IP1

Neurosensory Network Functionality, Adaptation, and Robustness: Paradigms for Data-driven Control and Learning

High-dimensional networked biological systems are ubiquitous and characterized by a large connectivity graph whose structure determines how the system operates as a whole. Typically the connectivity is so complex (and unknown as well) that the functionality, control and robustness of the network of interest is impossible to characterize using currently available methods. A full understanding of this computational process encoded throughout a nervous system that transforms sensory input into motor representations requires the ability to generate proxy models for the activity of sensory neurons, decision-making circuits, and motor circuits in a behaving animal. Our objective is to use emerging model discovery methods to extract the underlying engineering principles of cognitive capability, namely those that allow complex networks to learn and enact control and functionality in the robust manner observed in neurosensory systems.

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IP2

Mathematical and Experimental Models of Cell Invasion with Fluorescent Cell Cycle Indicators

Fluorescent cell cycle indicators, such as FUCCI, allow us to visualise the cell cycle in individual cells. FUCCI reveals real-time information about cell cycle dynamics in individual cells, and can be used to explore how the cell cycle relates to the location of cells, local cell density, and different microenvironments. In this talk we will describe how FUCCI technology can be incorporated into continuum and discrete models of cell invasion. Using experimental data from scratch assays with FUCCI-transduced melanoma cells, we show how mathematical models can be used to predict key features of the experiments. Some analysis of travelling wave solutions of the models will also be presented.

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IP3

Modeling Data on the TCR-frequency Distribution of Naive T Cells

The human naive TCR repertoire is extremely diverse and measuring its frequency distribution directly is challenging. We report a strong relation between the frequency of TCR a and chains of naive T cells in blood samples and their probability of being generated by V(D)J recombination. This is unexpected because in adults, the vast majority of naive T cells are produced by peripheral division rather than thymic generation. To examine if re-combination probabilities can indeed explain the frequency differences between TCRs in the naive compartment, we develop mathematical models describing naive T-cell dynamics, and compared their predictions with sequencing data. We establish the presence of a small fraction, but a large number, of TCR sequences that are frequently observed and have high thymic generation probabilities. These results demonstrate an unexpectedly large role for VDJ- recombination probabilities in shaping the TCR-frequency distribution, casting doubt on the role of TCR-specific competition between naive T-cell specificities.

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IP4

Predicting Cardiovascular Disease Progression in Adults and Children with Personalized Simulations

Cardiovascular disease is the leading cause of death worldwide, with nearly 1 in 4 deaths caused by heart disease alone. In children, congenital heart disease affects 1 in 100 infants, and is the leading cause of infant mortality in the US. Patient-specific modeling based on medical image data increasingly enables personalized medicine and individualized treatment planning in cardiovascular disease patients, providing key links between the mechanical environment and subsequent disease progression. We will discuss recent methodological advances in cardiovascular simulations, including (1) fluid-structure interaction methods as a step towards whole-heart modeling, (2) unified finite element methods for fluid and solid mechanics with realistic biological tissue models, and (3) uncertainty quantification to assess confidence in simulation predictions. Clinical application of these methods will be demonstrated in: 1) coronary blood flow simulations for assessment of vein graft failure in coronary bypass graft patients, and 2) prediction of disease progression in pediatric pulmonary hypertension. We will also provide an overview of our open source SimVascular project, which makes our tools available to the scientific community (www.simvascular.org). Finally, we will provide an outlook on recent successes and challenges of translating modeling tools to the clinic.

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IP5

A Rule Based Approach to Development

Development of animals proceeds from bulk, through simple spherical shapes to folds and tubes. Emerging geometrical shapes are robust for a given species and can be maintained when moved to different parts of the embryo or if the size is varied. Despite conceptually similar processes of progression through development, the resulting geometrical shapes can be very different between species. How can we reconcile this robustness with overall variability? The progression from bulk, to tubes and folds coincides with the progressive - first apical basal and then planar – polarization of cells. To explore if cellular polarization may enable development with the ability to create diversity of robust and stable shapes we developed a tool that allows to simulate thousands of polarized cells in 3D. We find that cellular polarity enables stable complex folded shapes. When set in the context of pancreatic organoids, One polarity (Apical basal) coupled with differential growth rates is sufficient to explain emergence of folded lumens in pancreatic organoids. With two, apical basal and planar, mutually perpendicular polarities, the model recovers main stages of

sea urchin gastrulation

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IP6

Mathematical Modeling of Drug Response Variability and Optimal Dosing in Oncology and Immuno-oncology

Leveraging, through modeling and simulations, the time-course of tumor size and biomarkers in oncology has been shown to be a relevant approach to avoid unnecessary toxicity, improve efficiency of active drugs thus enabling an optimization of resource spending in patient care. In this presentation, we will discuss several modeling efforts aimed at predicting efficacy of anti-cancer drugs and optimizing therapeutic dosing regimen. Some technical features of parameter estimation techniques in a patient-population context will also be discussed. Finally, as immuno-oncology is becoming established as one of the main areas of focus for drug development, we will discuss the potential role of mathematical modeling as a valuable tool in this specific area to better explore the role of disease heterogeneity and improve the identification of responders and the design of clinical trials.

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IP7

Mathematical Models of Targeted Cancer Treatments and Drug Resistance

The talk will discuss the use of mathematical models for understanding targeted cancer therapies. One area of focus is the treatment of chronic lymphocytic leukemia with tyrosine kinase inhibitors. I will explore how mathematical approaches have helped elucidate the mechanism of action of the targeted drug ibrutinib, and will discuss how evolutionary models, based on patient-specific parameters, can make individualized predictions about treatment outcomes. Another focus of the talk is the use of oncolytic viruses to kill cancer cells and drive cancers into remission. These are viruses that specifically infect cancer cells and spread throughout tumors. I will discuss mathematical models applied to experimental data that analyze virus spread in a spatially structured setting, concentrating on the interactions of the virus with innate immune mechanisms that determine the outcome of virus spread.

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IP8

Linking Local Decisions with Global Outcomes in Networks: Case Studies in Behavior and Population Health

How can multilevel feedback control on global, emergent properties of self-organizing networks shape the algorithms actors use to guide their own individual behaviors, even when the global outcome cannot be individually observed? We will discuss example systems from evolutionary biology, infectious disease epidemiology, and social networks that exhibit this type of behavior. We will also briefly consider what types of scenarios may allow analytic approximations to provide useful insight, and when instead we may best be served by computational simulation experiments. We will conclude with some broad mathematical challenges that could advance our ability to tackle these types of questions. Brief Bio: Fefferman is an Associate Professor at the University of Tennessee, Knoxville in both the Departments of Ecology and Evolutionary Biology & Mathematics. She uses mathematical modeling to explore the behavior, evolution, and control of complex systems with application areas ranging from basic science (evolutionary sociobiology and epidemiology) to deployable tools (biosurveillance, cyber-security, and wildlife conservation). Fefferman has been an active member of NIMBioS (the National Institute for Mathematical and Biological Synthesis), both the CCICADA and START Centers (US DHS Centers of Excellence), and has served on scientific advisory boards for the EPA, Mathematical Biosciences Institute (MBI), and Los Alamos National Laboratories.

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CP1

Revealing Causal Hematological Regulatory Networks

The process of producing all of the body's blood cells is robustly regulated by an extensive network of cytokines (small proteins secreted by blood cells and other tissues). Generally speaking, the principal (and often secondary, tertiary etc.) role of each of these molecules has been identified. However, given the fundamental role of the hematopoietic system and its constituents to organismal health, many cytokines perform ancillary functions within network structures that remain to be elucidated.
vspace1em Oftentimes, hematopoietic dysregulation in the form of blood pathologies can help to identify dynamical relationships that we are unable to discern in healthy individuals. Cyclic thrombocytopenia (CTP–sustained and periodic oscillations in megakaryocyte/platelet numbers) is one such dynamical disease. We analyzed time series data from an individual with CTP using standard Fourier and statistical approaches (periodogram and correlation analysis) in addition to convergent cross mapping (Sugihara et al., Detecting causality in complex ecosystems. *Science 338(6106).* 496–500, 2012) to infer causal relationships amongst 64 cytokines (and their gene expressions), uncovering a plethora of novel relationships. These results further refine our understanding of the many networks that support the production of blood cells and immunological responses, and may help to identify novel therapies and drug targets.

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CP1

The Dynamic Nature of Functional Brain Networks of Emotional Regulation

Numerous psychiatric disorders, including Major Depressive Disorder (MDD) and others are all thought to have underlying abnormalities in emotion regulation. Mostly, fMRI (functional MRI) scans of the patients either in resting state or while they are performing tasks are used to

deduce network connectivity. The norm in the inference of neuroimaging network connectivity is to characterize a static representation of connectivity structure. However, such representations mask dynamic variation in the neural response as complex brain system interactions evolve over time. This talk will propose a pipeline for describing some of the dynamic aspects of emotion regulation network connectivity. The pipeline will use probabilistic boolean networks to generate dynamic effective connectivity signatures. The signatures along with clinical data will then be used to group the patients and extract key features that capture variation.

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CP1

Inference and Control in Biological Networks

Over the past two decades, the significance of data for biology in general and genetics in particular has seen a remarkable increase due to advances in computing. The primary goal of any study involving one of these big data applications is to unlock the inapparent complexity. The relevance of any data set is therefore closely tied to the ability of the analytical tools used to extract meaningful information from it. One such important piece of information is the set of interactions in a multivariate system. This is a central problem of network biology with large datasets representing network configurations(microarrays, neural spikes etc.) with almost no information of the governing dynamics. In the present work, we solve the statistical mechanics analog of the network inference problem i.e. the inverse Ising problem. Biological networks are often directed, hierarchical and exchange matter and energy with their surroundings. This means that their recorded configurations don't correspond to thermodynamic equilibrium but to a non-equilibrium steady state(NESS). We use a dynamic version of the maximum likelihood method to characterize this NESS and successfully reconstruct model networks with asymmetric interactions. Guided by recent works for controlling symmetric networks obeying detailed balance, we propose necessary variations needed to extend the present network control algorithms to asymmetric networks, getting closer to in-vivo biological control.

