mathematical models of gradient-induced cell polarization in yeast using spatial stochastic simulations. We found that noise in the gradient input reduced both the extent of polarization (amplification) and the accuracy (tracking). The cell takes advantage of several strategies to filter this noise including slow dynamics, two-stage signaling, and positive feedback. On the other hand, the internal stochastic dynamics of the cell contributed to more robust polarization. Using a model of the yeast polarisome, we demonstrated that stochastic simulations produced superior amplification and tracking than deterministic simulations of the same model. In addition, stochastic dynamics could better describe wild-type and mutant phenotypes.

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MS34

Following Hydrodynamic Signals in Underwater Locomotion

I will discuss underwater motion synchronization in the context of a finite dipole dynamical system. The emphasis in this work is on using a low-order modeling and computational approach and the underlying motivation comes from our efforts to understand the role of fluid-structure interactions in fish locomotion and fish schooling

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MS34

Helical Swimming in Viscoelastic and Porous Media

Many bacteria swim by rotating helical flagella. We study the motility of the flagellum using a model system - a motorized helical coil that rotates along its axial direction. By immersing this model flagellum in a viscoelastic fluid, we reveal in experiments how fluid viscoelasticity affects such swimming motility. Using a modified boundary element method, we also discuss the effect of spatial confinement, such as a porous medium, on helical swimming in a stokes flow.

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MS34

Modeling the Undulatory Swimming of Sperm: Mechanics, Biochemistry, and Hydrodynamics

Sperm are known to exhibit two distinct types of motility. One is characterized by constant amplitude, symmetrical waveforms. The other is characterized by asymmetrical waveforms, which are correlated with an increase in calcium concentration. The goal of this work is to model the undulatory swimming of sperm swimming in a viscous, incompressible fluid using the method of regularized Stokeslets. Varying waveforms will be considered via a preferred curvature function. Results showing emergent waveforms, swimming speeds, and trajectories will be compared to experimental data. Results for hydrodynamic interactions and new research areas will be presented.

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MS34

Locomotion at Low Reynolds Number: Some Theoretical Topics

I will address some theoretical aspects of locomotion at low Reynolds number. First, the hydrodynamic model for

helices in viscous fluids will be explained and applied to the analysis of motility of Spiroplasma bacterium. Second, impact of medium viscoelasticity on the low-Reynolds-number swimming will be explored based on a two-fluid model for polymer solutions. These studies will eventually be useful for understanding the motility of filamentous bacteria in non-Newtonian environments.

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MS35

Patient Specific Subset Selection and Parameter Estimation of an HIV-1 Model with Censored Observations

Mathematical modeling is becoming a more common tool in predicting the dynamics of biological systems. In order to make patient specific assessments, a patient specific model calibration problem must be formulated and solved. In general, these models may have many biologically relevant parameters in varying degrees of identifiability. In this work we consider an ordinary differential equation model for the in-vivo dynamics of an HIV-1 infection, and estimate on a patient specific basis a best estimable set of parameters using subset selection and sensitivity analysis. Additionally, we account for the censored nature of the clinical data with an appropriate statistical framework. In combining the subset selection results with estimates for the censored data we are able to compute estimates for the identifiable parameters for each patient in the dataset.

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MS35

Modeling Patient Response to HIV Using Artificial Neural Networks

Models of HIV infection based on artificial neural networks can capture the nonlinear dynamics of this complicated system without making biological assumptions about poorly understood mechanisms. We use this technique coupled with past patient CD-4 count, CD-8 count, viral load and drug adherence to predict future patient health. The predictive ability of this model will be analyzed under a variety of conditions. In addition we will analyze the most predictive components of the patient data.

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MS35

Mathematical Problems in the Diagnosis and Treatment of Breast Cancer

The problems of detecting, determining the proliferation rate, and the order of drugs to treat breast cancer will be discussed. Electrical Impedance Spectroscopy will be described as an adjunct to mammography for detecting breast cancer. Models to predict the proliferation rate of cancer cells as a function of the number of Her2 genes or receptors will be described. Models explaining why giving Adriamycin before CMF has a significantly better outcome that alternating the drugs will be presented. All the mathematical models will be compared with patient and experimental cell proliferation data.

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MS35

Mathematical Modeling of Cancer Immunotherapy

Immunotherapy, a treatment approach that enhances the body's natural ability to fight cancers, is becoming increasingly prevalent in many multi-stage treatment programs that also include chemotherapy, radiation and surgery. The critical importance of the immune system in combating cancer has been verified clinically, as well as through mathematical models. In this talk, we will discuss both biological and mathematical questions about how a cancer grows, how a cancer interacts with an immune system, and treatment approaches that harness the power of the immune system to slow or even stop cancer progression.

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MS37

Discrepant Predictions Among Models of Cardiac Cells

As mathematical modeling of cardiac cells has become increasingly accepted as a research tool, the number of models of cardiac electrophysiology has increased dramatically. As a result, in many cases multiple models have been created to describe the same species and region of the heart. However, these models, which would be expected to generate similar predictions, often differ significantly. We will discuss the implications of disagreement among models and suggest ways to address this issue.

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MS37

Curve Fitting to Sparse Experimental data: Implications for the Dynamics of Cardiac Electrophysiology Models

Mathematical models and computer simulation have become widely used in the field of cardiac electrophysiology; however, experimental data used in the construction of these models is often sparse or incomplete, leading to mathematically problematic assumptions. Here we investigate the sensitivity of the Ten Tusscher-Panfilov (TP) human ventricular cell model to function definitions chosen by modelers and present results illustrating the sensitivity of the TP model dynamics in both single-cell and tissue simulations.

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MS37

The Statistics of Calcium-mediated Focal Excita-

tions in Cardiac Tissue

In this talk we present a minimal model of calcium mediated focal excitations in cardiac tissue. Using this model we describe the essential features which dictate the timing statistics and morphology of these focal excitations. These results provide precise criteria for the occurrence of focal excitations in cardiac tissue, and will serve as a guide to determine the propensity of calcium-mediated triggered arrhythmias in the heart.

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MS37

Meta-bifurcation Analysis of a Mean-field Model of the Human Cortex

Bifurcation analysis has little use for physiological models, with many parameters in large ranges of admissible values. I will explain how automated bifurcation analysis of many parameter sets identifies robust behaviour. The example is a mean-field model of electrocortical activity. The metabifurcation approach unveils correlations between parameters and the response to anesthetic agent, with implications for monitoring of anesthesia. We consider a local as well as a space dependent model which exhibits various Turing-type bifurcations.

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MS38

Spatially Adaptive Stochastic Numerical Methods for Intrinsic Fluctuations in Reaction-Diffusion Systems

An interesting regime in which to study reaction-diffusion systems is one where the local concentrations of molecular species are large enough to be described by a continuum field while also being small enough that local density fluctuations are significant. For many biological systems such a regime is of particular importance. This includes the study of mechanisms underlying cell signaling, cell polarization, and directed cell motility through detection of shallow concentration gradients. To study these systems we shall formulate models in terms of stochastic partial differential equations that account for intrinsic fluctuations in the concentration fields associated with these processes. To perform investigations and simulations in practice, a number of challenges arise in approximating the solutions of such SPDE's. Further issues arise when considering non-periodic domains with complex geometries which arise naturally in such biological systems. In this talk, we address these issues with new approaches to obtain spatially adaptive numerical discretizations for SPDE's. We also specifically address the issue of how to discretize stochastic terms at coarse-refined interfaces. As an application of the methods we present results for cellular gradient sensing. We also present results for pattern formation phenomena exhibited by reaction-diffusion systems sensitive to local spontaneous fluctuations.

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MS38

Boundary Integral Methods for Biomolecule Diffusion and Association: Challenges and Progress

Boundary-integral equations are well known as an alternative approach for solving partial-differential equations for biomolecular electrostatics and diffusion. Traditionally, however, their appealing theoretical advantages (for instance, only surfaces are discretized rather than a large volume) have been mitigated by serious practical limitations, including speed and the problems of moving surfaces. This talk will highlight recent BIE advances that promise to lift these limitations and create new possibilities for fast, accurate modeling of biomolecular association.

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MS38

Molecular and Subcellular Modeling of Cardiac Troponin C Calcium Handling

We model the molecular basis of diffusion-limited calcium binding to the myofilament protein, Troponin C. Our approach utilizes a molecular surface generated from the Troponin C crystallographic structure and accounts for binding based on a potential of mean force computed from molecular dynamics. We find that a combination of a diffusional and post-encounter descriptions predict an association closer to experimental estimates. Moreover, we explore the effect of alterations in calcium binding by Troponin C on calcium signaling in cardiac ventricular myocytes.

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MS38

Level-set Variational Implicit-Solvent Approach to Biomolecular Interactions

A novel variational approach to the molecular solvation with a continuum solvent is introduced. In this approach, an effective free-energy functional of all possible solute-

solvent interfaces is minimized to determine equilibrium conformations and minimum solvation free energies. The functional consists of volume and surface energies of solutes, solute-solvent dispersive interactions, and electrostatic contributions. Solute molecular mechanics can be coupled with the variational solvation. A robust level-set method is developed to track numerically such equilibrium solute-solvent interfaces. Extensive numerical results with comparison with molecular dynamics simulations demonstrate the success of this new approach in capturing the hydrophobic interaction and drying-and-wetting fluctuation between multiple equilibrium states. These properties are in general difficult to describe by most of the existing implicit-solvent models in which ad hoc solute-solvent interfaces are pre-defined and different parts of the free energy are decoupled. This is joint work with Li-Tien Cheng, Zhongming Wang, Yang Xie, Shenggao Zhou, Piotr Setny, Jianwei Che, Joachim Dzubiella, and J. Andrew McCammon.

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MS39

Uniqueness and Asymptotic Stability of Equilibria in a Reversible, Non-Complex-Balanced Reaction Network

The allosteric ternary complex model is frequently used in pharmacology to represent the interaction of a receptor with two ligands. Tacit conditions on the rate constants result in that equilibria are unique, detailed-balanced and globally asymptotically stable. However, these conditions cannot be verified experimentally or enforced in finite-precision numerical computations, leaving open the possibility that the uniqueness and asymptotic stability of equilibria are not robust features. We describe transformations of the Jacobian matrix of the mass-action species-formation map which lead to the uniqueness of equilibria and the existence of quadratic Lyapunov function, without restrictions on the positive rate constants. The result on the uniqueness of equilibria is quite general, while the requirements for getting the quadratic Lyapunov function are rather stringent and hopefully can be relaxed.

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MS39

Perspectives on the Global Attractor Conjecture

Recent results by Craciun, Nazarov, and Pantea, and by Anderson have introduced some new ideas – like k-variable systems, endotactic networks, and partitioning along a sequence – into the attack on the global attractor conjecture. I will discuss a geometric reformulation of this conjecture. This reformulation clarifies the proof techniques involved in both results, and articulates directions for further progress.

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MS39

Persistence and Global stability in Biochemical Interaction Networks

The Global Attractor Conjecture and the Persistence Conjecture are two of the most important open problems in Chemical Reaction Network Theory and have received a lot of attention in recent years. In this talk I will describe the class of *endotactic* systems, explain its relevance in the context of persistence, and present recent partial results towards proofs of the two conjectures mentioned above. This is joint work with Gheorghe Craciun.

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MS39

Non-persistent Reaction Networks with Regular Dynamics

Consider a closed chemical kinetics system with general rate functions which are increasing in their arguments. A species is called critical if it appears in more than one complex. We show that if either there are no critical species or there is one critical species which appears at most once in each linkage class then every solution approaches an equilibrium point and the concentrations which tend to zero can be determined. Results from monotone flows and compartmental systems are used.

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MS40

Monocyte Innate Immune Response to Vitamin D

Vitamin D circulates in serum mostly bound to vitamin D binding protein (DBP). Cathelicidin (CAMP) induction is an innate immune response of human monocytes dependent on vitamin D. Using in vitro experimental results and reported characteristics of the vitamin D system, a mathematical model was developed to project free vitamin D levels and CAMP induction. Analysis by modeling suggests the impact of DBP genetic variations and the validity of the intracrine mechanism of CAMP induction.

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MS40

Insights Into Cell Membrane Microdomain Organization from Live Cell Single Particle Tracking of the IgE High Affinity Receptor FceRI of Mast Cells

Live cell single particle tracking studies using quantum dot labeled IgE bound to its high-affinity FceRI receptor provide direct evidence for the confinement of receptors within the micrometer scale. Using time series analysis we characterize an excess of short (¡ 70 nm) jumps in data of unstimulated cells suggesting membranes contain submicrometer barriers to receptor movement. After stimulation, receptor mobility decays rapidly to a lower plateau, indicating a further level of receptor confinement including cross-linking.