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CP1

Fast Cheater Migration Stabilizes Coexistence in a Public Goods Dilemma on Networks

Cooperation is frequently considered an unsustainable strategy: if an entire population is cooperating, each individual can increase its overall fitness by choosing not to cooperate, thereby still receiving all the benefit of its cooperating neighbors while no longer expending its own energy. Observable cooperation in naturally-occurring public goods games is consequently of great interest, as such systems offer insight into both the emergence and sustainability of cooperation. Here we consider a population that obeys a public goods game on a network of discrete regions (that we call nests), between any two of which individuals are free to migrate. We construct a system of piecewise-smooth ordinary differential equations that couple the within-nest population dynamics and the between-nest migratory dynamics. Through a combination of analytical and numerical methods, we show that if the workers within the population migrate sufficiently fast relative to the cheaters, the network loses stability first through a Hopf bifurcation, then a torus bifurcation, after which one or more nests collapse. Our results indicate that fast moving cheaters can act to stabilize worker-cheater coexistence within network that would otherwise collapse.

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CP2

Investigating the Coexistence of Cryptic Nematode Species using Individual-based Modelling

Recent experimental work has demonstrated the robust coexistence of a community of four cryptic *Litoditis marina* (nematode) species. Important differences in functionality and stress tolerance between the cryptic species were discovered, which are hypothesized to play a role in mediating their coexistence. To help untangle the mechanisms governing the dynamics of this system, we turn to individual-based modelling. This approach captures both the system's individual variability and its spatial heterogeneity, two important features which can support the coexistence of competing species. The model incorporates the fundamental demographic processes occurring in the community: reproduction, competition, mobility, and resource use. Data characterizing the four cryptic species (in terms of their growth rates, dispersal ability, competitive interactions, and responses to changing abiotic conditions) are used to parameterize the model. Differences in the cryptic species' stress tolerances play an important role in the dynamics of the system, while the persistence of the underlying competition structure is sensitive to biotic changes. Our results provide insights into the fundamental mechanisms underlying the coexistence of these cryptic species, as well as the functionality of such communities threatened by climate-related abiotic changes.

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CP2

Optimizing Organisms in Fluctuating, Memoryful Environments

Populations of organisms can use memory of past environments to increase their expected log growth rate. We quantify this increase in a simple setup and find that the quality of an organism's memory is given by the predictive information, the mutual information between an organism state and the future environment. Then we examine design principles for sensors that try to maximize their predictive information, finding that even large randomly-wired sensors fail to capture much predictive information. This, in turn, suggests that we can aid machine learning efforts to build predictive machines by studying the learning rules of real biological sensors.

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CP2

Dynamical Consequences of Mechanical Interactions in Growing Microbial Consortia

Advances in synthetic biology allow us to engineer bacterial collectives with pre-specified characteristics. However, the behavior of these collectives is difficult to understand, as cellular growth and division as well as extra-cellular fluid flow lead to complex, changing arrangements of cells within the population. To rationally engineer and control the behavior of cell collectives we need theoretical and computational tools to understand their emergent spatiotemporal dynamics. Here, we present an agent-based model that allows growing cells to detect and respond to mechanical interactions. Crucially, our model couples the dynamics of cell growth to the cells environment: Mechanical constraints can affect cellular growth rate and a cell may alter its behavior in response to these constraints. This coupling links the mechanical forces that influence cell growth and emergent behaviors in cell assemblies. We illustrate our approach by showing how mechanical interactions can impact the dynamics of bacterial collectives growing in microfluidic traps.

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CP2

Genetic Processes Effects on Predator-prey Communities

Much work has been done to understand how feedbacks between ecological and evolutionary processes qualitatively alter the dynamics of natural communities. However, there has been relatively little work done on how underlying genetic processes impact the effects of these eco-evolutionary feedbacks. Here, we investigate a coupled model of a predator evolving in a trait controlled by two potentially linked genetic loci, each with two possible alleles, which determine the predator's interactions with two prey species. We show that recombination between the two loci and the magnitude of the effects of each locus affect the persistence of alleles and the cycling of the predator and the prey. Importantly, our work highlights that aspects of genetics within one species play an important role in population dynamics of interacting species.

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CP2

Phase Diagrams of Run-and-Tumble Processes

Motivated by the observation of rippling patterns in colonies of Myxobacteria, we study a "simplest' modes for dynamics of populations, where agents run either left or right with constant speed, and reverse direction depending on local population densities in a nonlinear fashion. Linear analysis and simulations reveal how shot noise perturbations can give rise to rippling behavior and predict wavelengths. The talk will explain the basic mechanism and highlight the relevance of a systematic stability analysis for the coherent structures observed. We identify classes of nonlinearities that allow for such complex patterns, and show that more generally such processes can be classified, depending on tumbling parameters, into three different macroscopic phases, "equidistribution', "ripples and waves', and "blowup and clustering'.

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CP3

Transient Regulation of Glutamate Dehydrogenase (GDH) Deamination Activity with GTP Inhibition

Recent discovery of hyperinsulinism/hyperammonemia syndrome (HI/HA), the most common cause of recurrent hypoglycaemia in early infancy, has reinvigorated interest in glutamate dehydrogenase (GDH) as a key regulator of amino acid and ammonia metabolism. In HI/HA syndrome, excessive insulin secretion by pancreatic beta-cells and defective ammonium metabolism in the liver are linked with impaired GDH sensitivity to its inhibitor GTP. However, how GDH becomes insensitive to its natural inhibitor GTP and consequently causes over activity by missense mutations remain a mystery. Here, we report allosteric regulation of GDH activity mediated jointly by the regulatory cofactor NADH and the GTP. Hexameric structure of GDH with interprotomer asymmetricities posies it for functional heterogeneity, in which transgenic simultaneous occurrences of both GDH.NADH.GTP open and closed type protomers eventually establishes robust GDH systems. With this transient regulation, GDH-catalysed oxidative deaminated product alpha-ketoglutarte maintains constant ratio with the inputs of GTP, in the face of wide variation of GTP and GDH concentrations. We have further illustrated that HI/HA related mutations can alter this dynamics and thereby the robustness property of the system, causing GTP-insensitivity and overactivity of GDH.

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CP3

Unveiling Molecular Mechanisms of Kinesin-5 Function using Multiscale Computational Techniques

Molecular motor protein Kinesin-5 (Eg5) is a member of kinesin superfamily that is critical for bipolar spindle assembly and spindle maintenance during mitosis. As a result it is a promising chemotherapeutic target for cancer treatment. While a number of small-molecule drugs that interact with Eg5 have been identified, little is known about the molecular mechanisms by which they inhibit Eg5 function. Furthermore, multi-motor systems can exhibit qualitatively diverse behavior for different drugs, in some cases showing non-linear dependence of motor velocity on drug concentration. We study molecular mechanisms behind function of individual Eg5 and multi-motor systems involving it using computational modeling techniques. Besides apparent fundamental value this work has direct implications for clinical applications, where in depth understanding of Eg5-drug interaction is important.

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CP3

Visual Transduction: A Signaling Paradigm Across Scale Orders

Visual transduction in rod and cone photoreceptor cells is one of the best experimentally quantified G-protein signaling cascades. Here photons of light are converted by a biochemical process into a systems response by diffusion of the 2nd messengers cGMP and Ca2+. These messengers then cause the opening or closing of gated ion channels. The morphology of photoreceptor cells is finely structured with a repeating pattern of hundreds of membrane folds throughout the outersegment. These make for two disparate geometric scales. This feature renders it computationally expensive as is. This talk will present a spatiotemporal, homogenized and numerically implemented finite element model of cone phototransduction. The role of homogenization is to simplify the geometry while recasting the smaller scales into a novel partial differential equations law. The model is validated through its comparison with a standard finite element diffusion model set to the original geometry. The homogenized models performance in both time of simulation and memory use will be compared to the standard diffusion models. Some comparisons with well-stirred and longitudinal diffusion models will also be made to underscore the importance of using 3d resolved models. This numerical project is joint work with Giovanni Caruso. It builds on an investigation done for rods by an ongoing interdisciplinary team of researchers that, non-exhaustively, also includes E. DiBenedetto and V. Gurevich.

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CP4

Fast Separatrix Computation of Attraction Basins in Competing Ecosystems

The evolution of an interacting population ecosystem involving predators and prey or competing species is essentially determined by its present status. Separatrix manifolds partition the phase space in attraction basins for its omega-limit sets. In recent investigations we developed algorithms for the detection of points on these manifolds using an efficient backward integration in time or through a bisection routine. For the latter approach, the scheme to detect separatrix points for asymptotically stable equilibria proves to be computationally expensive and is not robust enough for periodic orbits. To graphically reconstruct these manifolds, described by implicit equations, the points are interpolated with the implicit Radial Basis Function Partition of Unity method. Here, we present an ad hoc bisection-like algorithm that speeds up the procedure. A suitable extension even allows treatment of periodic orbits. Numerical results on populations competition models are presented.

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CP4

Cellular Decision Making Models in Microorganisms

Decision making is ubiquitous throughout all levels of biological complexity, from social insect colonies to multicellular organisms to individual cells. Here we present a theoretical study of cellular decision making mechanisms that describe the choice between different extracellular carbon sources. Such decision making mechanisms give rise to different consumption strategies the cell can adopt in response to the specific growth rate supported by each nutrient, as well as their environmental abundance; cells thus often show contrasting expression levels between their cognate metabolic pathways. In the present work, the system of coupled differential equations that represent the decision making processes are studied by means of bifurcation analysis and stochastic time-dependent simulations. We show that by assigning values to the sugar alternatives in correspondence with the growth rate each of them support, the transition between a deadlock state and decision deadlock breaking is enabled by the strength and nature of the inhibition signal. By comparing the dynamic behaviour of two different inhibitory signalling strategies, we find that the consumption regimes available to the cell are dependent on the structure of the inhibition signalling motif. Our results accentuate the importance of the inhibition signalling motif in cellular decision making and motivate a functional and integrated study of decision making of cells and microorganisms.

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CP4

Numerical Methods for Ecological Diffusion and Ecological Telegraphers Models on Domains with Movement Constraints

The ecological diffusion equation connects animal movement with landscape heterogeneity. The ecological telegraphers equation adds correlated movement choices and speed constraints in habitat-driven movement models. We develop methods for solving these equations on irregular domains with constraints to animal movement such as coastlines, rivers, and highways. We then apply these methods to model elk following the retreat of the snowline in the spring.

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CP4

Timescale Analysis for Eco-evolutionary Time Series Data

Traditionally, evolution, or changes in gene frequencies, is perceived as occurring very slowly compared to ecological rates of change (e.g., changes in population abundances). Recent empirical studies suggest that ecology and evolution may change at similar rates. However, there is debate about how fast evolution can be relative to ecology. We present a method based on the theory of fast-slow dynamical systems to estimate the relative rates of ecological and evolutionary change from abundance and phenotypic time series data. When applied to a suite of empirical data sets, we find in many cases that ecology and evolution have comparable time scales. These results show that the traditional assumption of slow evolution does not always hold in empirical systems. In addition, this reinforces the idea that a new theory addressing the concurrent interactions between ecological and evolutionary processes (i.e., eco-evolutionary dynamics) is needed.

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CP4

Discrete Time Drought Models: A Mathematical Comparison among the United States' Biomes

Due to the significant impact droughts have had on the modern world, many scholarly studies have been done that analyze drought trends. Markov chains and ARIMA time series models have been used to study drought in specific locations such as Maharashtra, India and the Laohahe River basin in northeast China, but the scope of these studies does not extend to multiple locations or biomes. This talk presents a mathematical analysis of drought conditions for different locations/biomes around the United States of America (USA) using publicly-available data published by the United States Drought Monitor. Each major USA biome is represented by one or more cities, and the United States Drought Monitors drought rating for each of the nine selected cities was recorded every week between January 2000 and April 2013. Using a discrete-time Markov chain model, the steady state distribution and the mean first passage times for each drought state of each city are calculated. Also, the data is analyzed using a statistical time series model to determine statistical worsening of drought conditions over time. The Markov chain and time series approaches yield remarkably similar estimates for the desired parameters. Finally, statistical tests are performed on the steady state distributions to determine

which cities experienced statistically different drought conditions. The long-term drought conditions for each city are statistically different from Columbia, SC in at least one state of drought.

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CP4

Small Organisms Causing Big Problems: Modeling Heterosigma Akashiwo

A specific species of phytoplankton, Heterosigma Akashiwo, has been the cause of harmful algal blooms (HABs) in waterways around the world causing millions of dollars in damage to farmed animals and destroying ecosystems. Developing a fundamental understanding of their movements and interactions through phototaxis and chemotaxis is vital to comprehending why these HABs start to form and how they can be prevented. In this talk, we attempt to create a complex and biologically accurate mathematical and computational model reflecting the movement of an ecology of plankton, incorporating phototaxis, chemotaxis, and the fluid dynamics that may be affecting the flow. We present and analyze a succession of models together with a sequence of laboratory and computational experiments that inform the mathematical ideas underlying the model. Lastly, we discuss further experiments and research necessary for our continued insight into problems that we are encountering, such as planktons formation of aggregations, the gaps in-between those aggregations, and the difficulty of expanding our models to higher dimensions biologically, mathematically, and computationally.

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CP5

Biomagnetic Fluid Flow Along with Ferrous Ferric Oxide Particles in a Cylindrical Tube with Induced Magnetic Effects

The biomagnetic fluid flow together with ferrous ferric oxide particles in a cylindrical tube under the periodic pressure and magnetic field is studied. Analytical solutions corresponding to the fluid velocity and particles velocity have been derived in explicit forms. As the innovation, the motion of the fluid is generated by a time-dependent pressure gradient of an arbitrary form. The particular case of cosine oscillations is studied. An external magnetic field is applied perpendicular to the cylindrical tube. The governing nonlinear partial differential equations are solved analytically with the help of the Laplace and finite Hankel transform. The influence of magnetic field on the fluid velocity and particles velocity is easily studied by using the obtained analytical solutions. Results corresponding to pulsatile pressure gradient show that the external magnetic field significantly influences the fluid velocity and ferric oxide particles velocity, namely, the increasing of Hartman number leads to a slowing of fluid flow and ferric oxide particles. The ferrous ferric oxide particles are moving in the same trend like fluid but with smaller velocity. Our results, based on the analytical solutions, are compared with some numerical and experimental results from the literature. The obtained analytical solutions afford a comprehensive insight into more complicated flow conditions and can be an important advantage for some practical problems.

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CP5

On the use of Convected Coordinate Systems in the Mechanics of Continuous Media Derived from a QR Factorization of $\mathbf{F}$

An oblique, Cartesian, coordinate system arises from the geometry affiliated with a Gram-Schmidt (**QR**) factorization of the deformation gradient $\mathbf{F}$, wherein $\mathbf{Q}$ is an orthogonal matrix and $\mathbf{R}$ is an upper-triangular matrix. Here a cube deforms into a parallelepiped whose edges are oblique and serve as the base vectors for a physical coordinate system. Components for the metric tensor, its dual, and their rates, evaluated in this convected, physical, coordinate system, are established for *any* state of deformation. Strains and strain rates are defined and quantified in terms of these metrics and their rates. Quotient laws and their affiliated Jacobians are constructed that govern how vector and tensor fields map between this oblique, physical, coordinate system, where constitutive equations are ideally cast, and the rectangular, Cartesian, coordinate systems of the Eulerian and Lagrangian configurations, where boundary value problems are solved. This presentation is dedicated to the memory of Arthur Lodge.

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CP5

Incorporating Rheology and Concentration Gradients in Blood Flow Simulations

Blood flow simulations have applications from drug delivery to coronary artery bypass surgery. However, despite the potential, current approaches are macroscopic and oversimplified or microscopic, but computationally demanding and applications limited. We aim to bridge the gap between the two by using macroscopic models that are better connected to the bloods variable microstructure and thus can account for the complex flow behavior of blood. Rheologically, blood is a complex fluid which exhibits shear thinning, viscoelasticity, and thixotropy a time dependent viscosity. Moreover, as blood is a concentrated suspension of red blood cells (RBCs), often for capillary flow, concentration gradients characterized by a depleted RBC layer near the walls will form. In this work, we present two models. The first is a bulk rheology model for blood which is based on a structural kinetics approach and incorporates a viscoelastic element at high shear rates representing the individual RBC contributions [Horner J. S., M. J. Armstrong, N. J. Wagner, and A. N. Beris, J. Rheol., 62(2), (2018)]. The second is a two phase fluid model which describes the RBC depletion layer formation. We compare the combined models to experimental results for bulk rheology measurements on human blood for physiologically relevant flow conditions. Finally, we incorporate the models into CFD flow simulations to demonstrate the effect that the aforementioned complexities have on in vivo flow.

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CP5

Assessing Physical Control Mechanisms in Lung Branching Morphogenesis

We have developed several models of the physical control of branching morphogenesis in the lung, considering a variety of factors, including transport and mechanics. How reasonable a model initially seems is not necessarily correlated with its explanatory power. In this talk, we will present a variety of models of branching morphogenesis, and compare their implications.

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CP5

Biomechanical Model of Glioblastoma Multiforme Onset and Growth

Patients diagnosed with glioblastoma multiforme (GBM) are expected to survive only 14 months and die due to the pressure that the tumor builds in the brain as well as the formation of peritumoral edema (PTE). With the view to investigating the early stages of brain tumor development, we develop a biomechanical model of GBM onset. The model is derived using principles of mass and momentum balances and explicitly includes pressure dynamics within the disease brain and the ability/inability of healthy tissue to repair itself in response to these cues. As a first step, we assume an implicit tumor that exerts pressure at a healthy boundary causing the boundary to move into healthy tissue with a velocity v (thought of as the tumor growth rate). We investigate three velocity regimes: where v is an order of magnitude slower than the time-scale of healthy brain tissue renormalization (benign tumor); where v is an order of magnitude higher than the time-scale of healthy brain tissue renormalization (high-grade tumor); a transition between these. Our model shows a correlation between the tumor velocity and the formation of PTE, which is an indicator of tumor malignancy. The resulting model includes time-varying diffusion on a moving domain, which presents unique numerical challenges. We propose a scheme to solve such equations, validating our method with a test problem as well as theoretical analysis using techniques from asymptotic methods in order to complete this research aim.

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CP5

A Mechanism for the Proliferative Control of Tissue Mechanics in the Absence of Growth

During the development of a multicellular organism, cells coordinate their activities to generate mechanical forces, which in turn drive tissue deformation and eventually define the shape of the adult tissue. Broadly speaking, it is recognized that mechanical forces can be generated through differential growth and the activity of the cytoskeleton. Based on quantitative analyses of live imaging of the Drosophila dorsal thorax, we suggest a novel mechanism that can generate contractile forces within the plane of an epithelia - via cell proliferation in the absence of growth. Utilizing force inference techniques, we demonstrate that it is not the gradient of junction tension but the divergence of junction-tension associated stresses that induces the area constriction of the proliferating tissue. Using the vertex model simulations, we show that the local averaged stresses can be roughly elevated by a fold of mechanism is robust to disordered cell shapes and the division anisotropy, but can be dominated by growth. In competition with growth, we identify the parameter regime where this mechanism is effective and suggest experiments to test this new mechanism.

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CP6

Extinction in Stochastic Epidemic Models with Seasonality

We consider stochastic SIS and SIR epidemic models, where the internal noise is due to the random interactions of individuals in the population. We provide an overview of the general theoretic framework that allows one to understand noise-induced rare events, such as spontaneous disease extinction. Although there are many paths to extinction, there is one path termed the optimal path that is probabilistically most likely to occur. In this work, we demonstrate how to extend the theory to identify the optimal path to extinction when seasonality in the contact rate is included in the models.

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CP6

Analyzing an Epidemic Diseases with Multiple

Transmission Pathways

Emerging infectious diseases are a threat to biodiversity and fungal pathogens have caused rapid declines in amphibian populations around the globe (McCraw and Gurr, 2012). Gray et al (2015) identifies Batrachochytrium salamandrivorans (Bsal) as an emerging fungal pathogen that caused rapid die-offs of nave salamanders in Europe and predicts North America will soon experience similar devastation if no policy actions are taken and the pathogen emerges. Epidemic dynamics of infectious diseases with multiple routes of transmission are complex. Mathematical models can be used to determine invasion potential and identify which transmission pathway is dominant, can ultimately help identify appropriate intervention strategies. We developed compartmental host-pathogen models to examine transmission dynamics of an emerging fungal pathogen on an amphibian population. Multiple stages of infection are incorporated into the model, allowing disease-induced mortality and zoospore shedding rates to increase as the disease progresses. Parameter sensitivity analysis using the Latin Hypercube Sampling (LHS) with the Partial Rank Correlation Coefficient (PRCC), calculations of the basic reproductive number, and numerical simulations shed insight into pathogen dynamics.