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MS40

Initiation and Regulation of Mast Cell Signaling through the FceRI Pathway

Mechanisms of signal initiation and regulation from the high affinity IgE receptor (FceRI) remain in question. FceRI subunit phosphorylation and Syk activation dynamics were measured using biochemical methods and FRET respectively, under experimental conditions that modulate levels of Lyn and Fyn kinases. Results are being integrated into a rules-based mathematical model that provides insight into the opposing role of Lyn in receptor phosphorylation and in negative regulatory loops that limit mast cell responses.

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MS40

Modeling Vitamin D Regulation in Monocytes

We derive from elementary interactions and parameters from the literature a model of Cathelicidin (CAMP) activation in monocytes from vitamin D stimulation. We include extracellular and intracellular volumes, binding proteins, enzymes, transcription factors, and the CAMP gene. We predict that extravasion will increase activation of CAMP based on changes in extracellular volume fraction. The model corroborates data showing alteration in enzymatic conversion of vitamin D to an active metabolite shifts CAMP expression levels.

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MS41

A Multi-scale Approach to Spatially Distributed Regulatory Networks

Reaction diffusion networks describing biochemical regulation of cell function are characterized by a high degree of complexity. While established techniques exist for understanding the purely temporal behaviour of these systems, investigation of their spatio-temporal behaviour is considerably more challenging. Ill present a new bifurcation technique capable of mapping parameter spaces of systems involving regulators with substantially different diffusivitys, common where membrane bound and cytosolic components are involved. The primary benefits of this method are: 1) It simultaneously detects both excitable and instability driven dynamics, 2) An approximate system of nonlinear ODEs is analyzed instead of the full system of PDEs, 3) Established bifurcation software such as Auto can be used, 4) It can be applied to highly complex systems involving many interacting regulators. As an example, Ill discuss a polarity system developed in tandem with experimental collaborators describing Rho-GTPase / Phosphoinositide kinetics. I'll discuss the interaction of this system with external stimuli and a strategy for modulating sensitivity and response thresholds.

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MS41

Mathematical Modeling of Tumor Heterogeneity and the Role of HER2 in Breast Cancer Stem Cells

Cancer stem cells (CSCs) have been identified in primary breast cancer tissues and cell lines. The size of CSC population varies a lot among cancer tissues and cell lines but is associated with aggressiveness of breast cancer. In this study, we develop a mathematical model to explore the key factors which control the size of CSC during tumor cell growth both in vitro and in vivo. Our mathematical

model and experimental data suggest that there is a negative feedback mechanism to control the balance between CSC and non-stem cancer cells. We further calculate how feedback sensitivities and robustness can be regulated by different intrinsic and extrinsic factors.

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MS41

A Computational Study of Cell Population Heterogeneity

Bistability (multi-stability) of intracellular regulatory networks are often used to infer the existence of different gene expression states of individual cells. Here, we ask if bistable intracellular dynamics, which may originate from many different feedback regulations, always result in the bimodal dis- tribution of cells during growth? We address this question by investigating three intracellular regulatory motifs that all are capable of producing bistability: autoactivation, cross-activation, and cross-repression. Based on a multi-scale model that integrates intracellular dynamics and cell division along with their stochastic effects, we found that cross-repression can lead to robust bimodal distribution of cells in a population; in contrast, purely active intracellular networks.

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MS41

External Noise Control in Auto-regulated Biological Networks

External noise control in auto-regulated biological networks External noises in signaling usually come from fluctuations in the signal stimulus or environmental changes. It has been proposed how external noises are filtered by slow deterministic downstream feedback reactions in signal transduction pathways. Here we will talk about how the inherent stochasticity in downstream multiscale feedback loops interplays with the external noise to affect the signal precision. Moreover, in a process of pattern formation, where the signal stimulus is distributed in a graded way, we show how the response of the downstream stochastic feedback loops to the external noise changes spatially.

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MS42

Modeling the Role of the Bacterium *Xylella fastidiosa* in the Development of Plant Diseases

The role of biofilms within bacterial infections has been a topic of recent interest due to the prevalence of the biofilm mode of life as well as the inability to fully eliminate the bacteria within the biofilm. Despite multiple diseases causing widespread damage to the citrus, wine, and other fruit industries, there has been little attention paid to modeling the development and progression of these plantal infections. After a brief introduction to biofilms and bacterial infections, a multiphase modeling framework will be used to examine the dynamic behavior of the biological system. Perturbation analysis will be used to determine potential causes and tendencies of patterns discovered within the biofilm.

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MS42

The Influence of Hindered Transport on the Development of Platelet Thrombi Under Flow

Vascular injury triggers two intertwined processes, platelet deposition and coagulation, and can lead to the formation of an intravascular clot (thrombus) that may grow to occlude the vessel. Formation of the thrombus involves complex biochemical, biophysical, and biomechanical interactions that are also dynamic and spatially-distributed, and occur on multiple spatial and temporal scales. We previously developed a spatial-temporal mathematical model of these interactions and looked at the interplay between physical factors (flow, transport to the clot, platelet distribution within the blood) and biochemical ones in determining the growth of the clot. Here we extend this model to include reduction of the advection and diffusion of the coagulation proteins in regions of the clot with high platelet number density. The effect of this reduction, in conjunction with limitations on fluid and platelet transport through dense regions of the clot, can be profound. Our results suggest a possible physical mechanism for limiting thrombus growth.

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MS42

Modeling Hydrodynamic Contributions to Ameboid Cell Motility

Understanding the methods by which cells move is a fundamental problem in modern biology. Recent evidence has shown that the fluid dynamics of cytoplasm can play a vital role in cellular motility. The slime mold Physarum polycephalum provides an excellent model organism for the study of amoeboid motion. In this research, we use both analytic and computational models to investigate intracellular fluid flow in a simple model of Physarum. In both cases, of we are specifically interested in stresses generated by cytoplasmic flow which act in the direction of cellular motility. In our numerical model, the Immersed Boundary Method is used to account for such stresses. We investigate the relationship between contraction waves, flow waves and locomotive forces, and attempt characterize conditions nec-

essary to generate directed motion.

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MS43

Modeling of Hyaluronan Clearance: Application to Estimation of Lymph Flow

The macromolecule hyaluronan (HA) takes part in the regulation of tissue water and protein homeostasis. Lymph flow may be a major pathway of transport of HA. A six-compartment model is presented which describes plasma, interstitial and lymph flow fluid exchange as well as production, transport and degradation of HA. This model is applied to study fluid shifts during orthostatic stress and the stress of ultrafiltration during dialysis. To track fluid volume distribution the rate of lymph flow, difficult to estimate, needs to be quantified. This paper will discuss how HA can provide a marker in estimating this flow.

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MS43

Scalability and Dimension Reduction in Multiscale Models of Physiological Systems

Physiological control systems are associated with a multitude of time and space scales and often involve signaling pathways of considerable combinatorial complexity. This presents major challenges to model development and highlights the need for scalability of models along with reliable model reduction strategies. Here, an automated approach for the development of reduced, scalable models that combines aggregation, time scale separation, and truncation techniques is demonstrated using a multiscale model of the cardiac myocyte.

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MS43

A Spatially Distributed Model of the Inverse Problem of the Energetic of Consciousness

Computational compartmentalized models of brain energy metabolism and cerebral hemodynamics play a big role in advancing our understanding of the coupling between brain activity and energy metabolism, testing hypothesis about metabolic activity in the different compartments , and interpreting functional neuroimaging. The models that have been published in the literature so far are spatially lumped, describing the typical behavior of homogeneous cellular compartments. While many of these models have been adequately validated with in vivo data, for their own nature they are unable to provide any insight about interaction between ensembles of cells in a neighborhood. Moreover, the reduced metabolic pathway adopted by several models pose some limitations when it comes to interpreting phenomena potentially controlled by changes in facilitators availability. In this talk we present a spatially distributed model aiming at better capturing the details of astrocyte-neuron metabolic interactions to gain a deeper knowledge of the roles of neuron and astrocyte in brain metabolism. The modular design of the model allows a progression from simpler to progressively more detailed descriptions of the metabolism in the cellular components, so as to provide a framework for the emergence of important, yet to be discovered metabolic relations. The complex issue of parameter estimation and sensitivity of the model will be addressed within the Bayesian framework.

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MS43

The Impact of Gravity during Head-up Tilt

Upon head-up tilt or sit-to-stand the body changes position involving pooling of blood in the extremities due to impact of gravity. This phenomenon is observed in all upright animals ranging from monkeys to giraffes. The changes in hydrostatic forces lead to changes in upper body blood pressure, which induce regulation of central and peripheral quantities that in turn brings blood pressure back to homeostatic levels. In this talk we will use modeling to address how blood pressure responds to gravitational changes, and discuss how control system may respond following a gravitational change. Results will be shown for humans during head-up tilt and sit-to-stand as well and for giraffes simulating the change in gravity imposed when they lift their head after drinking.

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MS44

Stochastic Neuronal Dynamics on Complex Networks

We consider a class of dynamical systems defined on networks that are of the same type as neuronal dynamics, and we consider families of networks with complex structures on several scales. The coarse-grained dynamics lead to meanfield limits with complicated dynamical structures. All of this can be carefully described, and in some cases, rigorized, using techniques from stochastic analysis, spectral graph theory, and category theory.

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MS44

Reliability and Modular Decompositions of Oscillator Networks

An oscillator network receiving a fluctuating stimulus is *reliable* if repeated presentations of the same stimulus elicits essentially identical responses each time; a network's reliability impacts its ability to encode information. This talk presents an analysis of phase oscillator networks that can be decomposed into modules connected by acyclic graphs. For such networks, I will explain how sources of unreliability can be localized, and address questions concerning downstream propagation of unreliability once it's produced.

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MS44

Synchronous Firing Events in Stochastic Model Neuron Systems

We are interested in the synchronous dynamics of simple pulse-coupled models for neuron dynamics. These time correlations in firing times are seen experimentally. In our model, the size of synchronous firing events depends on the probabilistic dynamics between such events as well as the network structure representing the neuron connections. We presents both analytical results and numerical simulations of these global dynamics.

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MS44

The Structure of Network Activity in the Neocortex

Abstact not available at time of publication.

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MS45

A Model for Myelosuppression and the Influence of Timing in Drug Administration

We investigate possible pharmaceutical interventions using a structured model for the regulation of blood cells taking the form of a system of nonlinear delay differential equations. This model contains multiple time delays to incorporate maturation and lifespan times of the different cell species, together with feedback control mechanisms: some of the delays are therefore state-dependent. Concentrating on the regulation of neutrophils, we analyse equilibrium solutions and their destabilisation by Hopf and secondary bifurcations, giving a dynamical interpretation to neutropenic episodes and obtaining conditions for the simultaneous stability of multiple equilibria. This model is used to represent the effect of current chemotherapeutic regimens on neutrophil levels, emphasizing the influence of scheduling, as well as the remedial use of G-CSF.

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MS45

Pharmacodynamic Models of Delayed Drug Effects

Pharmacodynamics is science that relates the time courses of drug concentrations and pharmacological effects in humans and animals. This talk will be focused on models of biological systems altered by drugs with states that can be considered as pharmacodynamic responses. There have been two approaches of modeling pharmacodynamic delays: one involves a series of transit compartments and another delay times. Examples of applications of both types of models in various therapeutic areas will be provided.

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MS45

What is Pharmacometrics - How Can Modeling Help ?

Modeling and Simulation-based Biopharmaceutical Sciences have become eye-catching in academia, industry and regulatory authorities. This is a natural turning point since the declining productivity in pharmaceutical industry observed in the last decade. Novel tools, including modelling and simulation (M&S) can help reducing the overall cost of drug development by as much as 50%. The importance of mathematics required in this discipline exerts pressure to take immediate actions to make mathematicians real contributors to this evolving field of pharmacometrics.

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MS45

Predicting the Drug Release Kinetics of Matrix Tablets.

Sustained release tablets are used to maintain a consistent concentration drug in the body. One way to form these tablets is to mix a soluble drug, non-soluble polymer and non-active components, and then to compress the mixture at high pressure and temperature. The pressure and heat

cause the polymer particles to fuse, creating barriers that slow the dissolution and diffusion of the drug out of the tablet. The challenge is to predict the release kinetics of the drug from the polymer/excipient matrix tablet. In this talk we present several mathematical models that can be used to describe the release kinetics: a random walk model, a continuous model, and a hybrid cellular automaton model. The predictions of all three models show good qualitative agreement with experimental release curves, and simulated tablets could provide tools for designing better controlled release devices.