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CP6

Probability and Time to Infection in Stochastic Models of Infectious Diseases

One of the biggest concerns to public health is emerging and re-emerging infectious diseases. Many recent outbreaks of emerging diseases have zoonotic origins. Spillover infections from zoonotic sources, such as SARS and MERS, have resulted in disease outbreaks in human populations. In addition, some human diseases have re-emerged, such as measles and pertussis, due to vaccine waning or lack of vaccine protection. We apply stochastic multigroup models, Markov chain models, and branching process approximations to investigate the probability and time to spillover infection from a zoonotic source in emerging diseases and the probability of an outbreak in human diseases. Differences in the transmission patterns and the longevity of infection affect the probability of an outbreak. In the recent emerging infectious diseases SARS or MERS, amplification and spread of infection have been attributed to highly infectious individuals known as superspreaders. The models show that probability of an outbreak is much greater when an infection is initiated by a superspreader as compared to a nonsuperspreader. In the case of re-emerging infectious diseases, such as measles, disease outbreaks are more likely if initiated by susceptible individuals with a long duration of infection, than by susceptible individuals with a short duration of infection.

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CP6

Analysis of an Insect Vectors of Phytoplasmas Model with Life History Trait and Size Structure in Host Vineyards

In this paper a multistage host-vector epidemiological model with physiological age structure and spatial insect spreading. The population of insect population is described throughout its life history trait consisting of five stages of development termed eggs, larval, pupal and moth adult (male and female). Male and female are subcompartimented via SEI epidemilogical model while the population of plant is describd using an SEIR model. We investigate the global dynamic of this model.

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CP6

Continuous Approximations of Agent-Based Models with State Changes

We are often interested in modeling situations where the exposure and absorption of a chemical above a critical threshold changes the state of an organism. For example, we may wish to determine the survival probabilities of cells or organisms exposed to pollutants or toxic stimuli. An agent-based model can easily capture the essential elements of this model, but meaningful analysis is difficult. We can, however, use the precise definition of the discrete agent-based simulation of chemical absorption-led state changes to motivate the derivation of continuous PDE models describing features of the simulation. Our agent-based model initializes agents as well as a chemical concentration in the region. The agents perform random walks, absorbing a proportion of the chemicals in their paths. By adapting the continuous random walk derivation, we can derive models to calculate the probability density function (PDF) of the location of the agent as well as the time-dependent PDFs of the location of each state of the agent. We can also calculate the expected time for the agent to switch states.

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CP7

A Framework for Model Analysis Across Multiple Experiment Regimes: Investigating Effects of Zinc on Xylella Fastidiosa as a Case Study

Mathematical models using ordinary differential equations are ubiquitous in analyzing dynamical biological systems. However, presence of various uncertainties introduces problems with identifiability of the unknown parameters of the model which are usually estimated using data from experiments. Since the model analysis might be dependent upon a neighborhood of the numerical estimates of the parameters, parameter identifiability should be addressed beforehand to capture biologically relevant parameter space. Here, we propose a framework to analyze models using data from different experiment regimes which addresses parameter identifiability when there is rather limited prior information about their possible estimates. It uses the data to

make an informed decision about the region in the parameter space over which we then conduct global sensitivity analysis to determine important processes of the model. We also discuss algorithmic modifications done for computational viability of the proposed methodology. As a case study, we develop a compartmental model for growth dynamics and biofilm formation of a bacterial plant pathogen and use our framework to identify possible effects of zinc on the bacterial populations in different metabolic states.

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CP7

Introducing *MuMoT*: A *Mu*ltiscale *Mo*delling *T*ool for Life Scientists

Understanding biological, chemical and physical interactions in natural systems is of the utmost interest in the life sciences. Interaction patterns can be intriguing and their analysis often requires complex methods and a profound mathematical knowledge. Here, we present MuMoT - a Multiscale Modelling Tool that is designed to make multifaceted mathematical analyses accessible to a wider community of life scientists through their automation, whilst providing a simple-to-use state-of-the-art mathematical tool box. This open-source software tool allows complex and comprehensive model analysis based on simple input in the form of, but not limited to, chemical reactions. The software tool automates, for example, dynamical systems analysis, the derivation of the Master equation and Fokker-Planck equation, stochastic simulations, and network analysis. As MuMoT runs inside Jupyter notebooks systems can be studied in an interactive way, allowing model exploration and visualisation in publication-ready easily-modifiable graphical output. MuMoT embeds analytical and numerical methods in an interactive workflow and could therefore be of interest to experts and non-experts alike. The presentation will consist of a demonstration of MuMoT's functionality based on a model of collective decision making in house-hunting honeybees.

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CP7

Efficient Maximum Likelihood Model Identification and Parameter Inference from Single-cell Distribution Data

Recent advances in single-cell experimental techniques have provided unprecedented access to the mechanisms underlying fundamental cellular processes. In particular, techniques assaying populations of single cells, including fluorescence-activated cell sorting and single-cell RNA-seq (scRNA-seq), have highlighted the importance of cellular noise—stochastic fluctuations within and heterogeneity between genetically identical cells. Despite growing availability of such single-cell distribution data, limitations in computational methods for model identification and parameter inference remain a bottleneck for developing accurate mechanistic descriptions of cellular processes. Existing methods typically make simplifying assumptions about the underlying biochemical model, impose limits on model size/complexity, or require prior knowledge of model parameter values. I will present a novel maximum likelihood-based method for model identification and parameter inference—distribution Monte Carlo Expectation-Maximization with Modified Cross-Entropy Method (dMCEM^2)—that does not have these limitations. Building upon a method developed for single-cell time series data, dMCEM^2 enables automated, computationally efficient identification and inference of stochastic biochemical models from single-cell distribution data. Using both synthetic and real-world scRNA-seq data, I will demonstrate the ability of dMCEM^2 to accurately construct models of single-cell gene expression.

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CP7

Estimating the Time Elapsed Since Exposure to Infection

Data from Human Challenge Studies provides a unique window into the progression of disease. In such experiments, subjects are infected with a pathogen of interest, e.g., H1N1, H3N2 or RSV, and biomarkers are collected at regular intervals. Gene expression data sets produced by such experiments have yielded a wealth of information. In particular, the signal that can be extracted from the data is well-organized, coherent, and evolves in time. Well known pathways associated with the host immune response are readily re-discovered as well as additional biomarkers that are less well understood. In this presentation we summarize our results on the DARPA Prometheus Program related to the prediction of contagion and respiratory infection. In particular, we will argue that infection can be detected within the first 5 hours of exposure. Additionally, it is possible to estimate the number of hours that have elapsed since a subject was exposed to the pathogen. We will demonstrate the use of a new tool for comparative analysis, CALCOM, being developed at Colorado State University. It permits the user to access well-known machine learning libraries including googles AI tool tensor flow, the general purpose machine learning package scikit-learn, as well as novel algorithms developed by our group.

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CP7

Extensions of K-means and LBG Clustering to the

Grassmannian

Recent advances in data processing on the Grassmann manifold have shown considerable promise for capturing variations in the state of patterns in high dimensions. The classification of points on Grassmannians permits the exploitation of the subspace data representation and reduces the question of data similarity to the geometric framework of angles between subspaces. In this presentation we illustrate the extension of several clustering algorithms on vector spaces to analogous algorithms on the Grassmannian. The key ingredients include the ability to measure distance between subspaces, to move a given subspace in the direction of another along a geodesic, and to compute the average of a collection of subspaces. We apply these tools to the extension of both k-means and LBG clustering. We illustrate the application of these ideas to gene expression data sets produced by human clinical challenges. The goal is to identify novel biomarkers for early detection of infection.

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CP7

Exploring Optimal Parameters of Models using Dynamical Systems with Conservation Laws

Many biological systems are modelled by using differential algebraic equations, for example, physiologically based pharmacokinetic models in computational pharmacy. These models are typically composed of many compartments or, equivalently, of equations that represent organs or tissues, thereby often having a larger number of parameters than that of available data. This causes a difficulty in parameter estimations because when the parameters of the models are determined by minimizing the error between the outputs of the models and the available data, the optimal solution may not be determined uniquely. Instead, the set of optimal solutions may form a manifold and a method for exploring such manifolds would be helpful for determining biologically meaningful parameters in these situations. In this talk, we propose a method for exploring such a manifold that is defined as a set of optimal solutions of nonlinear least squares problems. In our method, we introduce a dynamical system with the respective terms in the sum of the least squares problem as conserved quantities. The points on the orbits of this system starting from an optimal solution are on the manifold and hence the optimal solutions as well due to the conservation laws. An application to parameter estimation of a model for allergology is also shown.

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CP8

Mathematical Modeling of Zika in Colombia Considering Mutation

We analyze the Zika virus transmission dynamics on human and mosquito populations. Mosquitoes play a role of infectious agents and vector of the Zika virus (ZIKV). In this sense, we set out a mathematical model with constant size population for the evolution of the infected humans with ZIKV and analyze its qualitative dynamics. The epidemic threshold parameter R_0 for the extinction of disease is computed. Numerical simulations of the model varying the parameters corroborate the theoretical results regarding R_0. The parameters of the mathematical model of the Zika epidemic are estimated using real data from Zika prevalence in Colombia for 2016. We find the reproduction number for this particular case which allow us to understand and explain the Zika epidemic in Colombia.

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CP8

Influence of Concurrency, Partner Choice, and Viral Suppression on Racial Disparity in the Prevalence of HIV Infected Women

We present a mathematical model of the transmission of HIV through sexual contact in a population stratified by sexual behavior and race/ethnicity. The model also includes the effect of concurrency through the force of infection term, variations in population mixing (partner choice), and non-uniform Highly Active Anti-Retroviral Treatment (HAART) leading to viral suppression. We use this mathematical model to understand the non-uniform spread of HIV in women who were infected through heterosexual contact. Numerical simulations of the reproduction number as a function of concurrency, viral suppression level, and mixing show a reservoir of disease present in both heterosexual and MSM populations. Statistical analysis of parameter values shows that viral suppression level, mixing and progression to AIDS without viral suppression have a strong correlation (either positive or negative) with the number of HIV positive women. Concurrency and assortative mixing are shown to be essential to reproduce infection levels in women, as reported by 2010 data from the Center for Disease Control (CDC).

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CP8

A Mathematical Model and Inference Method for

Bacterial Colonization in Hospital Units Applied to Active Surveillance Data for Carbapenem-resistant Enterobacteriaceae

Widespread use of antibiotics has resulted in an increase in antimicrobial-resistant microorganisms. Although not all bacterial contact results in infection, patients can become asymptomatically colonized reservoirs of transmission, leading to a higher probability of infection and/or transmission of bacteria to other patients. As a result, many hospitals have begun active surveillance of high-risk patients. We present a mathematical model and inference method for in-hospital bacterial colonization and transmission of carbapenem-resistant Enterobacteriaceae that is tailored for use with active surveillance data. The model and inference method make use of the full detailed state of the hospital unit, which takes into account the colonization status of each individual in the unit and not merely the number of colonized patients at any given time. The inference method computes the likelihood of all possible histories consistent with partial observations. The inference method is tested by computer simulation and also applied to data from a 13-bed rehabilitation unit to identify the parameters for the patient-patient transmission rate, pre-existing colonization probability, and prior-to-new-patient transmission probability. Besides identifying the parameters, we predict the effects on the total prevalence of changing the parameters and estimate the increase in total prevalence attributable to patient-patient transmission above the baseline pre-existing colonization.

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CP8

Modeling Zika Virus Transmission Dynamics: Parameter Estimates, Disease Characteristics, and Prevention

The recent devastating spread of Zika virus (ZIKV) across Americas has posed a public health emergency of international concern. Because of limited data, much remains uncertain about parameters related to transmission dynamics of ZIKV. In this talk, I will present a method for parameter estimation that utilizes mathematical models and a recently investigated complex-step derivative approximation. Applying our method to epidemic data from the ZIKV outbreaks in French Polynesia and Yap Island, we found that the parameters that can be estimated vary from Island to Island, suggesting that the same set of parameters cannot be estimated from every data set, and thus the parameter estimation based on standard techniques may provide misinformation about the ZIKV transmission dynamics. Our method allowed us to estimate ZIKV related parameters with substantially reliable confidence intervals. I will also provide the basic reproduction number estimated by our method, and explore the effectiveness of potential prevention strategies for controlling zika epidemics.

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CP8

Optimal PTH Treatment for Osteoporosis

A pulsatile administration of PTH leads to bone formation in patients, while a continuous administration of PTH has the opposite effect. The reason for this phenomenon is thought to be the inhibitory effect that PTH has on osteoblast apoptosis rate, see for example Ross et al. (2017) and references therein. Here we use variational calculus to formally analyze the locally optimal structure for the pulse shape, and the effect of noise in a model derived from that of Ross et. al. References: Mathematical Model of Bone Remodelling Captures the Antiresorptive and Anabolic Actions of Various Therapies, David Ross and Khamir Mehta and Antonio Cabal, Bulletin of Mathematical Biology, 2017.

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CP9

Classification of Tolerant, Resistant and Susceptible Mice using Time Series Data

The broad goal of our research is to detect and characterize signatures related to the immune system's response to infection. In particular, we are interested in identifying features characterizing immune responses related to tolerance, resistance and susceptible reactions. To this end we explore the behavioral response of laboratory mice before and after being infected with Salmonella. Telemetry from these mice are collected at one sample per minute using surgically implanted devices. We use the resulting time series, along with autopsy data, to analyze and cluster using tools from machine learning and dynamical systems analysis.

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CP9

A Mathematical Model of Viruses as Instigators of Cancer Immunotherapy

Tumours are extremely heterogeneous environments that contain a legion of cancerous and non-cancerous cells with various molecular signatures. This variety of phenotypes contributes to tumour resistance against traditional therapies. Therefore, novel cancer therapies are being investi-

gated to target these highly variable tumours. One therapy is the use of oncolytic viruses to prey upon the weakened antiviral response pathways and efficient metabolism of cancer cells. These viruses can be genetically engineered to stimulate the bodys natural immune responses and instigate endogenous tumour destruction. Some mathematical models of tumour growth explicitly model a constant cell cycle length using discrete delay differential equations. In this work, we present a mathematical model of tumour growth that incorporates tumour cell cycle length heterogeneity by modelling cell cycle length via distributed delay differential equations. We show that our model is a more general form of the discrete delay case. In the untreated scenario, we characterize the local stability of the cancer free equilibrium as a function of cell cycle length heterogeneity. Finally, by modelling the relationship between oncolytic viruses and immune cell recruitment, we show that immune involvement is necessary for tumour extinction and provide an explicit bound on immune efficiency to ensure sustained complete remission.

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CP9

Modeling the Kinetics of Antigens and Antibodies for Analysis of the Mechanism of Allergy

Immune response against alien substances in human bodies are necessary for protection of their bodies, which may end up developing the allergy if it works excessively. Allergy occurs as a result of immune responses including the production of antibodies to alien substances, or antigens, and the consequent production of certain chemical substances. Many experiments on allergy have been conducted over the years, so that the mechanism of it has been revealed to some extent. This situation enables us to conduct modeling and simulations making use of the available data obtained through the experiments as a new approach to the study of allergy. More precisely, by describing the experiments with the models and the simulations, hidden values related to the mechanism can be explored, which could be helpful for more detailed investigations on allergy. In this talk, we propose a model of the kinetics of antigens and antibodies in the human body and apply it to the experimental data obtained by Husby et al. The brief discussion on the values of estimated parameters from the data is shown as well.

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CP9

Mathematical Modeling of the Acute Inflammatory Response and Energy Consumption

When an external agent, such as a pathogen, enters the body, an acute inflammatory response is activated to eliminate the invader. In some patients, however, an overreaction of the immune system may occur, which can lead to collateral tissue damage and, in the extreme, organ failure and septic death. Studies have found an association between sepsis and depletion in the levels of adenosine triphosphate (ATP), increase in nitric oxide production, and accumulation of lactate. In this work we present a differential equations model that represents the dynamics of ATP, nitric oxide, and lactate in relation to the acute inflammatory response and employ this model to explore the roles of these substances in shaping this response. We use the bifurcation structure of the model system with respect the pathogen growth rate to characterize this parameter's effect on long-term outcome and to inform the instantiation of heterogeneous virtual patient populations utilized to carry out a survival analysis to validate the model. We then apply the model to study alterations in the inflammatory response and survival outcomes in metabolically altered conditions such as hypoglycemia, hyperglycemia, and hypoxia.

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CP10

Diffusive Coupling and Division Waves in a Response / Signaling Model of the Early *Drosophila* Embryo

Response / Signaling (RS) oscillators provide a simple, qualitatively correct model for cell cycle interactions in populations of cells that divide via mitosis. In an RS model, cells interact with each other to speed up or delay cell cycle progression in a phase-dependent manner. Recently, S-phase associated waves of cyclin proteins were shown to drive so-called division waves in early *Drosophila* embryos. We demonstrate that a biphasic RS oscillator model is a good fit for cyclin interactions among *Drosophila* embryonic nuclei, we show that diffusively coupled RS oscillators can generate division waves with biologically realistic characteristics, and we prove that division waves in the resulting system are a consequence of the geometry of the developing embryo.

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CP10

Cortical Microtubules Deflect in Response to Cell-surface Curvature

Abstract not available at time of publication.

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CP10

Competition Drives Transport through the Nuclear Pore

Transport through nuclear pores is the sole mechanism by which material moves between the cytoplasm and the cell nucleus. These pores, which are on the order of 50 nanometers in diameter and 50-80 nanometers in length, achieve cargo transport that is both fast and specific. One of the central challenges in understanding nuclear transport is understanding how the pore can achieve both speed and specificity. In this talk, we propose a novel physical mechanism for enhanced flux of specific cargos through the pore based on competition for elastically-tethered binding sites in the pore interior.

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CP10

Examining Pulsed Contractions in the Early C. Elegans Embryo through Modeling and Data Analysis

Pulsatile behavior occurs in a wide variety of biological contexts, from protein concentration pulses in slime molds and Rho pulses in human osteosarcoma cells, to actomyosin pulses in the early C. elegans embryo. To understand this type of pulsatile behavior, we examine the C. elegans system from two perspectives: modeling and analysis. First, we have modeled an excitable reaction-diffusion-advection system with the initial aim of recreating pulsatile dynamics like those seen in C. elegans, which can display a wide range of pulsatile behavior for different mutants. This model goes beyond others through the addition of mechanical stresses, allowing us to make insights into the connections between mechanics and pulsatile behavior. On the data analysis side, instead of examining pulses as individual spots and tracking them throughout time, we analyze our data on the scale of the whole embryo. This allows us to use dimensional reduction methods on experimental movies, and combining this analysis with tools such as autocorrelation analysis and PIV analysis to discern differences between mutants. The tools we develop can also be used on the model data, giving a way to begin connecting model and experiment.

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CP10

Modeling the Migration of Astrocytes During Retinal Development

Retinal vasculature is essential for adequate oxygen supply to the inner layers of the retina, the light sensitive tissue in the eye. In embryonic development, formation of the retinal vasculature via angiogenesis is critically dependent on prior establishment of a mesh of astrocytes, which are a type of brain glial cell. Astrocytes emerge from the optic nerve head and then migrate over the retinal surface as a proliferating cell population in a radially symmetric manner. Astrocytes begin as stem cells, termed astrocyte precursor cells (APCs), then transition to immature perinatal astrocytes (IPAs) which eventually transition to mature astrocytes. We develop a partial differential equation model describing the migration of astrocytes where APCs and IPAs are represented as two subpopulations. Numerical simulations are compared to experimental data to assist in elucidating the mechanisms responsible for the distribution of astrocytes.

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CP11

Numerical Methods for Solving and Optimizing Multiscale Models of Hepatitis C Virus Dynamics

Age-structured multiscale models have been developed to study viral dynamics. However, they are notoriously difficult to solve. Here, we investigate the numerical solutions of a multiscale model of hepatitis C virus (HCV) dynamics during antiviral treatment and compare them with analytical approximations. First, starting from a simple numerical solution that also considers an integral approximated over previous iterations, we show that the short-term approximation holds for only a few hours and the long-term approximation is an underestimate of the PDE model solution. This is expected since in the long-term approximation, new infection events are being ignored from initiation of antiviral treatment. We then highlight the importance of having a numerical solution that takes into account previous iterations for the associated integral, making problematic the use of canned solvers. Second, we demonstrate that the governing differential equations are stiff and the stability of the numerical scheme should be considered. Third, we show that considerable gain in efficiency can be achieved by using adaptive stepsize methods over fixed

stepsize methods for simulating realistic scenarios when solving multiscale models numerically. Finally, we compare between several numerical schemes that are suitable and show the benefit of using the Rosenbrock method, an implicit adaptive stepsize method that is both efficient and stable.