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MS46

Rigorous Relationship between Two Stochastic-reaction Diffusion Models for the Time Required to First Find a Binding Site

We compare two reduced models for a protein diffusing to a stationary binding site. The first model is a Smoluchowski diffusion limited reaction and the second is the so called Doi λ-ρ model -where λ is the binding rate and ρ is the radius of the binding region. Both models are described by partial differential equations for the probability density the molecule is at a specific point in space at a given time. The question we ask is how the two models are related as the binding parameter in the Doi model is varied. In particular, we study the limit of the Doi model for large binding rate and in what sense the Doi model can be interpreted as an approximation of the Smoluchowski model.

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MS46

Solution of the Effective Fokker-Planck Equation for High Dimensional Chemical Systems

When modelling biochemical reactions within cells, it is vitally important to take into account the effect of intrinsic noise in the system, due to the small copy numbers of some of the chemical species. Deterministic systems can give vastly different types of behaviour for the same parameter sets of reaction rates as their stochastic analogues, giving us an incorrect view of the bifurcation behaviour. The stochastic description of this problem gives rise to a multi-dimensional Markov jump process, which can be approximated by a system of stochastic differential equations. Long-time behaviour of the process can be better understood by looking at the steady-state solution of the corresponding Fokker-Planck equation. In this talk we consider a new finite element method which uses simulated trajectories of the Markov-jump process to inform the choice of mesh in order to approximate this invariant distribution for systems of 3 chemical species. We will also briefly outline how this method can be used in conjunction with appropriate multiscale methods in order to approximate the invariant distribution of up to 3 slow species for much higher dimensional systems.

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MS46

Modeling Intrinsic Noise in Gene Expression Circuits

The fundamental processes involved in gene expression are inherently random. This intrinsic stochasticity can give rise to phenotypic heterogeneity even if the cells in a population are genetically identical. Correspondingly, there is considerable interest in understanding how different cellular regulatory mechanisms impact the stochasticity or 'noise' in gene expression. Of particular interest are mechanisms involving small RNAs, which are often central elements of global regulatory pathways. In this talk, I will discuss stochastic modeling approaches for gene expression circuits. Using different analytical tools (e.g. queueing theory and variational approaches) in combination with stochastic simulations, we analyze the effects of regulatory mechanisms on the intrinsic noise in gene expression. The derived results also suggest novel experimental applications, validated by stochastic simulations, for inferring gene expression parameters using regulation by small RNAs.

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MS46

Isolating Intrinsic Noise Sources in a Stochastic Genetic Switch

The stochastic mutual repressor model is analysed using perturbation methods. This simple model of a gene circuit consists of two genes and three promotor states. Either of the two protein products can dimerize, forming a repressor molecule that binds to the promotor of the other gene. When the repressor is bound to a promotor, the corresponding gene is not transcribed and no protein is produced. Either one of the promotors can be repressed at any given time or both can be unrepressed, leaving three possible promotor states. This model is analysed in its bistable regime in which the deterministic limit exhibits two stable fixed points and an unstable saddle, and the case of small noise is considered. On small time scales, the stochastic process fluctuates near one of the stable fixed points, and on large time scales, a metastable transition can occur, where fluctuations drive the system past the unstable saddle to the other stable fixed point. To explore how different intrinsic noise sources affect these transitions, fluctuations in protein production and degradation are eliminated, leaving fluctuations in the promotor state as the only source of noise in the system. The process without protein noise is then compared to the process with weak protein noise, using perturbation methods and Monte-Carlo simulations. It is found that some significant differences in the random process emerge when the intrinsic noise source is removed.

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MS47

Modeling Cancer Progression Due to Somatic Evolution

During progression, tumor cells begin to reproduce inappropriately, acquire nutrients and oxygen, evade the host immune system, remodel their environment, invade surrounding tissues and recapitulate their organization via metastases. Progression results from somatic evolution due to rapid mutation and strong selection. Simulations show that nutrient limitation promotes invasiveness. Weak immune clearance promotes metastasis, while strong immune clearance prevents secondary tumors and can produce spontaneous remission. Improved understanding of cancer evolution may suggest more effective therapies.

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MS47

Modeling Collective Cell Migration: Wound Healing and Cancer Metastasis

We do modeling for collective migration of epithelial cells. Individual crawling cells on 2D substrate are represented by dipole-stress with their polarity in continuum. Cell-cell and cell-substrate interactions are realized by visco-elastic relaxation and viscous drag forces, respectively. This framework is applied to the mechanisms of wound healing and cancer metastasis. We show that the wound closure is essentially mechanical and the integrin up-regulation and cadherin down-regulation are sufficient for the metastatic transition in cancer.

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MS47

Effect of Stretch-dependent Proliferation on Collective Cell Migration

Necrotizing enterocolitis is an intestinal inflammatory disease that is a major cause of death in premature infants. A recently developed mathematical model of cell layer migration during experimental necrotizing enterocolitis based on an assumption of elastic deformation of the cell layer leads to a generalized Stefan problem. Analysis and numerical results indicate that a large class of constitutive equations for the dependence of proliferation on stretch leads to traveling wave solutions with constant wave speed.

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MS47

Multiscale Modeling of Bacterial Chemotaxis

Bacteria such as E. coli can respond to a self-produced chemoattractant and self-organize into population patterns including aggregates, networks, radial and spiral streams. To explain these patterns I will present a hybrid model that incorporates a cell-based description of signal transduction and cell movement, and a continuum description of the extracellular attractant. The model predicts that the formation of aggregates and radial streams results from modulation of the local attractant concentration by the cells, and spiral streams from a swimming bias of the cells near the surface of the substrate. I will also present the continuum limits of the hybrid model under different signal regimes.

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MS48

Using Computer Simulation Combined with Experimentation to Explore Notch Dynamics During Angiogenesis

Abstract not available at time of publication.

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MS48

Vascular Patterning by Matrix-Mediated Paracrine Signalling

During embryonic vasculogenesis, the earliest mechanism of blood vessel morphogenesis, isolated vascular cell progenitors called angioblasts assemble into a characteristic network pattern. So far, however, the mechanisms underlying the coalescence and patterning of angioblasts remain unclear. In this talk I will present a hybrid cell-based /continuous model relying on realistic biological assumptions. The model is used to study the dynamics of network formation as well as the role of cell shape and cell density in this process. I will conclude by discussing some experimental validation efforts carried out so far as well as other related studies still in progress.

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MS48

Cell Behavior Patterns During Neurovascular Formation: A Rule-Oriented Modeling Study

We present a strategy to characterize patterns in human cell responses to stimulation by angiogenic and neurotrophic growth factors. We introduce a Rules-as-Agents mathematical framework that allows rapid comparison of cell behavior hypotheses to experiments. This is coupled to a hybrid state machine representation of cells, whose properties are explored by a search algorithm. Results show the interaction of tip and stalk endothelial cells, and predict how cell behaviors integrate to form 3D capillary struc-

tures.

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MS48

A Viscoelastic Model of Blood Capillary Extension and Regression: Derivation, Analysis, and Simulation

This work studies a fundamental problem in blood capillary growth: how the cell proliferation or death induces the stress response and the capillary extension or regression. We develop a one-dimensional viscoelastic model of blood capillary extension/regression under nonlinear friction with surroundings, analyze its solution properties, and simulate various growth patterns in angiogenesis. The mathematical model treats the cell density as the growth pressure eliciting a viscoelastic response from the cells, which again induces extension or regression of the capillary. Nonlinear analysis provides some conditions to guarantee the global existence of biologically meaningful solutions, while linear analysis and numerical simulations predict global biological solutions exist provided the change in cell density is sufficiently slow in time. Examples with blow-ups are captured by numerical approximations and the global solutions are recovered by slow growth processes. Numerical simulations demonstrate this model can reproduce angiogenesis experiments under several biological conditions including blood vessel extension without proliferation and blood vessel regression.

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MS49

Fluid Dynamics and Bacterial Disinfection

Bacterial bio?lms are widely acknowledged to be sources of recalcitrant infections and colonization in a variety of medical, environmental and industrial settings. This recalcitrance is evidenced by recurrence of the infection, even after extremely long application of biocides or antibiotics. Explanations for this tolerance include physical protection of the bacteria by the surrounding extracellular matrix, physiological protection arising from nutrient gradients formed by the spatial distribution of the bacteria within the bio?lm and the existence of specialized phenotypes of bacteria that forgo reproduction in order to evade the antimicrobial agent. This talk will focus on the analysis of recent models that incorporate all of these tol- erance mechanisms into a model of bio?lm dynamics. In particular, we will focus on the a?ect of the external ?ow environment on the disinfection process. The contrast between dynamics within free channels and partially blocked channels indicates that the spatial environment plays a much stronger role than has been previously thought.

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MS49

A Langrangian Technique for Modeling Moving Structures in a Viscoelastic Fluid

A common set of viscoelastic fluids are polymer solutions composed of long chain molecules in a viscous solvent, often modeled by the Oldroyd-B constitutive equation. I consider the case in which fluid inertia is negligible, and present a regularized Lagrangian formulation of the Stokes-Oldroyd-B equations. This is a novel numerical technique that is ideal for modeling immersed interfaces.

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MS49

The Motility Analysis of the Lyme Disease Spirochete through Viscous Fluids

Borrelia burgdorferi exists in an enzootic cycle involving the transmission between arthropod vectors, Ixodes scapularis, and mammalian reservoirs. While either escaping from or disseminating within the host, the spirochetes will encounter both visco-elastic networks of complex polymers and diverse viscous fluids. The in vitro behavior of *Borrelia* in gelatin matrices (2-5%) resembles the pathogens movements in the chronically infected mouse. Ficoll solutions (0-30%) are used to probe the speed-torque relationship of borrelial flagellum and motors.

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MS49

Computational Explorations of Cellular Blebbing

Blebbing occurs when the cytoskeleton detaches from the cell membrane, resulting in the pressure-driven flow of cytosol towards the area of detachment and the local expansion of the cell membrane. Recent interest has focused on cells that use blebbing for migrating through three dimensional fibrous matrices. In particular, metastatic cancer cells have been shown to use blebs for motility. A dynamic computational model of the cell is presented that includes mechanics of and the interactions between the intracellular fluid, the actin cortex, the cell membrane, and the cytoskeleton. The computational model is used to explore the relative roles of cytoplasmic viscosity, intracellular drag, and cytoplasmic elasticity on bleb expansion dynamics. The model is also used to investigate outstanding hypotheses on intracellular pressure propagation.

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MS50

Optimal Control of Treatments and Prevention in a Two Strain Malaria-HIV/AIDS Co-infection Model

Abstract not available at time of publication.

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MS50

Bistability and Long-term Cure in a Within-host Model of Hepatitis C

Existing within-host mathematical models for Hepatitis C viral (HCV) infection generally predicts (unrealistic) rebound after cessation of treatment. A standard model for HCV can exhibit bistability (backward bifurcation) under biologically relevant conditions; this allows the model to predict a permanent cure even after treatment stops. The model is parameterized to generate all the clinically observed patient profiles. Under bistability, the model can be used to estimate the efficacy and/or duration of treatment ensuring permanent cure.

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MS50

Impact of Malaria Control on the Competition between *Plasmodium falciparum* and *Plasmodium vivax*

The malaria parasites *Plasmodium falciparum* and *Plasmodium vivax* have overlapping spatial distributions, creating substantial challenges for malaria control. We developed a mathematical model describing the dynamics of *P. vivax* and *P. falciparum* in the human and mosquito populations and fit this model to clinical case data to understand how improving control measures in a region affects the competition between the two *Plasmodium* species.

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MS50

Seasonality in Avian Influenza H5N1

Highly pathogenic avian influenza (HPAI) of subtype H5N1 has been infecting humans since its first appearance in 1997. The number of human cases exhibits seasonality, which peaks in the winter months. In this research, we study what causes seasonality in the H5N1 human cases. We propose three potential drivers for seasonality and compose seven models. We investigate which one of these models best explains the seasonality in H5N1 human cases.

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MS51

Dynamical Sensitivity and Stability: Suprathreshold Conditional Bursting Induced by Transient Potassium Promotes Information Transfer

Sources of noise are ubiquitous in sensory processing, yet highly structured neural activity in the form of oscillations and synchrony is commonly observed. Much recent attention has focused on the potentially constructive role of noise in generating structured spiking.

Here we present a neural model exhibiting strong correlation transfer in two distinct dynamical modes. In both the oscillatory and bursting regimes, correlated noisy inputs produce correlated output spike trains as in classical stochastic synchrony. However, the bursting regime shows stronger signal fidelity, as measured by the Shannon mutual information.