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CP11

Surface Protein Distribution of Influenza Drug Resistant Mutants

Influenza antivirals inhibit the action of surface proteins, preventing replication of the virus. Mutations that cause drug resistance alter the surface proteins of the virus, allowing the surface protein to function properly in spite of the presence of an antiviral. When a drug resistant mutation first occurs, the resulting virus might still retain some of the wild-type, drug- susceptible, surface proteins. A recent study has shown that having wild-type surface proteins on a drug resistant mutant alters how easily the mutant virus will spread to other cells, particularly in the presence of antiviral treatment. For this reason, we need to understand the distribution of wild-type and resistant surface proteins on newly-formed drug resistant mutants. This study uses a mathematical model of intracellular viral replication to track creation of wild-type and mutant surface proteins inside the cell, allowing us to determine what type of surface proteins are present on newly formed mutant virions. Specifically, the model will be used to study how the timing of the drug resistance mutation alters the distribution of surface proteins on the resulting virions.

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CP11

The Role of E-antigen in Hepatitis B Virus Infection

During chronic Hepatitis B infection spontaneous seroconversion of e-antigen can be observed. E-antigen seroconversion is related to a decay in viral level and is hence a goal of antiviral treatment. In this study we want to gain understanding of the difference in timing of e-antigen seroconversion under treatment and in the untreated cases. To reveal possible mechanisms yielding these differences, we propose a mathematical model that considers e-antigen, the corresponding antibody (HBeAb) and e-antigen-antibody complexes. Since not much is known about the formation of HBeAb, the focus of our investigations lies on determining the mechanisms of antibody production and function.

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CP11

Optimal Control in HIV Chemotherapy with Termination Viral Load and Latent Reservoir

Although a number of cost-effective strategies have been proposed for the chemotherapy of HIV infection, the termination level of viral load and the latent reservoir is barely considered. However, the viral load at the termination time is an important biomarker because suppressing viral load to below the detection limit is a major objective of current antiretroviral therapy. The pool size of latently infected cells at the termination time may also play a critical role in predicting a rapid viral rebound to the pre-treatment level or post-treatment control. In this work, we formulate an optimal control problem by incorporating the termination level in terms of viral load, latently and productively infected T cells into an existing HIV model. The necessary condition for this optimal system is derived using the Pontryagin's maximum principle. Numerical analysis is carried out using Runge-Kutta 4 method for the forward-backward sweep. Our results suggest that introducing the termination viral load into the control provides a better strategy in HIV chemotherapy.

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CP11

Mechanisms of Virus-virus Coexistence in the Human Respiratory Tract

Molecular diagnostic techniques have revealed that approximately 43% of the patients hospitalized with influenza-like illness are infected by more than one viral pathogen sometimes leading to long-lasting infections. It is not clear how the heterologous viruses interact within the respiratory tract of the infected host to lengthen the duration of what are usually short, self-limiting infections. We develop a mathematical model which allows for susceptible cells in the respiratory tract to regenerate, and single cells to be infected simultaneously with two different respiratory viruses (superinfection) to investigate the possibility of chronic coinfections. To assess the full behavioral dynamics of coinfection, mathematical analysis along with numerical simulation is performed considering superinfection with and without cell regeneration in the model. We use respiratory syncytial virus and influenza A virus coinfection as an example to explore model outcomes. We find a possible mechanism for chronic coinfection in the inclusion of both superinfection and cellular regeneration in the model.

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CP12

Quantifying the Relationship Between PSA and Tumor Growth by Modeling Angiogenesis

Prostate-specific antigen (PSA) is used as a diagnostic tool for determining prostate cancer tumor burden. However, PSA is known to be a poor biomarker since it does not correlate well to tumor burden. To improve its prognostic potential, we need to better understand how PSA leaks out of the tumor and into the serum. In order to do this, it is essential to think about changes in vascular morphology both in growing tumors as well as in those under treatment. We develop a mathematical model of angiogenesis in relation to tumor growth. Ours is the first model that incorporates angiogenesis in the context of prostate cancer growth and PSA dynamics. Unlike existing models we can replicate a variety of tumor growth dynamics for a given PSA time course profile. We validate our model with mouse xenograft data, and can use this model to show that for given patient PSA data we may achieve varying tumor growth profiles. Coupled with additional data on vessel morphology, our model can also explain why even as PSA levels decrease, a patient may have poor treatment outcomes.

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CP12

Modeling Continuous Levels of Cell Differentiation in Acute Myeloid Leukemia and Multidrug Resistance

Recent advances in biotechnology demonstrate continuous cellular differentiation which brings in new modeling opportunities. In particular, single-cell RNA sequencing data that characterizes the cellular states in extremely high-dimensions can be processed with data analysis techniques, and the cell states are mapped into a lower dimensional continuum space. Motivated from such data, we develop a mathematical model of cell density on a continuous state space representing cellular differentiation and drug resistance. We follow the cell trajectories not only on the reduced continuum space, but also on graphs, and model the directed and random movements with partial differential equations. In addition, we compare our continuum model with classical models that assume discrete cell states and characterize the cases when the continuum and discrete models yield distinctive dynamics. Finally, we show two examples using our continuum approach to study hematopoietic stem cell differentiation and multidrug resistance. We show that the model can be used to predict the evolution of abnormal differentiation processes such as those observed during the pathogenesis of acute myeloid leukemia, and study the emerging heterogeneity of multidrug resistance regarding tumor turnover rate and proliferating proportion.

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CP12

Quantifying Tumor Heterogeneity and Drug Resistance in Triple Negative Breast Cancer

Triple negative breast cancer (TNBC) is an aggressive, highly robust malignancy, which accounts for 15-20% of breast cancers. Since TNBCs are insensitive to hormonal therapies, treatment options are limited to cytotoxic chemotherapy. However, TNBCs often evade elimination during the first round of chemotherapy, with a 34% rate of distant recurrence. TNBC cells are poorly differentiated, resulting in the growth of biologically heterogeneous tumors. This heterogeneity is the likely source of TNBC robustness. We discuss thermodynamic and information-theoretic methods of quantifying tumor heterogeneity, from both transcriptional and proteomic profiles, as well as life-cycle patterns. These methods draw on tools from the intersection of probability, dynamical systems, and network theory. We then apply these metrics to cultivated TNBC cell lines, and evaluate them as predictors of tumor viability and drug resistance. We will conclude with a discussion of the theoretical interpretations of these results.

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CP12

Glioblastoma Recurrence and the Role of MGMT Promoter Methylation

Glioblastoma, also known as glioblastoma multiforme (GBM), is an extremely fast-growing and lethal form of brain cancer. Typically GBM is treated with temozolomide (TMZ), a cytotoxic drug that damages DNA and triggers cell death. Promoter methylation of the DNA repair gene

MGMT has been associated with sensitivity to TMZ, while increased expression of MGMT has been associated with TMZ resistance. However, the evolutionary processes driving the emergence and outgrowth of TMZ-resistant tumor subpopulations are still poorly understood. We have developed a stochastic model, parameterized using clinical and experimental data, to investigate the role of MGMT methylation in TMZ resistance during the standard treatment regimen for GBM (surgery, chemotherapy and radiation). We use the model to study the impact of TMZ treatment on mechanisms of MGMT methylation and demethylation within GBM cells. In addition, we investigate the optimal number of doses administered during adjuvant chemotherapy and its connection to methylation status at diagnosis.

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MS1

Fluctuating Hydrodynamics for Biological Membranes: Role of Curvature in Drift-Diffusion Dynamics

We develop fluctuating hydrodynamics approaches to extend Saffman-Delbruck theory to capture the collective drift-diffusion dynamics of proteins within curved lipid bilayer membranes. Our approach is at the level of fluid interfaces having any compact manifold shape. Using analytic and computational approaches, we show how Gaussian curvature can significantly impact dissipation within the curved two dimensional membrane fluid to augment the collective drift-diffusion dynamics of protein inclusions. We also present general results on the collective drift-diffusion dynamics when heterogeneous curved structures are present in the membrane geometry showing how these local Gaussian curvature effects influence hydrodynamic coupling in some interesting ways.

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MS1

Mechanics of Traversal of Immature and Diseased Red Blood Cells in Human Spleen and Consequences for Hereditary Blood Disorders

The function of the spleen in filtering the abnormal red blood cells (RBCs) in circulation has been studied extensively, but the role of the spleen in blood disorders and erythropoiesis has not been fully understood. Here, we employ a two-component RBC model to simulate the dynamics of healthy, diseased and immature RBCs traversing the interendothelial slit (IES) in the spleen. First, we demonstrate that RBCs lose surface area when crossing IES in hereditary spherocytosis (HS) due to the weakened cohesion between the lipid bilayer and the cytoskeleton. Second, we find that RBCs are elongated after traversing IES in hereditary elliptocytosis (HE) because of the impaired RBC elasticity. In severe forms of HE, RBCs break into fragments. Our simulations of HS and HE RBCs crossing IES suggest that the spleen not only filters the abnormal RBCs, but also contributes to pathological alternations of RBCs in blood disorders. Finally, we find that reticulocytes release vesicles during their passage of IES to reduce redundant surface area and subsequently develop the biconcave shape, implying that the spleen facilitates the maturation of reticulocytes. Taken together, our study consolidates the possible physiopathological roles of the spleen in nursing the young RBCs and assessing the mechanical fitness of healthy and diseased RBCs, thereby controlling the quality of blood in circulation.

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MS1

Hydrodynamics of Transient Cell-Cell Contact Suggests a Role for Plasma Membrane Permeability and Optimal Active Protrusion Length for T Cell Receptor Triggering

Abstract not available at time of publication.

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MS1

Chiral Edge Fluctuations of Colloidal Membranes

We study edge fluctuations of a flat colloidal membrane comprised of a monolayer of aligned filamentous viruses. Experiments reveal that a peak in the spectrum of the in-plane edge fluctuations arises for sufficiently strong virus chirality. Accounting for internal liquid crystalline degrees of freedom by the length, curvature, and geodesic torsion of the edge, we calculate the spectrum of the edge fluctuations. The theory quantitatively describes the experimental data, demonstrating that chirality couples in-plane and out-of-plane edge fluctuations to produce the peak.

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MS2

How Local and Global Neuronal Network Structure Influence Synchronous Events

We have developed a network model where one can independently modulate both local and global features of the network connectivity. Our application of local microstructures is based on the SONET model [Zhao et al., 2011], where one can specify the frequencies of different two-edge motifs in the network. We have extended this approach to allow for the inclusion of global structure in the patterns of connections, such as connections based on an underlying geometry. Using this model, we investigated how the influence of microstructure (motifs) on the emergence of synchronous events is modulated by spatial features of the network.