We analyze the dynamics of our model using slow-fast decomposition to describe the bifurcation between bursting and regular oscillation. Furthermore, the local Lyapunov exponent reveals transient instability in the burst trajectory that may account for the observed gain in mutual information.

Our model system displays a dynamical repertoire similar to that observed in mouse olfactory mitral cells, the primary output cells of the olfactory bulb. We discuss the possibility that heterogeneous populations of such cells, exhibiting a range of A-type potassium conductance, could provide meaningful responses across a range of sensory conditions.

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MS51

Higher Order Interactions in Microcircuits: A Mechanistic View

Recent experimental studies find that the activity patterns of many neural circuits are well described by pairwise maximum entropy (PME) models which require only the activity of single neurons and neuron pairs even in cases where circuit architecture and input signals seem likely to create a richer set of outputs. Why is this the case? We study spike patterns in a general class of circuits, and draw general principles about the effects of network architecture and input statistics on the complexity of output spiking patterns.

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MS51

The Influence of Network Structure on Neuronal Network Dynamics

We investigate the influence of network structure on the dy-

namics of neuronal networks, with a focus on the emergence of synchronous oscillations. Network structure is specified using the framework of second order networks, a network model that captures second order statistics (correlations) among the connections between neurons. We demonstrate that the frequency of a chain motif in the network plays a crucial role in influencing network dynamics, not only modulating the emergence of synchrony but also possibly increasing the range of possible network behaviors.

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MS51
On Tiling and Noise Correlations

Using examples from visual and auditory processing, I will describe two strategies that are used in the brain to control varibility. While the two examples come from different sensory systems, both can be mapped onto the problem of close packing with irregular objects.

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MS52
Why Fast Negative Feedback is Necessary for Electrical Bursting in Pituitary Cells

Pituitary lactotrophs and somatotrophs often exhibit electrical bursts of activity, while pituitary gonadotrophs typically do not (unless stimulated). Using the dynamic clamp, we have shown that adding a fast-activating potassium current to a spiking cell converts it to a bursting cell. However, this fails when the activation of the added current is too slow. In this presentation we use a fast-slow analysis of a pituitary cell model to understand these behaviors. We demonstrate a key role for a folded node singularity and the resulting canard-induced mixed mode oscillations.

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MS52
A Minimal Model for a Slow Pacemaking Neuron

I present a phenomenological model for slow pacemaking neurons. These are neurons that generate very regular periodic oscillations of the membrane potential. Many of these neurons differentially respond to various types of excitatory stimulation (i.e. AMPA and NMDA). We modify FitzHugh-Nagumo oscillator and shown that the differential responses are due to a nonlinearity introduced by a current that depends on an ion concentration. We discuss implications of our results for a broad class of neurons.

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MS52
Interaction of Multiple Respiratory Rhythm Generation Mechanisms

Neurons in the pre-Bötzinger complex (pBC) within the mammalian brainstem produce the inspiratory phase of the respiratory rhythm. Experimental results have suggested that multiple bursting mechanisms based on a calcium-activated nonspecific cationic (CAN) current, a persistent sodium (NaP) current, and Ca dynamics may be incorporated within the pBC. Previous modeling works have studied only subsets of these mechanisms. In this study, we consider a single-compartment model of a pBC inspiratory neuron, which encompasses all these features. We discuss the mathematical analysis of the interaction of these bursting mechanisms, which requires treatment of a system incorporating three slow variables.

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MS52
Canard-Induced Mixed Mode Oscillations In Pituitary Lactotrophs

We combine geometric singular perturbation theory and bifurcation analysis to investigate the mixed-mode dynamics in a 3-timescale pituitary lactotroph model. Until recently, all prior studies of this cell model have used various reductions to reformulate it as a 2-timescale problem. One of the key results from this reduction is that the oscillatory behaviour arises from canard dynamics. Here, we review the 2-timescale results and extend that work by considering the full 3-timescale problem.

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MS53
Memory Effects in Diffusion Processes

Drug delivery from a polymeric device is usually modeled using the diffusion equation established by combining Ficks law for the flux with mass conservation law. To capture the delay effect induced by polymeric matrices, viscoelastic effects should be included in the mathematical model. In this talk we discuss several possibilities to model such effects that lead to integro-differential equations. Numerical simulations illustrating the key role of viscosity in controlled

drug release are presented.

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MS53

Use of Population Balances in Modelling and Simulation of Drug Release from Collagen Matrices

Drug safety and efficacy can be greatly improved by encapsulating the pharmaceutical agent within a polymer matrix. We analyze a model in which the drug is released in the process of hydrolytic degradation and erosion of polymers. Tracking concentrations of polymers with different chain length separately with population balances allows to assign them different diffusion coefficients. The resulting reaction-diffusion process is modelled in 2D/3D. We investigate the model parameters for which prolonged systematic administration of drug is reached.

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MS53

Modeling of Drug Delivery from Collagen Matrices Including Different Spatial Scales

In this talk we consider controlled drug release from biodegradable collagen matrices. We investigate enzymatic degradation which is besides the penetration of water and the swelling of the matrix the relevant mechanism in this context. The thereby induced evolving microstructure leads to the release of physically entrapped active agent. We derive a macroscopic model description using formal asymptotic expansion in a level-set framework. We complete the results by numerical simulations which are compared with experimental data.

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MS53

Drug Delivery into the Anterior Camera of the Eye: From Drops to Therapeutic Lens

Mathematical models to describe drug concentration profiles of topically administered drug in the anterior chamber have been proposed by several authors. The aim of this talk is to present a 2D mathematical model to predict the drug concentration in the anterior chamber when therapeutical contact lenses are used. The mathematical model takes into account i) diffusion processes in several compartments of the eye : lens, cornea and anterior chamber; (ii) metabolic consuming processes of the drug: in the cornea and anterior chamber; (iii) the convection process induced by the circulation of the humor aqueous in the anterior chamber.

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MS54

Joint High-dimensional Bayesian Variable and Covariance Selection with an Application to eQTL Analysis

We describe a Bayesian technique to (a) perform a sparse joint selection of significant predictor variables and significant inverse covariance matrix elements of the response variables in a high-dimensional linear Gaussian sparse seemingly unrelated regression (SSUR) setting and (b) perform an association analysis between the high-dimensional sets of predictors and responses in such a setting. To search the high-dimensional model space, where both the number of predictors and the number of possibly correlated responses can be larger than the sample size, we demonstrate that a marginalization-based collapsed Gibbs sampler, in combination with spike and slab type of priors, offers a computationally feasible and efficient solution. As an example, we apply our method to an expression quantitative trait loci (eQTL) analysis on publicly available single neucleotide polymorphism (SNP) and gene expression data for humans where the primary interest lies in finding the significant associations between the sets of SNPs and possibly correlated genetic transcripts. Our method also allows for inference on the sparse regulatory network of the transcripts (response variables) after accounting for the effect of the SNPs (predictor variables). We exploit properties of Gaussian graphical models to make statements concerning conditional independence of the responses. Joint work with Bani K. Mallick.

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MS54

Parameter Estimation in Subdiffusion Model with Proteins for Nanoscale Biophysics

Subdiffusion is a phenomenon observed in nanoscale single molecule biophysics experiments. We consider extended fractional Ornstein-Uhlenbeck type stochastic integro-differential equation model driven by fractional Brownian motion. This model can be derived from interacting particle systems. Our model is

$$dY_t = X_t dt,$$

$$m\, dX_t = -\theta \left(\int_{-\infty}^{t} X_u K_H(t-u) du \right) dt - U'(X_t) dt + \sqrt{2\theta\kappa_B T}\, dW_t^H$$

where $K_H(t) = 2H(2H-1)|t|^{2H-2}$ for $t \neq 0$, (W_t^H) is fractional Brownian motion with Hurst parameter $H \in (1/2, 1)$, $U(x)$ is an external potential and ψ is the strength of the potential, κ_B is the Boltzmann constant, T is the underlying temperature and θ is the unknown parameter. Under harmonic potential $U(x) = m\psi x^2/2$, we have $U'(x) = m\psi x$ where m is the mass of the particle. The process (Y_t) is observed at discrete time points. We estimate θ by method of moments and study the properties of the estimator.

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MS54

Accounting for Extrinsic Variability in the Estimation of Stochastic Rate Constants

Single-cell
recordings of transcriptional and post-transcriptional processes reveal the inherent stochasticity of cellular events. However, to a large extent the observed variability in isogenic cell populations is due to extrinsic factors, such as difference in expression capacity, cell volume and cell cycle stage - to name a few. Thus, such experimental data represents a convolution of effects from stochastic kinetics and extrinsic noise sources. Recent parameter inference schemes for single-cell data just account for variability due to molecular noise. In this talk, I will discuss a Bayesian inference scheme which de-convolutes the two sources of variability and enables us to obtain optimal estimates of stochastic rate constants of low copy-number events and extract statistical information about cell-to-cell variability. In contrast to previous attempts, we model extrinsic noise by a variability in the abundance of mass-conserved species, rather than a variability in kinetic parameters. We apply the scheme to a simple model of the osmo-stress induced transcriptional activation in budding yeast.

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MS54

Statistical Inference for Biochemical Reaction Network Models

For a given biochemical network of interest, it is often desirable to estimate its reaction constants. I shall discuss several different approaches to rate constants estimation from partial trajectory data. The presentation will discuss the LSE as well Bayesian and MLE approaches as well as possible conditions on the data process which guarantee identifiability and estimators consistency. We shall also consider ways of approximating the likelihood of a partially observed biochemical network with certain other likelihoods (e.g., Gaussian) for which inference problem is simplified.

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MS56

Cell-based Computational Models of Collective Cell Behavior and Cell-ECM Interactions During Angiogenesis

Abstract not available at time of publication.

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MS56

Statistical Quantification of Vascular Patterning During Developmental Angiogenesis in the Retina of the Mouse

Abstract not available at time of publication.

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MS56

A Particle-Based Modeling Framework for Migration, Growth and Juxtacrine Signaling

Angiogenesis is guided by a complex interplay of signaling, migration and growth. We present a particle-based model that captures these dynamics at the cellular scale, including a model for actin-polymerization driven migration, cell-cell mediated juxtacrine signaling as observed during tip cell selection and growth and proliferation. In parallel, we develop a set of computational tools for the extraction of relevant statistical metrics on biological experiments that allow for modular model validation and parameter estimation.

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MS56

Growing Capillaries with the Phase-field Model

Understanding tumor induced angiogenesis is a challenging problem with important consequences for diagnosis and treatment of cancer. We present a multi-scale phase-field

model that combines the benefits of continuum physics description and the capability of tracking individual cells. The model allows us to discuss the role of the endothelial cells' chemotactic response and proliferation rate as key factors that tailor the neovascular network. We verify the effect of the vessels' mechanical properties in vascular patterning by including in our phase-field description of angiogenesis the blood flow and the elastic properties of tissues. We also test the predictions of our theoretical model against relevant experimental approaches in mice that displayed distinctive vascular patterns. The model reproduces the in vivo patterns of newly formed vascular networks, providing quantitative and qualitative results for branch density and vessel diameter on the order of the ones measured experimentally in mouse tissues. Our results highlight the ability of mathematical models to suggest relevant hypotheses with respect to the role of different parameters in this process, hence underlining the necessary collaboration between mathematical modeling, in vivo imaging and molecular biology techniques to improve current diagnostic and therapeutic tools.

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MS57

Efficient Power Strokes in Jellyfish Swimming

We use vortex methods to study a bell-shaped swimmer which is a model for jellyfish. We use represent the vorticity in the flow using vortex sheets consisting of vortex blobs of varying core size. We study freely-swimming jellyfish with different body shapes and kinematics, and show how larger strokes yield increased swimming speeds but decreased efficiency. We then present a reduced model to determine the efficiency-maximizing power stroke for a jet-propelled swimmer.

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MS57

Pumping Mechanism of the Tubular Sea Squirt Heart

Tubular valveless hearts are common in many invertebrates, such as Drosophilia or Ciona, and are also found in the early stages of vertebrate cardiac morphogenesis. This diversity of hearts motivates the question of how scaling affects fluid transport for several mechanisms of valveless pumping. Physical and numerical models are used to quantify pumping efficiency as a function of Womersley number for peristalsis and dynamic suction pumping.

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MS57

Feeding Currents Generated by Upside Down Jellyfish in the Presence of Background Flow

The mostly sessile upside-down jellyfish *Cassiopea spp.* is used to study the effects of jellyfish kinematics on the flow of surrounding fluid. We present 2D models simulated using the immersed boundary method of ambient flow interacting with organism kinematics and discuss the construction of 3D models. The influence of speed, direction, and variability of ambient flow and presence of secondary structures as well as the implications for particle transport are discussed.

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MS57

Flow through Flexible, Deforming Macrophytes

In natural water bodies such as embayments and estuaries, macrophytes can have a significant and complex effect on water flow. Using a two-dimensional hydrodynamic model, we first represent macrophytes as a simple porous layer, studying velocities, shear stress, and mixing while varying the number of patches and height and density of the plants. We then compare with results from a more complex model in which the macrophytes are treated more realistically as flexible and deforming.

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MS58

An HIV Model: Theoretical Analysis and Experimental Verification

In the talk I will propose a HIV-infection model . I shall discuss its global behavior and investigate for the global stability of the disease free equilibrium. The existence of the endemic equilibria will be analyzed. The observed data was in a city in China. This data was used to determine the parameters in the model using the least-squares approach. The effectiveness of the model would be established by comparing the theoretical results with data obtained from a local government agency in the same city.

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MS58

Avian Influenza: Modeling and Implications for Control

Abstract not available at time of publication.

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MS58

Evaluation of Diagnostic Test for Lymphatic Filariasis in Papua New Guinea using a Mathematical Model'

Papua New Guinea (PNG) has the highest prevalence of the mosquito-borne Lymphatic Filariasis (LF) disease in the world. Mass Drug Administration (MDA) has been the most feasible strategy, but in PNG previous rounds of MDA have not been successful. Success of MDA depends on our ability to accurately identify infected individuals but the value of the available LF diagnostic tests has not been validated. This study analyzes the impact of tests using PNG MDA field trials data.

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MS58

Dynamics of Influenza Virus Infection with Immune Responses'

Influenza virus infection remains a public health problem worldwide. The biological mechanisms underlying viral control during infection are not fully understood. We developed a new mathematical model including both innate and adaptive immune responses to study the within-host dynamics of equine influenza virus infection in horses. By comparing modeling predictions with both interferon and viral kinetic data, we examined the relative roles of target cell availability, innate and adaptive immune responses in controlling the virus. This study provides a detailed and quantitative understanding of the biological factors that can explain the virus and interferon kinetics during a typical influenza virus infection.

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MS59

How Firing Rate is Reflected in Network Topology

For integrate-and-fire neuronal networks with complex connectivity topology, we study the dependence of their pulse rate on the underlying architectural connectivity statistics. We derive the distribution of the firing rate from this dependence and determine when the underlying scale-free architectural connectivity gives rise to a scale-free pulse-rate distribution. We identify the scaling of the pairwise coupling between the dynamical units in this network class that keeps their pulse rates bounded in the infinite-network limit.

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MS59

Transient Propagation and Traveling Waves of Activity in Integrate-and-fire Neural Networks

Computational models for propagation of neural activity in the neural tissue usually describe the brain matter as a vast interconnected network of neurons comprised of large number of cells with similar properties, such as integrate and fire neurons. We use a set of integro-differential equations to describe the neural firing patterns during wave initiation and propagation. In addition, we investigate how the presence of inhomogeneities in synaptic connections impacts the network dynamics.

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MS59

The Essential Role of Phase-Delayed Inhibition in the Decoding of Synchronized Neural Oscillations

Synchronized oscillations of neural populations are a coding tool commonly employed by the brain, implying that a neural mechanism must exist that is capable of decoding coherent, periodic activity. There are two biologically realistic mechanisms: high decoder spike thresholds or phase-delayed inhibition. In this work, we show that phase-delayed inhibition is the more robust mechanism, and the only mechanism which creates a true synchrony filter that dynamically adapts to fluctuating input.

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MS59

Steps Towards Coarse-Graining Inhomogeous Neuronal Network Dynamics

The cascade-induced total synchronous events may be somewhat unrealistic when considering the cortex. From an analytical perspective, we propose a basic scheme which is capable of capturing the multiple-firing-events (MFEs) of small to moderate magnitude which occur in coupled systems of excitatory and inhibitory neurons. This scheme starts out by simply evolving the population-dynamics equations for homogenous networks (i.e., the master equations), and incorporate MFEs into the population-dynamics equations by estimating the probability of generating an MFEs.

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MS60

Hysteresis and a Mechanism for REM Sleep Generation

Waking and sleep states are regulated by the coordinated activity of neuronal populations in the brainstem and hypothalamus whose synaptic interactions define a sleep-wake regulatory network. Mathematical models of this network contain mechanisms operating on multiple time scales. We exploit the naturally-arising slow time scale of the homeostatic sleep drive and apply fast-slow analysis to investigate network dynamics, thereby generating testable predictions regarding the generation of rapid eye movement (REM) sleep.

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MS60

Coupled Flip-flops: Noise and Analysis for a Sleep-wake Cycle Model

Transitions between the wake state and REM and non-REM sleep states may be governed by a regulatory network composed of coupled flip-flops. One flip-flop network controls sleep-wake transitions while the REM-nonREM cycle is controlled by a separate flip-flop. We analyze the effects of different sources of noise on a single flip-flop network focusing on changes in state durations. This analysis provides insights regarding the interaction dynamics of coupled flip-flops subject to physiological variability.

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MS60

Markov State Kinetic Model for P2X2 Receptor-Channel Gating: Bistability and Desensitization

ATP-gated P2X2 receptor-channels exhibit pore dilation and desensitization. A Markov state model describing the gating properties of these receptors is developed. The model assumes that P2X2Rs undergo calcium-independent desensitization, causing a decrease in the total conductance, or pore dilation, causing a shift in the reversal potential. A toggle switch is used to describe calcium-dependent desensitization. The model provides a rationale for the lack of sustained current growth in dilating P2X2Rs.

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MS60

Using Maps to Predict Activation Order in Multiphase Rhythms

We consider a network of three heterogeneous coupled units, each described by a planar dynamical system on two timescales, motivated by recent models for respiratory rhythmogenesis. Each unit's intrinsic dynamics supports an active state and an inactive state. We analyze solutions in which the units take turns activating, allowing for any activation order, including multiple activations of two of the units between activations of the third. The analysis proceeds via the derivation of a set of explicit maps between the pairs of slow variables corresponding to the inactive units on each cycle. Evaluation of these maps on a few key curves in their domains can be used to constrain all possible activation orders in a given network and to obtain boundary curves between all regions of initial conditions producing different activation patterns.

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MS61

In-Vivo Microscopy Overcoming Diffraction Limit Through Nanostructured Gold Film

Abstract not available at time of publication.

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MS61

Plasmonics and Dispersion Relations for Medicine with Prisms and Laser

Abstract not available at time of publication.

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MS61

Applications in Nanotechnology and Materials for Medicine and BioScience Discipline

Abstract not available at time of publication.

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PP1

Bridging Cell and Tissue Scale Models for Nutrient Diffusion and Uptake in Articular Cartilage.

Nutrient diffusion and nutrient loss due to cellular uptake are crucial mechanisms influencing homeostasis in articular cartilage. Using reaction-diffusion finite-element simulations, we study relationships between models in which cells are represented explicitly and models in which cellular contributions are aggregated via a cell volume fraction and macroscopic nutrient loss term. Uncertainty due to cell size and configuration is studied with the aim of identifying optimal representations for the nutrient loss term in the macroscopic models.

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PP1

Modeling Hepatitis C Viral Dynamics: Sensitivity, Identifiability, and Parameter Estimation

The recent influx of biomedical data has assisted the development of models to understand the behavior of many human diseases. The practical immeasurability of most of the model components makes theoretical consideration about parameter estimation particularly relevant. We present sensitivity and identifiability analyses as the first step in determining unknown parameters in a mathematical model for hepatitis C viral infection. Also, we show results of parameter estimation using available data from the existing literature.

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PP1

Detecting and Measuring the Influence of Functional Coupling on Protein Fitness

Random mutations in a protein may improve, diminish or have neutral effects on its structural stability, ability to function or both. We study these mutational effects on a target protein by exploring all low-energy sequences and their corresponding structures, using well-established computational protein design algorithms. The mutational outcomes are then defined using energetic data to understand how side-chain replacement affects fitness. Cooperative effects between positions are also determined using thermodynamic cycles.

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PP1

Sensitivity Analysis of a Mathematical Model of Antibody Mediated Immune Responses

A mathematical model has been proposed that describes tumor-immune interactions, focusing on the role of antibodies. The model is based on the clinical evidence, which states that antibodies can directly kill cancerous cells. The model describes tumor-immune cell interactions using a system of differential equations. Parameter estimates and model validations use data from published mouse studies. A variable sensitivity analysis is done on the model. The sensitivity analysis reveals that the variable to which the model is most sensitive is patient specific and can be measured. Computer simulations highlight the importance of antibodies in cancer therapy.

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PP1

Neuronal transmission of timing precision: dependence on intrinsic and synaptic properties

Motivated by processing of timing information in the auditory system, we are looking at cellular and synaptic properties affecting the precision of spike timing through synaptic transmission. We have shown in minimal neuronal models that both improvement and deterioration of precision is possible, depending on the input times distribution and synaptic strength. In a conductance-based model we include more nuanced intrinsic and synaptic properties, including currents that switch the neuron from integrator to coincidence detector.

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PP1

3D Improved Mathematical Model for Lumbar Intervertebral Ligaments (lils)

In Lumbar Spinal Surgery, a common maneouvre is the distraction or non-saggital extension of the Lumbar Intervertebral Ligaments (LILs) System. To determine accurately the viscoleastic forces exerted by LILs constitutes an important data in Bioengineering and Mathematical Biomechanics. Previously, we presented a 2D LILs Model related to the equation Force/Distraction Length. In this new contribution this initial 2D model has been evolutioned into a 3D Model with the addition of the distraction speed parameter.We detail the mathematical optimization development with basic simulations and graphics. F Casesnoves MSc (Physics/Applied Mathematics) REFERENCES: 'Spinal Biomechanics Mathematical Model for Lumbar Intervertebral Ligaments' Casesnoves, F. Peer-reviewed Presentation-Poster SIAM Conference.2011 SIAM Conference on Computational Science and Engineering. Reno, Nevada, USA. February 2011.

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PP1

A Mathematical Spatiotemporal Model of Gnrh Neurons

Gonadotropin-releasing hormone (GnRH) neurons are hypothalamic neurons that govern fertility in mammals. The mechanisms underlying the pulsatile release of GnRH are not well understood. Some mathematical models have been developed to explain the properties of bursting and calcium transients in Soma. It was suggested that the site of action potential initiation might be in dendrite. Our goal is to construct a mathematical model to understand how the dendrites of GnRH neurons contribute to bursting.

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PP1

The Effect of Antibody Attachment on the Infectivity of Virus Invasion

We study the diffusion of a virus population through a mucus layer and the attachment of antibodies to the surface of individual virions. In particular, the distribution of the antibody copy number, the number of attached antibodies to each virion, is tracked using models based on stochastic path simulation, on continuum PDE modeling, and hybrid models. Several semi-analytical estimates for scaling behavior with respect to various physical parameters in the system are also derived.

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PP1

Hopf Bifurcation and Oscillatory Solutions in Gene Regulatory Networks with Delays

This work combines theoretical analysis with computer and

numerical simulations to identify the dynamics of a gene regulatory network consisting of three nodes with multiple delays. Results show that cell density can generate monostability, multistability, and multi-rhythmicity in a synthetic unitary cellular system. Occurrence of oscillation and stability persistence of an equilibrium can coexist in a bistable system. In addition, a network with multiple timescales has the potential to generate multi-rhythmicity through time delay, including delay-induced relaxation oscillation, competitive-to-cooperative oscillation, and mixed-mode oscillation.

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PP1

A Stochastic Multiscale Model of Esophageal Adenocarcinoma

The mathematical development of this cellular level stochastic model of EA includes two hallmarks of cancer advancement: accumulation of mutations and clonal expansion of cell populations on the pathway to detection. Through stochastic birth/death processes of both initiated and dysplastic crypts, the model inherently provides realistic heterogeneity of tumor number and size distributions in individuals. These Luria-Delbrck distributions help analyze the efficacies of biopsy sampling techniques, screening strategies, optimal surveillance and ultimate survival rates.

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PP1

Quantifying the Influence of Drug Resistance Mechanisms Used in Mathematical Models When Assessing the Public Health Impact of PrEP Interventions.

The expected reduction in HIV transmission from pre-exposure prophylaxis (PrEP) varies significantly across mathematical models due to the broad spectrum of assumptions regarding mechanisms of generation and spread of drug-resistance. We reviewed published modeling studies to identify key assumptions regarding resistance implemented. We used a hierarchical epidemic model under identical epidemic and intervention conditions to investigate under what conditions drug-resistance will have a positive impact on the predicted public health impact of oral PrEP interventions.