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MS2

Learning Recurrent Dynamics in Spiking Networks

Spiking activity of neurons engaged in learning and performing a task show complex spatiotemporal dynamics. While the output of recurrent network models can learn to perform various tasks, the possible range of recurrent dynamics that emerge after learning remains unknown. Here we extend a previously developed Recursive Least Squares algorithm and show that modifying the recurrent connectivity provides sufficient flexibility for synaptic and spiking rate dynamics of spiking networks to produce a wide range of spatiotemporal activity. We identify sufficient conditions for successful learning, characterize two types of learning errors, and assess the network capacity. Finally, we apply the training method to stabilize irregular spiking activity of a balanced network and construct a recurrent connectivity that can reproduce the heterogeneous spiking rate patterns of cortical neurons engaged in motor planning and movement. Our findings show that recurrent spiking networks possess a vast computational capability that can support the diverse activity patterns in the brain.

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MS2

Combinatorial Geometry of Threshold Linear Networks

Threshold-linear networks (TLNs) are models of neural networks that consist of simple, perceptron-like neurons and exhibit nonlinear dynamics that are determined by the networks connectivity. The combination of their mathematical tractability along with the richness of their dynamics makes TLNs a good candidate for the study of the connectivity-dynamics problem. We find that it is the combinatorial properties of the connectivity that encodes much of the information about the dynamics of a TLN. In particular, to any network we associate to it an oriented matroid that captures this combinatorial information and determines both local and global properties of the dynamics. Furthermore, the geometric notion of simplicial cells and theirs flips from oriented matroid theory provide a combinatorial bifurcation diagram for these networks, a valuable tool for understanding the complete repertoire of dynamics that can enfold on a fixed network architecture.

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MS2

Learning C. Elegans Nervous System Functions From its Dynome

We propose a data-driven approach to represent neuronal network dynamics as a Probabilistic Graphical Model (PGM). Our approach learns the PGM structure by applying dimension reduction to network response dynamics evoked by stimuli. The outcome model captures how stimuli propagate through the network and thus represents causal dependencies between neurons and stimuli, i.e., functional connectome. The benefit of using a PGM as the functional connectome is that posterior inference can be performed efficiently and circumvent the complexities in the direct inference. In particular, posterior inference reveals the relations between known stimuli and downstream neurons or allows to query which stimuli associated with downstream neurons. We apply our methodology to Caenorhabditis elegans (C. elegans) somatic nervous system to validate and show an example of our approach. Our model for the full somatic nervous system enables us to obtain and verify underlying neuronal pathways for known behavioral scenarios and to detect possible pathways for novel scenarios.

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MS3

Canard-induced Early Afterdepolarizations: Ducks in the Heart

Cardiac alternans are electrical oscillations observed during the repolarization phase of the cardiac action potential. These electrical oscillations alter the normal cardiac refractory period and have been correlated with cardiac arrhythmias. As such, the identification and control of the mechanisms that generate cardiac alternans has significant clinical implications. In a recent minimal model for the electrical activity in cardiac myocytes, it was found that alternans were observed over large, open parameter sets and were an intrinsic feature of the deterministic model (rather than a product of stochastic fluctuations). The precise mechanisms that control the alternans, however, have yet to be identified. In this work, we show that the alternans are canard-induced mixed-mode oscillations. We identify the geometric structures that organise the alternans in the phase and parameter spaces, and use our geometric theory to determine how the alternans can be eliminated.

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MS3

Effectiveness of Alternans Termination Methods Differs for Voltage- and Calcium-driven Alternans

It has been well established that oscillations in cardiac action potential duration and/or shape known as alternans can be driven by instabilities associated with the cell's voltage or intracellular calcium concentration. However, most methods to eliminate alternans have been analyzed in the context of the voltage-driven mechanism. Here, we use a model that can produce alternans through both voltage and calcium mechanisms to study the effectiveness of several different methods in terminating alternans. We show that for both single cells and tissue the effectiveness of the methods depends on the alternans mechanism. In particular, alternans driven partially or fully by calcium tends to be more difficult to eliminate than voltage-driven alternans.

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MS3

Heart Rhythm Control using a Novel Anti-arrhythmic Pacing Protocol

Cardiac alternans, a beat-to-beat alternation in action potential duration (APD), can lead to fatal arrhythmias. During periodic pacing, changes in diastolic interval (DI) depend on subsequent changes in APD, thus enhancing cardiac instabilities through a feedback mechanism. Recently, an anti-arrhythmic Constant DI pacing protocol was proposed and shown to be effective in suppressing alternans in 0D and 1D in-silico studies. However, previous experimental validation of Constant DI pacing in the heart has been unsuccessful due to the spatio-temporal complexity of 2D cardiac tissue and the technical challenges in its real-time implementation. Here, we developed a novel closed loop system to detect T-waves from real-time ECG data, enabling successful implementation of Constant DI pacing protocol, and performed high-resolution optical mapping experiments on isolated whole rabbit hearts to validate its anti-arrhythmic effects. The results were compared with: (1) Periodic pacing (feedback inherent) and (2) pacing with heart rate variability (HRV) (feedback modulation) introduced by using either Gaussian or Physiological patterns. We observed that Constant DI pacing significantly suppressed alternans in the heart, while maintaining APD spatial dispersion and flattening the slope of the APD restitution curve, compared to traditional Periodic pacing. In addition, introduction of HRV in Periodic pacing failed to prevent cardiac alternans, and was arrhythmogenic.

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MS3

Stochastic Pacing Inhibits Discordant Cardiac Alternans

Depressed heart rate variability is a well-established risk factor for sudden cardiac death in survivors of acute myocardial infarction and for those with congestive heart failure. However, it remains unknown whether this is a causal relationship, or whether heart rate variability simply correlates with the severity of cardiac damage. Here, we suggest a causal link between depressed heart rate variability and the propensity for the development of more deadly arrhythmias. In numerical simulations we observe an inverse relationship between the variance of stochastic pacing and the occurrence of spatially discordant alternans, an arrhythmia which is widely believed to facilitate the development of cardiac fibrillation. By analyzing the effect of conduction velocity restitution, cellular dynamics, electrotonic coupling, and stochastic pacing on the nodal dynamics of spatially discordant alternans, we provide intuition for this observed behavior and propose control strategies to inhibit discordant alternans.

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MS4

Mathematical Modeling of Cytoneme-based Morphogen Gradient Formation

In developmental biology, an important problem is understanding the mechanisms underlying the formation of morphogen concentration gradients. The most commonly hypothesized mechanism involves the diffusion and degradation of morphogens from a localized source. Recently, however, an alternative mechanism has been proposed, which is based on direct cell-to-cell contacts mediated by thin, actin-rich cellular extensions known as cytonemes. In this talk we review our recent work on the mathematical modeling of cytoneme-based morphogenesis. In particular, we explore how the active motor-driven transport of morphogens along cytonemes determines various properties of the morphogen gradient such as its spatial range, accumulation time, and robustness to external perturbations.

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MS4

Signal Transduction and Polarization in Dictyostelium Discoideum

Chemotaxis is a dynamic cellular process, comprised of direction sensing, polarization and locomotion, that leads to the directed movement of eukaryotic cells along extracellular gra- dients. As a primary step in the response of an individual cell to a spatial stimulus, direction sensing has attracted numerous theoretical treatments aimed at explaining experimental observations in a variety of cell types. Here we discuss a new model of direction sensing based on experiments using Dictyostelium discoideum (Dicty). The model is built around reaction-diffusion-translocation system that involves 3 main component processes: a signal detection step based on G-protein-coupled receptors (GPCR) for cyclic AMP (cAMP), a transduction step based on a heterotrimetic G protein Ga2?, and an activation step of a monomeric G-protein Ras. The model can predict the experimentally-observed response of cells treated with latrunculin A, which removes feedback from downstream pro- cesses, under a variety of stimulus protocols. We show that the response at the level of Ras activation encodes sufficient memory to eliminate the back-of-the wave problem, and the effects of diffusion and cell shape on direction sensing are also investigated. In contrast with existing LEGI models of chemotaxis, the results do not require a disparity between the diffusion coefficients of the Ras activator GEF and the Ras inhibitor GAP.

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MS4

Modeling the Dynamics of Cdc42 Oscillation in Fission Yeast

We present a mathematical model of the core mechanism responsible for the regulation of polarized growth dynamics by the small GTPase Cdc42. The model is based on the competition of growth zones of Cdc42 localized at the cell tips for a common substrate (inactive Cdc42) that diffuses in the cytosol. We consider several potential ways of implementing negative feedback between Cd42 and its GEF in this model that would be consistent with the observed oscillations of Cdc42 in fission yeast. We analyze the bifurcations in this model as the cell length increases, and total amount of Cdc42 and GEF increase. Symmetric antiphase oscillations at two tips emerge via saddle-homoclinic bifurcations or Hopf bifurcations. We find that a stable oscillation and a stable steady state can coexist, which is consistent with the experimental finding that only 50% of bipolar cells oscillate. Our model suggests that negative feedback is more likely to be acting through inhibition of GEF association rather than upregulation of GEF dissociation.

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MS4

Modeling the Interplay Between Cell Signalling and Cell Mechanics

Regulators of the actin cytoskeleton such Rho GTPases can modulate forces developed in cells by promoting actomyosin contraction. At the same time, through mechanosensing, tension is known to affect the activity of Rho GTPases. What happens when these effects act in concert? Using a minimal model (1 GTPase coupled to a Kelvin-Voigt element), we show that two-way feedback between signaling (RhoA) and mechanical tension (stretching) leads to a spectrum of cell behaviors, including contracted or relaxed cells, and cells that oscillate between these extremes. When such model cells are connected to one another in a row or in a 2D sheet (epithelium), we observe waves of contraction/relaxation and GTPase activity sweeping through the tissue. The minimal model lends itself to full bifurcation analysis, and suggests a mechanism that explains behavior observed in the context of development and collective cell behavior.

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MS5

Stochastic Population Models: The Dynamics of Disease Invasion

Disease invasion is the seemingly spontaneous introduction of a disease into a population from an external source. Real world examples include zoonotic spillover, as in ebola, or simple transport by immigration, as in the flu. The random nature of disease invasion is well described by stochastic disease models, which can capture the introduction or reintroduction of a disease as a large outbreak. This talk will present some of the mathematical machinery used to ana-

lyze stochastic population models that explicitly accounts for infection from an external source. Of particular interest is the outbreak vulnerability which describes the susceptibility of a population to disease invasion.