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PP1

Modeling the Role of the Bacterium *Xylella Fastidiosa* in the Development of Plant Diseases.

The role of biofilms within bacterial infections has been a topic of recent interest due to the prevalence of the biofilm mode of life as well as the inability to fully eliminate the bacteria within the biofilm. Despite multiple diseases causing widespread damage to the citrus, wine, and other fruit industries, there has been little attention paid to modeling the development and progression of these plantal infections. An introduction to biofilms and bacterial infections will be followed by a multiphase modeling framework used to examine the dynamic behavior of the biological system. Perturbation analysis is used to determine potential causes and tendencies of patterns discovered within the biofilm.

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PP1

Random and Regular Dynamics of Stochastically Driven Neuronal Networks

Dynamical properties of Integrate-and-Fire neuronal networks with multiple time scales of excitatory and inhibitory neuronal conductances driven by random Poisson trains of external spikes will be discussed. Both the asynchronous regime in which the network spikes arrive at completely random times and the synchronous regime in which network spikes arrive within periodically repeating, well-separated time periods, even though individual neurons spike randomly will be presented.

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PP1

A Gene Set Analysis of Acute Lymphocytic Leukemia

Gene set analysis allows us to determine gene set differences between B-type and T-type Acute Lymphocytic Leukemia. This work introduces a new gene set analysis approach based on logistic kernel machines which can model complex pathway effects, gene-gene interactions, and covariate effects. Simulation results show our estimation approach being comparable to better than Bayesian approaches at a much lower computational cost. As for hypothesis testing, we have an increased power compared to the score test.

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PP1

Interior-Point Methods for An Optimal Control Influenza Model

We introduce a discrete time model in order to study optimal control strategies for influenza transmission. We evaluate the effect of social distancing and antiviral treatment as control policies. Our goal is to minimize the number of infected individuals on a single influenza outbreak. We consider two different scenarios, limited and unlimited resources. We introduce an isoperimetric constraint in the case of limited number of treatment doses. The problem is solved by using Interior-Point Methods.

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PP1

Robust Dorsal-Ventral Patterning Across Organisms

The dorsal-ventral axis in many organisms is specified by gradients of bone morphogenetic proteins (BMPs). Extracellular proteins bind to and regulate BMPs to produce robust spatial patterns. In the developing fly, BMP protein is produced in a broad spatial domain, which later accumulates in a narrow band. However, in urchins, the BMP production and accumulation occurs in complementary spatial domains. Analysis of the PDE models reveals characteristic reaction rates crucial for correct patterning in both.

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PP1

Model of the Immune System with An Inflammatory Host Response to a Bacterial Infection

The immune system is a complex network of cell interactions which challenges the technology and skills of biologists and mathematicians who study it. We present a general, four component model of the immune systems inflammatory response using ordinary differential equations. We focus on the anti-inflammatory responses effect on the overall result of an infection and other components. The model has equilibria representing the clearance of infection, host overwhelmed by infection, chronic infection and chronic inflammation.

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PP1

Global Parametric Analysis of Heterotrimeric G-Protein Signaling

Heterotrimeric G-proteins play a critical role in converting external stimuli into internal responses. Many paralogues of each G-protein subunit are present in mammalian genomes, and thus how specific responses are obtained for a given signal is an important question. In this study, differential-equation-based kinetic models have been used to understand in detail the dynamic mechanisms of G-protein signal transduction. Influences of parameters on the behavior of the system were also investigated.

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PP1

Amplification of Synaptic Inputs by Dendritic Spines

Dendritic spines are the site of contact for the majority of excitatory synapses in the mammalian brain, and as a result are the first step in the signaling between dendritic inputs and neuronal actional potential output. In this combined theoretical and experimental study, it is demonstrated that spines provide a uniformly high impedance compartment across the dendritic arbor that amplifies local depolarization. This spine amplification increases nonlinear voltage-dependent conductance activation and promotes electrical interaction among coactive inputs, enhancing neuronal response.

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PP1

Qualitatively Stable Numerical Methods for Dy-

namical Systems in Ecology

Qualitatively stable numerical methods are formulated and analyzed for multi-dimensional autonomous dynamical systems. The proposed new methods are positive and elementary-stable, and are based on an extension of the nonstandard discretization rules, i.e., a nonlocal modeling of the nonlinear functions and a nonstandard discretization of the time-derivative. This approach leads to significant qualitative improvements in the behavior of the numerical solution. Applications of the proposed new methods to specific biological systems are also presented.

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PP1

Inflammation and Cholesterol: Friend Or Foe in Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia affecting the elderly, leading to debilitating memory loss and significant cognitive decline. The exact mechanism of pathogenesis is not well understood. Here, we present an organ level model that studies the role of cholesterol metabolism and inflammation in the early stages of AD, demonstrating the importance of brain cholesterol on the expression of beta amyloid. The model has been further validated with experimental data.

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PP1

Stochastic Simulation of Biochemical Systems with Randomly Fluctuating Rate Constants

The phenomenon of dynamic disorder has been observed to cause random fluctuations of the reaction rate constant of a certain biomolecules. To quantify the uncertainty arising from this random fluctuations, we investigate how one can simulate such biochemical systems. We take the Gillespie's stochastic simulation algorithm for simulation the evolution of a chemical system, and propose a modification that incorporates the random rate constants, whilst enforcing a given distribution of the rate constants. This modified algorithm, when applied to the single enzyme reaction system, produces simulation outputs that corroborate by the experimental results.

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PP1

Structural Adaptation of Microvessels in Disease States

Hypertension, diabetes, and obesity are associated with impaired microvascular function. A.R. Pries and T.W. Secomb developed a model of vascular adaptation based on physiological conditions. Using their framework, we developed a model that incorporates signaling pathways relevant to diseases. Diameter changes is related to shear stress, wall thickness to circumferential stress, and area to smooth muscle mass. Our goal is to improve understanding of diseased adaptation and provide testable hypotheses for experimentalists and clinicians.

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PP1

Spatial Scale and Field Stability in a Modular Grid Cell to Place Cell Model

We present a neural network model containing entorhinal grid cells and hippocampal place cells, two key cell types involved in rodent navigation. The firing fields of both cell types vary systematically in spatial scale. In contrast to the common belief that place field size is determined by the scale of their grid cell inputs, our model predicts that non-spatial inputs to place cells may play a more important role in determining place field size.

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PP1

A Model for Hormonal Regulation of the Menstrual Cycle Applying to Women from Ages 20 to 51 Years

We present a system of 17 delay differential equations that models human menstrual cycle hormones and how they change with age. Key changes are declining AMH starting around age 30, decreased InhB about 10 years later, and increased FSH. These hormones are thus considered markers of ovarian function. Our model includes the declining primordial follicle pool that a woman is born with, the production of AMH by early follicles and InhB by small antral follicles.

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PP1

Mathematical Modeling of Bone Remodeling in Response to Osteoporosis Treatments

We present a mechanism based mathematical model describing the dynamics of bone remodeling that incorporates the molecular pathways regulating catabolic activity of Osteoclastic bone resorption and anabolic activity of Osteoblastic bone formation. The model incorporates, extends, and integrates available information in the literature and is consistent with various available data, including PTH administration. The proposed model provides useful insights into the bone remodeling process, enabling further testing of novel hypotheses and evaluating potential benefits of combination therapies.

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PP1

Zip Bifurcation in Non-Smooth Population Models

In this work a 3-dimensional ODE system is set up modelling the competition among two species of predators for one species of prey. We give a complete analysis of the asymptotic behavior for both the real and imaginary part of the eigenvalues associated to the linearized system at any nonisolated equilibrium point of the system. A concrete nosmooth model is introduced and some simulations in MATHEMATICA are carried out suggesting the occurence of zip bfurcation.

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PP1

Thermodynamically Compatible Model of Yield Stress Polymeric Fluids

We want to present some results on mathematical modeling of polymeric yield stress fluids which have the properties of both elastic solids and fluids. We try to investigate this problem using the approach of multiphase continuum mechanics. We develop the two-phase solid-fluid model which is thermodynamically compatible and its governing differential equations can be written in a conservative form. Such a model is convenient for application of advanced high-accuracy numerical methods and modeling of discontinuous solutions.

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PP1

A Mathematical Model for Protein Oscillations in Bacteria

In many cases oscillatory changes in protein concentration between cell poles cause the bacterium to reverse its directional movement. Our aim is to study whether such oscillations can arise independently from external triggers. A minimal model is developed with dynamics based solely on protein diffusion across the cytoplasm and protein interactions at the cell poles. A quantitative and qualitative analysis of the model shows existence of oscillating solutions under several scenarios of protein interaction.

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PP1

Mathematical Model to Quantify Dosing and Evaluate Effects of Modifications of Cancer Virotherapy

With the recent success of a clinical trial of cancer treatment using genetically engineered viruses, virotherapy is a definite possibility. Here we use mathematical modeling to understand the effect of this treatment under varied conditions. We investigate the utility of further genetic modifications (parameters) on the current oncolytic virus and thus help prioritize direction of genetic engineering efforts. We also present optimal parameter set to help treatment when applied on a case-by-case basis.

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PP1

A Framework for Exploring Dynamics of Genetic Diversity of Hiv Population in Hiv-Infected Patients

Due to rapidly evolving nature of HIV-1 virus, it maintains high level of genetic diversity in HIV-infected patients. It creates challenge to develop vaccines and drugs for preventing HIV epidemics. Understanding evolutionary forces that contribution to HIV evolution in infected patients is important. I will present a framework for exploring patterns of genetic diversity of the HIV population in an infected person. The framework is applied to HIV data sets from HIV-infected patients.

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PP1

A Shortest Path Tree Approach for Inferring and Exploring Gene Networks.

We address the problem of inferring gene networks from correlations in gene expression profiles using a shortest path tree approach. Correlations are mapped to distances and the ensemble of shortest path trees is determined and then visualized in an interactive network browser. An maximum entropy criterium applied to the distribution of link saliencies is used to determine the optimal metric. We compare the performance of our method to the benchmarks and provide a demonstration of the interactive network browser.

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PP1

Deformation of a Single Red Blood Cell in Bounded Poiseuille Flows

Deformation of a red blood cell in bounded two-dimensional Poiseuille flows is studied by using an immersed boundary method. An elastic spring model is applied to simulate the membrane of a RBC membrane. We investigate the motion and the deformation of a single RBC by varying the swelling ratio, the initial cell inclination angle, the Renolds number, the membrane bending stiffness, and the microchannel height. Two motions of oscillation and swing are observed.

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PP1

Modeling Blood Pressure Dynamics

This project discusses a patient–specific model predicting baroreflex regulation of blood pressure and heart rate during head–up tilt (HUT). The objective of our study is to estimate model parameters that allow prediction of patient specific arterial blood pressure dynamics. During steady state five upper body parameters were identifiable. Using optimized values for these parameters, the response to HUT was predicted by redefining four of the five parameters as piecewise linear functions.

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PP1

Modeling the Cofilin Pathway and Actin Dynamics in Cell Motility Activity of Mammary Carcinomas

Polymerization of actin cytoskeleton leads to cell migration, a vital part of normal physiology, from embryonic development to wound healing. However, it also occurs in the pathological setting of cancer metastasis. Here I present mathematical models of actin regulation by cofilin which has been identified as a critical determinant of metastasis. I will discuss results obtained from simulations and steady state analysis and their biological implications, as well as

modeling challenges that arise.

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PP1

Noise-Induced Transitions in Stochastic Neural Fields

Neural assemblies are composed of a very large number of entities, among which neurons, that form statistically homogeneous populations subject to an intense noise. I will show how one can rigorously derive, using probability theory, macroscopic equations on the dynamics of large-scale neural assemblies for plausible neuron models including spatial extension and propagation delays. Starting from these representations, I will analyze the dynamics of large-scale neural assemblies, and particularly the effect of noise and of heterogeneities on the dynamics. A particularly intriguing phenomenon will be emphasized: the generation of perfectly regular phase-locked oscillations when noise, or when network heterogeneities increase.

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PP1

Stochastic Trojan Y-chromosome Models for Eradication of an Invasive Fish Species

A wide variety of exotic aquatic species, which were introduced and established as a result of human activities in the US, in?icted enormous damage. In this presentation, I will talk about our work on finite-time extinction and recovery of an invasive fish species by stochastic models.

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PP1

Simplifying the Testing of Models of Flow-Cell Optical Biosensor Experiments for Global *a Priori* Identifiability

A number of models of flow-cell optical biosensor experiments are continuous-time uncontrolled linear switching systems (LSS) in state space form. Methods for testing LSS for global *a priori* identifiability assume that the model response can be observed for all possible switching behaviours which is unlikely in some settings. Exploiting features of the type of chemical interaction studied allows proposition of a simplified test of uncontrolled LSS for global *a priori* identifiability.

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PP1

Phase Locking in Chains of Half-Center Oscillators: Mechanisms Underlying the Metachronal Rhythm in the Crayfish Swimmeret System

Crayfish have four pairs of limbs that paddle sequentially during forward swimming in a posterior-to-anterior metachronal rhythm. A 25% phase-lag is maintained between neighboring limbs over a wide range of frequencies. In the isolated nodal cord, analogous neural activity is produced by a chain of interconnected local rhythm generating networks. We show how the phase response properties of the rhythm generating networks and the connectivity between them combine to produce the constant 25% phase-lags.

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PP1

Title: The Effects of Limb Coordination on the Swimming Efficiency of Crayfish

Limbs of crayfish, called swimmerets, move rhythmically in a metachronal wave that progresses from back to front during forward swimming. Neighboring swimmerets maintain phase-lags of about 25% over a wide range of frequencies. This "phase constancy" suggests that there may be mechanical advantages to this stroke pattern. We use the immersed-boundary method to simulate the coupled mechanics of the swimmerets and the surrounding fluid in order to explore how stroke patterns affect swimming efficiency.

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PP2

Polymerization-Driven, Adhesion-Mediated Actin

Traveling Waves in Motile Cells

Fish keratocyte cells, which usually exhibit rapid and steady motility, exhibit traveling waves of protrusion when moving on highly adhesive surfaces. We hypothesize that waving arises from a competition between actin and mature adhesions for VASP, a protein that promotes actin polymerization. We present a mathematical model formulated as an excitable system of partial differential equations with a nonlocal integral term and noise. Predictions from model simulation, including phase-shifted VASP waves, are confirmed by experiment.

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PP2

Mathematical Modelling of Dna Base Excision Repair

We consider the process of DNA base excision repair of alkylated base lesions which is initiated by the glycosylase Aag. Previous models have considered the multiple steps in the repair process, but our model has also included the additional possibility of cell death. Experimental results from the BER process after brief exposure of mammalian cells in culture to the alkylating agent MMS are compared with predictions from the mathematical model.

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PP2

Compressed Sensing in Retinal Image Processing

Retinal image processing transforms photons into membrane potentials via several nonlinear transformations. This process begins in a large network of photoreceptors and ends in a relatively small ganglion cell network. We posit the loss of visual information despite the decrease in network size is minimized via compressed sensing. Using an idealized mathematical model of the retina and a mean-field analytical reduction, we demonstrate firing patterns among ganglion cells can be used to reconstruct input images.

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PP2

Mathematical Investigation of Calcium Dynamics in Human Airway Smooth Muscle

Free cytoplasmic calcium ions in human airway smooth muscle cells are important in regulating the airway contraction that contributes to our normal breath. Experiments show, in the present of agonist, calcium oscillates and propagates in waves, which is essential to maintain airway contraction via crossbridge. Exploring what leads to the oscillatory behavior is a way to understand how the calcium affects our breath, which will be useful to the research of pathology of asthma.

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PP2

Initiation of Spiral Calcium Waves in a 3-D Cardiac Cell Based on Analysis of a 1-D Deterministic Model

Under certain conditions, spontaneous calcium sparks can lead to the propagation of self-initiated calcium waves in a heart cell. Such calcium waves can potentially cause cardiac arrhythmias. Studying a model of this phenomenon based on a system of coupled reaction-diffusion equations with stochastic release requires computationally intensive long-time simulations. An analysis of a 1-D deterministic version of the model provides parameters for the 3-D model that generates spontaneous recurrent calcium waves and self-sustaining spiral waves.

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PP2

A Transient Structured Tree Boundary Condition for Hemodynamic Modeling

The structured tree boundary condition is a physiologically based outflow boundary condition for the modeling of blood flow. However, the original formulation of this boundary condition requires one to assume that the modeled blood flow is periodic in time, which limits its applicability. By slightly modifying the original derivation, one may obtain a similar structured tree boundary condition that does not assume time-periodicity of the flow. We briefly explain how this boundary condition may be derived and compare it to results obtained from the original, time-periodic structured tree condition, as well as the Windkessel boundary condition. This comparison is done for both periodic and transient cases.

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PP2

A Multiscale Examination of Nonlinear Waves in the Cochlea

Sound is received and processed by mammals via mechanotransduction of traveling waves in the cochlea. Though linear math models for cochlear mechanics have been studied and well-documented, many nonlinearities in the traveling wave exist and have not been explained. Outer hair cell electromotility is a likely source for such nonlinearities and an attempt will be made to model the effects of this process.

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PP2

Modeling of Controlled-Release Drug Delivery from Polymer Microspheres Using Reaction-Diffusion Equations with Hindered Diffusion

Biodegradable
polymer microspheres are used for controlled-release drug delivery—administering medicine over extended time periods with a single dosage. Models of drug delivery from microspheres must treat the interdependent phenomena that contribute to drug release. A reaction-diffusion model is presented that couples autocatalytic polymer degradation mechanisms to the hindered diffusion in growing pores. Finite-difference solutions to the model equations capture microsphere-size-dependent release behavior observed experimentally and show the dependence of drug release profiles on polymer morphology.

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PP2

Computational Modeling of Tumor Response to Vascular-Targeting Therapies

A mathematical model that examines tumor-vasculature interactions is briefly presented in this work. I will discuss validation studies which demonstrate the model's ability to qualitatively predict: 1) tumor growth under a range of biological conditions, and 2) the effects of several cancer drugs, in particular those that target the vasculature. This study concludes with an exploration of how the model can be used to learn new things about treating cancer using vascular-targeting compounds.

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PP2

Modelling Foot-and-Mouth Disease Virus Infection in Bovine Epithelial Tissues Potential Determinants of Cell Lysis.

Foot-and-mouth disease (FMD) is a severe disease of cloven hoofed animals, including cattle, sheep and pigs. In this work a partial differential equations model of epithelium is developed to investigate potential determinants of the localisation of vesicular lesions, one of the key clinical signs of FMD, in certain epithelial tissues. Results relating to the impact on infection of tissue thickness and structure, and receptor distribution in different cell layers will be presented.

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PP2

Mathematical Modeling and Data Analysis for Cerebral Blood Flow

Transcranial doppler (TCD) and MRI are both used to measure cerebral blood flow (CBF). TCD is inexpensive and widely available, but inaccurate in comparison to MRI. This inaccuracy can be attributed to a lack of geometric information about the cerebral arteries, specifically the angle of the artery with respect to the TCD probe, called the insonation angle. We provide a distribution for the insonation angle, which yields a more accurate estimate of CBF.

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PP2

Multiple Attractors of Intraguild Predation Models with Generalist Or Specialist Predator

Intraguild predation (IGP) is a combination of competition and predation which is the most basic system in food webs that contains three species where two species that are involved in a predator/prey relationship are also competing for a shared resource or prey. We formulate two intraguild predation (IGP: resource, IG prey and IG predator) models: one has a predator who is a generalist while the other one is a specialist. Both models have Holling-Type I functional response between resource-IG prey, resource-IG predator and Holling-Type III functional response between IG prey and IG predator. We prove sufficient conditions of the persistence and extinction of all possible scenarios for

these two models, which give us a complete picture on their global dynamics. These analytical results indicate that IGP model with generalist predator has "top down" regulation while IGP model with specialist predator has "bottom up" regulation. In addition, we show that both IGP models can have multiple interior equilibria. Our analysis and numerical simulations suggest that 1. Both IGP models can have multiple attractors with complicated dynamical pattern; 2. Only IGP model with specialist predator can have both boundary attractor and interior attractor: i.e., whether the system has the extinction of one species or the coexistence of three species dependent on initial conditions; 3. IGP model with generalist predator is prone to have stable dynamics.

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PP2

Wandering and Transitions of Pulses in Stochastic Neural Fields

We examine the dynamics of standing pulses (bumps) and traveling pulses in spatially extended neural fields with noise. Bumps in a stochastic neural field diffusively wander about the spatial domain. We can calculate the associated diffusion coefficient using a small noise expansion. Multiplicative noise can even shift bifurcations of the bump. Noise can also cause traveling pulses to switch their direction of propagation, which we study as transitions between two branches of a pitchfork bifurcation.

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PP2

A Mechanism for Robust Circadian Timekeeping: Stoichiometric Balance Through Double Negative Feedback Loop Structure.

Circadian clocks persist with a constant period (24-hour) even after a significant change of the expression level of clock genes. Although much is known about cellular circadian timekeeping, little is known about how these rhythms are sustained with a constant period. Here, we show how a universal motif of circadian timekeeping, where repressors bind activators rather than directly binding to DNA, can generate oscillations when activators and repressors are in stoichiometric balance. Furthermore, we find that, even in the presence of large changes in gene expression levels, an additional slow negative feedback loop keeps this stoichiometry in balance and maintains oscillations with a fixed period. To study these biochemical mechanisms of timekeeping, we develop the most accurate mathematical model of mammalian intracellular timekeeping, as well as a simplified model. These results explain why the network structure found naturally in circadian clocks can generate 24-hour oscillations in many conditions. Furthermore, our study provides a novel design for the biological oscillators where maintaining a fixed period is crucial.

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PP2

Molecular Network Structure Detection based on Oscilating Timecourses

With the advanced technology of the experiment, lots of timecourses data have been produced everyday. Most of mathematical model have used the timcourses to estimate the parameters of the model, whose structure is already determined by the knowledge about the biochemical networks. Here, we show that the structure of the molecular network can be revealed only with timecourses when they are oscillating. Furthermore, we found that a specific class of oscillating timecourses can determine the unique production rate and degradation rate of a canonical form of ODE model. Finally, we propose a new type of the model that can be constructed uniquely with the general oscillating timecourses.

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PP2

High Performance Simulations of Platelets in Flow

Studying the constituents of blood is of great importance to the fields of biology and medicine. However, observing blood in the vessels of live subjects is difficult. We have developed a hybrid computer simulation model using a Lattice Boltzmann method for fluid flow and subcellular elements to represent the platelets. To overcome the high computational cost of this method, it now runs on the massively parallel cards of graphical processing units (GPUs).

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PP2

Ensemble Modeling of Symptoms to Human Im-

mune Response of Influenza A Virus Infection

Deterministic models of a host-level response to influenza A virus (IAV) infection assume a perfect prediction, while an ensemble approach may account for patient and strain variability, and uncertainty in data used to calibrate the models. We generate an ensemble of parameter sets that represent a calibration to experimental data of viral titers and symptoms measured in humans with IAV infection to a host-level model with innate and adaptive immunities. Systemic, upper respiratory and lower respiratory symptoms are mapped to model interferon levels, and extent of upper and lower respiratory cells damage. In order to differentiate between upper and lower symptoms, we compartmentalize the respiratory tract into upper and lower compartments. Principal component analysis of the parameter ensembles provide a mapping strategy between model kinetic parameters and population-scale relevant clinical phenotypes (severity of infection, immunogenicity). The objective is to develop a methodology that performs an efficient abstraction of the host-level model to a population-scale model. Ensemble modeling, data reduction and response surface analysis are the core methods used in implementing this abstraction.

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PP2

Multiscale Population Dynamics Study of Heterotypic Cell Aggregation in a Shear Flow and Related Parameter Identification Problem

This work studied the process of polymorphonuclear neutrophils tethering to the vascular endothelial cells, and subsequential tumor cell emboliformation in a shear flow, an important process of tumor cell extravasation during metastasis. To the best of our knowledge, a multiscale near-wall aggregation model was developed, for the ?rst time, which incorporated the effects of both cell deformation and general ratios of heterotypic cells on the cell aggregation process. Quantitative agreement was found between numerical predictions and in vitro experiments. The effects of factors, including: intrinsic binding molecule properties, near-wall heterotypic cell concentrations, and cell deformations on the coagulation process, are discussed. The work also focused on application of Bayesian framework to the related parameter identification problems. It offered a systematic parameter identification tool specially tailored to the model proposed in earlier work and addressed the ratio change effects problem.

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PP2

Effect of Parity on Boundedness of Orbits in Lotka-Volterra Food Chains

Hairston, Slobodkin, and Smith conjectured that in food chains with three species, plants are not regulated by predation, which allows them to flourish. If another species is added, then plants become predator-limited by herbivores. Thus, plants can only accumulate in food chains with an odd number of species. Volterra proved, for any even number of species, solutions remain bounded. We prove, for an odd number of species, unbounded orbits exist, which validates the HSS Conjecture.

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PP2

Incorporating Drift into the First-Passage Kinetic Monte Carlo Method

First-Passage Kinetic Monte Carlo is a stochastic algorithm for simulating reaction-diffusion processes. Earlier versions of the algorithm rely on analytic solutions of the diffusion equation and do not allow for drift. We develop a variation of the algorithm using a discretization of the Fokker-Planck equation to incorporate drift arising from a potential energy function. We implement the algorithm in one dimension and analyze convergence. Next, we plan to extend to higher dimensions.

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PP2

An Adjoint-Based Method for Automatically Identifying Key Processes in a Nonlinear Mixed-Type

Pde Model of Cell Motility.

Here we present an adjoint-based mathematical method for determining which terms in a differential equation system are important for accurately calculating a user-defined quantity of interest. The method gives detailed information about how the balance of terms in a set of equations changes over time and/or space. The method is applied to nonlinear mixed-type PDEs that model cell motility, and is used to better understand how adhesion strength affects the velocity profile of the cell.

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PP2

Neurovascular Coupling During Cortical Spreading Depression: A Mathematical Model

Abstract. Cortical spreading depression (CSD) is a slowly moving wave of ionic and metabolic disturbances that propagates in cortical brain tissue. In addition to massive cellular depolarization, CSD involves significant changes in tissue perfusion and metabolism. However, despite their importance in CSD phenomenology, these changes have not been modeled. In this study, we develop a new mathematical model for CSD where the sodium-potassium ATPase, responsible for cellular polarization and recovery from CSD, operates at a rate that is dependent on local oxygen concentration. The supply of oxygen is determined by modeling flow through a lumped vascular tree where the effective radius is controlled by the extracellular potassium concentration. Our model replicates the qualitative and quantitative behavior of CSD found in experimental studies and elucidates the effect of oxygen deprivation on CSD recovery. Our key findings are that the metabolic activity of the cortex during CSD exceeds the physiological limits placed on oxygen delivery and that perfusion changes during CSD strengthen the intensity and lengthen the duration of the event. The vascular changes from our CSD model more accurately reflect experimental findings and allow for more precise prediction and hypothesis testing. Combined modeling and experimentation should accelerate understanding of the mechanisms of CSD.

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PP2

Evaluation of Diagnostic Test for Lymphatic Filariasis in Papua New Guinea Using a Mathematical Model

Papua New Guinea (PNG) has the highest prevalence of the mosquito-borne Lymphatic Filariasis (LF) disease in the world. Mass Drug Administration (MDA) has been the most feasible strategy, but in PNG previous rounds of MDA have not been successful. Success of MDA depends on our ability to accurately identify infected individuals but the value of the available LF diagnostic tests has not been validated. This study analyzes the impact of tests using PNG MDA field trials data.

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PP2

The Effect of Intramitochondrial Stochasticity on the Tricarboxylic Acid Cycle

While it is known that ODE models can accurately depict the behavior of large-scale systems, it has yet to be determined if they are capable of accurately capturing intramitochondrial dynamics of the tricarboxylic acid (TCA) cycle. Here we compare the dynamics predicted by a straightforward ODE model of the TCA to an analogous Markov process. Where the ODE model shows damped oscillations, the stochastic model shows sustained, limit-cycle-like behavior.

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PP2

Understanding Physiological Systems with Three Time Scales

Many physiological systems have the property that some processes evolve much faster than others, and mathematical models can be constructed to reflect this property. We are interested in the dynamics of a GnRH neuron model, which has at least three time scales, but methods for analysing models with three or more time scales are still limited. In this poster, progress that has been made on understanding systems with three time scales will be shown.

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PP2

Modelling Contractility and Antiparallel Flows in

Actomyosin Bundles.

I present a mathematical model in 1-D for an actomyosin bundle featuring antiparallel flows of antiparallel F-Actin. The model is able to relate these flows to the effect of cross-linking and bundling proteins and to the forces due to myosin II filaments and to stretching forces at the extreme tips of the bundle. The modeling is based on a coarse graining approach starting with a microscopic model which includes the description of chemical bonds as elastic springs and the force contribution of myosin filaments. In a second step we consider the asymptotic regime where the filament lengths are small compared to the overall bundle length and restrict to the highest order contributions. There, it becomes appearent that bundling proteins provide the viscosity of the filemant gel and are reasponsible for force transmission. Myosin filaments generate forces which are partly compensated by drag forces due to cross-linking proteins. The model is able to explain how the bundle of comparatively short Actin filaments interspersed with myosin II filaments can effectively contract the two tips of the actomyosin bundle. It gives a quantitative description of these forces and of the antiparallel flows of the two phases of antiparallel F-Actin.

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PP2
Optimal Control of Dengue with Periodicity

We formulate a problem of optimal control for dengue fever prevention of a serotype, by a functional purpose of direct and indirect costs linked to a system of nonlinear differential equations with periodic transmission dynamics in the human population coupled with periodic dynamics of incidence of the virus in the mosquito Aedes aegypti.

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PP2
Beta Oscillations in the Basal Ganglia Circuit

A key pathology in the development of Parkinson's disease is the occurrence of persistent beta oscillations, which are correlated with the difficulty of movement initiation. We investigate a network model composed of subthalamic nucleus (STN) and globus pallidus (GP) and derive analytic stability conditions describing when this circuit can generate beta oscillations. Furthermore, our analysis explains how changes in cortical and striatal input to the STN-GP network influence oscillations generated by the circuit.

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PP2
Models of Plankton Dynamics

Phytoplankton, and the zooplankton that graze upon them, play a crucial role in the dynamics observed at higher levels of the ecosystem and in climate change. There is a vast literature on differential equation models of plankton dynamics, and a recent trend in ecological models has considered plasticity in parameters and adaptation. In this work, we interpret adaptation as prey switching and use piecewise-smooth dynamical systems to model adaptation in a food chain.

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PP2
Spatio-Temporal Modelling of Cell Cycle Control

Models and simulations of metabolic processes often consider only temporal dependencies although processes in the cell are not spatially homogeneous. We focus on (enzymatic) reaction networks regulating the cell cycle of budding yeast of different complexity in the form of coupled ODEs, PDEs and algebraic equations including diffusive processes with up to 54 species on a cell geometry with nucleus, cytoplasm and cell membrane. We compare simulations of purely temporal vs. spatio-temporal models and interpret reaction rate constants. The availability of some regulators is studied differentiating reactions in the nucleus and cytoplasm.

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PP2
From Discrete to Continuous Models of Cell Movement: An Application to Medical Implants

Mathematical modeling of cell movement is needed to aid in the deeper understanding of vital processes such as embryogenesis, angiogenesis, tumor metastasis and immune

reactions to foreign bodies. In this work, we consider cell movement in response to external stimulus, incorporating both a random and a biased component. In order to model the random nature of the movement, an individual based (IBM) model is created to simulate cells moving in the presence of a heterogeneously distributed stimulus molecules. The discrete IBM model is then upscaled, starting with transition probabilities of the individuals at each site, to obtain a corresponding continuous differential equation (DE) model. Continuous models allow for a more general study of larger domains. Under traditional modeling assumptions the proposed new models reduce to previously developed models in the literature. Next, we present a set of numerical experiments which show very good agreement between the new continuous DE and discrete IBM models for a variety of different values of the parameters. Furthermore, applications of the new mathematical models to infection control on medical implants are also presented. This work is done in collaboration with faculty from both the Mathematics and Bioengineering Departments at UT Arlington.

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PP2

Data Mining and Machine Learning Methods to Improve Serodetection in the Mouse Model of Infectious Diseases

Data mining and machine learning approaches produce unique results by engineering the knowledge inherently generated from large volume data sets. Multiplex microbead assays developed by some of us are routinely used by major animal (mouse) facilities across the country to detect simultaneous detection of several pathogens. These pathogen surveillance studies generate a large amount of data that are typically used for detection but discarded subsequently with no future value. Each surveillance study in this process adds knowledge and can be used efficiently to improve the multiplex assay and its predictive power. Using powerful data-mining and machine learning methods we demonstrate the feasibility of such an approach. Our results show that (1) data mining techniques can be successfully applied to serodection of pathogens in mice with a reasonably high performance level; (2) the classification using features selected by a range of algorithms consistently outperformed those selected by statistical testing in terms of accuracy and robustness; and (3) the discriminatory features (molecular profiles) can be very different from one selection method to another. The tools developed in this project can be implemented for any large scale data generated in clinical translational research including proteomics, functional genomics and metabolomics.

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PP2

Mathematical Modeling of Chromosome Segregation in Bacteria.

During division, *Caulobacter crescentus* uses interactions between dynamic ParA filaments and ParB proteins to segregate copies of its circular chromosome. We present two mathematical models for bacterial chromosome movement; one is based on stochastic differential equations and the other uses partial differential equations. We propose that chromosome movement is facilitated by a biased diffusion mechanism in which ParB binds ParA filaments weakly and nonspecifically. Tight control of ParA filament dynamics is essential for proper segregation.

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PP2

Posterior Distributions in Parameter Estimation

Differential equation models in biology often include parameters whose values cannot be directly measured. To estimate unknown parameter values, we employ a Bayesian inference approach. This results in a distribution of parameters, which reflects the likelihood that a parameter will cause the model to match observed data. Motivated by data sets from inflammation studies, we explore relationships between the properties of the data available and characteristics of the parameter distribution obtained through various computational methods.

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PP2

Modelling of Endocrinological Networks

We present two differential equation models describing reproductive mechanisms: the human menstrual cycle and the bovine estrous cycle. Both models are based on a whole-body approach with fully coupled feedback mechanisms to describe the periodic dynamics of hormones, follicles, and corpus luteum. Elaborate numerical algorithms are used for simulation and parameter identification, which allows us to explore the models with respect to synchronization studies, phase interlocking, model reduction techniques, and model refinement.

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PP2

Prediction of Effective Elastic Properties of Osteons by Means of Multiscale Models and Homogenization Methods

Osteons, the basic structural units of cortical bone, have complex microstructures, making it a challenge to model and to simulate their effective elastic properties. We present models of different complexity and identify conditions under which they predict appropriate effective elastic properties. To that end we applied the numerical homogenization scheme in connection with the finite element method and studied the influence of geometrical parameters, the mesh size and the linear solver on the model outcome.

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Formation of Anti-Waves in Gap Junction Coupled Chains of Neurons

Using network models consisting of gap junction coupled Wang-Buszaki neurons, we demonstrate that it is possible to obtain not only synchronous activity between neurons but also a variety of constant phase shifts between 0 and π. We call these phase shifts intermediate stable phase-locked states. These phase shifts can produce a large variety of "wave-like" activity patterns in one-dimensional chains and two-dimensional arrays of neurons, which can be studied by reducing the system of equations to a phase model. The 2π periodic coupling functions of these models are charachterized by prominent higher order terms in their Fourier expansion, which can be varied by changing model parameters. We study how the relative contribution of the odd and even terms effect what solutions are possible, the basin of attraction of those solutions and their stability. These models may be applicable to the spinal central pattern generators of the dogfish and also to the developing neocortex of the neonatal rat.

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PP2

Numerical Computations of Multiphase Systems

In recent years, many biological phenomena involving complex mechanical and biochemical interactions of multiple components have been successfully modeled using a multiphase framework, including tumorigenesis, biofilm channel formation, and developmental processes. In this poster, I will examine the computational issues that are inherent in the numerical simulation of these multiphase models, and demonstrate some particular schemes which are both efficient and robust.

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An Optimal Control Approach for Modeling the Response to Head-Up Tilt

Short term cardiovascular responses to head-up tilt (HUT) experiments involve complex cardiovascular regulation in order to maintain blood pressure at homeostatic levels. This poster presents an optimal control approach to modeling effects of cardiovascular regulation due to HUT on efferents including heart rate, cardiac contractility, vascular resistance, and vessel compliance. The model consists of a five-compartment lumped parameter model, a physiologically based sub-model that describes gravitational effects during HUT, and finally a cardiovascular regulation model that adjusts those efferents mentioned.

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PP2

A Model of Self-Destructive Bacteria

In order to successfully invade the body *Salmonella Typhimurium* must outcompete the native colony of commensal microbiota that constantly lines the human intestine. Recently, studies have found evidence that invading pop-

ulations of *Salmonella Typhimurium* gain an environmental advantage over the commensal microbiota by provoking the body's inflammatory defenses. We developed a model exploring two hypotheses which seek to explain how self-sacrifice among invading bacteria can produce this environmental advantage.

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