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MS5

Large Deviations for Gaussian Diffusions with Delay

Dynamical systems driven by nonlinear delay SDEs with small noise can exhibit important rare events on long timescales. When there is no delay, classical large deviations theory quantifies rare events such as escapes from metastable fixed points. Near such fixed points, one can approximate nonlinear delay SDEs by linear delay SDEs. In this talk, we outline a fully explicit large deviations framework for (necessarily Gaussian) processes X_t driven by linear delay SDEs with small diffusion coefficients. Our approach enables fast numerical computation of the action functional controlling rare events for X_t and of the most likely paths transitioning from $X_0 = p$ to $X_T = q$. Via linear noise local approximations, we can then compute most likely routes of escape from metastable states for nonlinear delay SDEs. We apply our methodology to the detailed dynamics of a genetic regulatory circuit, namely the co-repressive toggle switch, which may be described by a nonlinear chemical Langevin SDE with delay.

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MS5

Rare Events Reconstruction of Most Likely Evolutionary Paths for Bacterial Populations

Abstract not available at time of publication.

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MS5

Statistical Inference and Model Selection using Efficient Sampling Algorithms on Next-generation, Single Cell Gene Expression Data

What happens when a mathematical physicist studying random processes collaborates with biologists studying stochastic gene expression in single cells? In this talk, I will first introduce an experimental technique—single-molecule RNA fluorescent in situ hybridization (sm RNA FISH)—which measures transcribed mRNA and the discrete state of activation in a single cell, and provides a "snapshot' of the stochastic process of gene expression. Then, I will discuss how we use a class of coarse-grained stochastic models, formulated as continuous-time and individual-based chemical reactions in a well-mixed environment, to infer kinetic properties of stochastic gene expression from the experimental data. I will present an accurate sampling procedure (up to 1000-fold speed-up compared to conventional algorithms) to efficiently solve the problem numerically. The increased efficiency permits us to go beyond standard fitting procedures and enter to the realm of statistical inference. In the final part of the talk, I will present a high-level description of how we carry out the full-scale Bayesian analysis on our continuous-time probabilistic models using data from discrete-time observations. The outcome of the analysis, the uncertainty quantification of the parameters and model structures, will be presented.

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MS6

Impact of Cell Dynamics and Tissue Rheology on the Development of Zebrafish Left-right Organizer

How do the material properties of a tissue impact biological processes such as embryonic development? In a developing embryo, individual cells undergo programmed shape changes to generate emergent macroscopic patterns that are essential for building functional organs, but the mechanisms involved in these precise changes remain less clear. Kupffers vesicle (KV), a transient organ that is responsible for specifying the left-right body axis of the zebrafish embryo, provides an excellent system to identify the factors that contribute to organogenesis and left-right embryo patterning. Although previous work has implicated intercellular tensions and extracellular matrix in this patterning, we conjecture that the dynamic motion of the KV through the tailbud may also play a role. Using a self-propelled Voronoi model, which incorporates both tissue rheology and cell motility, we investigate how the mechanical properties of highly dynamic cells surrounding the KV influence cell shape changes in the KV and consequently the left-right asymmetries in the embryo.

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MS6

Mechanistic Basis of Spindle Size Control and Scaling

The size and morphology of intracellular structures such as the nucleus, Golgi apparatus, and mitotic spindle dramatically vary between different cell types, yet the mechanisms that regulate the size of these structures are not understood. Interestingly, the size of most intracellular structures scales with cell size, i.e. larger cells tend to have larger nucleus and spindles. So far, many models

have been proposed to explain such scaling behavior, but rigorous testing of these models inside the cells is challenging, and often not feasible. To overcome this challenge, we combined the statistical framework of quantitative genetics, with cell biology and biophysics to develop a general methodology to quantitatively examine different models of spindle size control and scaling for the first mitotic spindle in *C. elegans*. We also use laser ablation technique to quantitatively measure changes in forces under different genetic perturbations. The combination of quantitative genetics with cell biology and biophysics provides a systematic and unbiased method to study mechanisms that contribute to size regulation of intracellular structure and also will give us a deeper understanding of the evolution of these structures.

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MS6

Minimal Models of Cell Mechanics Explain Transitions to Motility and Turning Behavior

We systematically explore minimal models of actin-based motility that include actin-myosin contraction balanced by viscous stresses in the actin network and uniform adhesion. In the models, transitions to motility and cell shape dynamics result from the balance between actin protrusion and myosin contraction; the latter causes the lamellipodial boundary to retract. The corresponding free-boundary problems involving a coupled nonlinear system of parabolic and elliptic equations are solved in two-dimensional geometries. For this, we have implemented a segregated solution strategy whereby the system is advanced by iteratively solving the uncoupled equations. A mass-conservative finite volume scheme and an implicit backward Euler method were used for numerical discretization. The solutions reproduce a variety of experimentally observed modes of motility and cell shapes determined by a small set of model parameters. When the contractility becomes sufficiently strong, cells break symmetry and move steadily along straight or circular trajectories. Parameter scanning revealed that robust cell turning occurs when low actin viscosity and fast protrusion destabilize the axial symmetry of a moving cell. It is also shown that the motility modes and cell shapes are sensitive to adhesion strength at the cell boundary.

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MS6

Mathematical Modeling of Glioblastoma Cell Migration and Tumor Growth

Glioblastoma is the most aggressive form of brain tumors with median survival of 15 months and 5-year survival rate of less than 5%. GBM is currently incurable due to the high proliferation and migration rates associated with tumor cells, which allow them to invade healthy tissue and evade current therapies. We are developing multiscale mathematical models to simulate cancer cell migration and proliferation to predict tumor growth and spreading. Such models will help interpret clinical data and guide the development of more effective therapies. Previously, we have developed a cell migration simulator that predicts the optimum environment for cell migration. However, to simulate tumor growth and spreading both migration and proliferation need to be considered. Here, we utilized Brownian dynamics to simulate tumor spreading of two genetically distinct GBM mouse models. We hypothesized that different genetic drivers will results in different cellular dynamics that will consequently affect tumor growth and spreading. We tracked tumor growth and individual cell movements and found the two genetic drivers produced different cellular dynamics: high proliferation/slow migration and low proliferation/fast migration. Using the measured parameters, we are simulating tumor growth to predict the spatial distribution of tumor cells and comparing it to bioluminescence and immunohistochemistry data acquired from our two mouse models.

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MS7

Comparing Methods for Estimating the Rate of Appearance of Exogenous Glucose in an Oral Glucose Tolerance Test

Differential equations-based mathematical models of whole body glucose-insulin dynamics have been developed to enable quantification of insulin resistance (IR) in individual participants. Specifically, the labeled oral minimal model (OMM*), describing glucose-insulin dynamics following an oral glucose tolerance test (OGTT) with two stable isotope tracers, provides estimates of an individual's hepatic IR. Developing a reliable mathematical characterization of the rate of appearance of exogenous glucose (Ra_{exo}) based on measured enrichments of stable isotopes is a necessary step in applying OMM*. Several different methods for computing Ra_{exo} have been published. We compared these methods for determining Ra_{exo} and identified methodological effects on estimates of hepatic IR obtained using OMM*. Each method was applied to OGTT data from a group of obese adolescent girls, and methods were compared based on inter-method variability and known physiology. The estimates of Ra_{exo} obtained using each method were incorporated into OMM* to assess the method dependence of resulting estimates of hepatic IR. Improved understanding of the available methods for estimating Ra_{exo} will provide insight into the aspects of exogenous glucose dynamics that affect estimates of hepatic IR and will facilitate interpre-

tation of data collected under these complex experimental protocols.

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MS7

Modeling Tissue-specific Insulin Resistance in Obese Adolescent Girls During an Oral Glucose Tolerance Test

Insulin resistance (IR) is a key element of the pathology of the metabolic syndrome, which now affects more than a third of the population in the United States. Understanding the contribution of abnormal hepatic glucose release to glucose concentrations following a meal is crucial for the assessment of potential new therapies to treat hyperglycemia. IR of hepatic tissue (hepatic IR) may be estimated using mathematical modeling of data from an oral glucose tolerance test (OGTT) protocol with two stable isotope tracers. However, due to unique adolescent associated IR, current models developed in adults do not optimally describe glucose dynamics in youth. Thus, we adapted a mathematical model of glucose-insulin dynamics during a labeled OGTT to describe hepatic IR in adolescent girls. We investigated the structural identifiability of the model, and this analysis informed the implementation of appropriate numerical approaches for subject-specific parameter estimation. Improved understanding of interactions between exogenous and endogenous glucose dynamics will facilitate the characterization of tissue-specific IR in individual patients and different disease conditions and may support the development of targeted therapeutic approaches.

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MS7

Modeling of Hepatic and Extra-hepatic Insulin Clearance Among Different Ethnicities

A recent mathematical model was the first to dissect hepatic fractional extraction (FEL) of insulin from extra-hepatic insulin clearance (CLP). The model employs insulin and C-peptide data of a frequently sampled intravenous glucose tolerance test (FSIGT). It calculates insulin secretion rate through deconvolution with a 2-compartment representation of C-peptide kinetics, and assigned parameters. Insulin kinetics has two compartments: liver and plasma. Delivery of insulin to the liver is assumed as the sum of the current insulin secretion rate and the insulin returning to the liver from the bloodstream. Delivery of insulin into the plasma includes the secreted insulin that survives first pass hepatic extraction and the intravenous insulin infusion. Both linear and saturable descriptions of hepatic insulin extraction are estimated individually; the preferred one is selected. With this model, we demonstrate that hepatic, but not extra-hepatic, insulin extraction is 1/3 lower in African American (AA) adult women compared to the European American (EA) ones, contributing to hyperinsulinemia in the AA. The model was then applied to FSIGT data from 203 children, age 7-13 years [55 AA, 88 EA, 60 HA (Hispanic American)], to examine whether the impairment in liver insulin extraction is seen since childhood. The model confirms the hepatic, but not extra-hepatic impairment in AA vs. EA children. Genetic factors might account for lower insulin extraction and hyperinsulinemia in AA.

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MS7

Longitudinal Modeling of Type 2 Diabetes Development and Progression

Glucose and insulin homeostasis constitutes a classic negative feedback loop. After a meal, plasma glucose rises, which induces insulin secretion from pancreatic beta cells, which restores glucose to baseline within hours by promoting uptake into muscle and fat and reducing glucose release from the liver. Aging and weight gain lead to reduced sensitivity of the target tissues to insulin, requiring increased insulin secretion to maintain normal glucose levels. In the minority of individuals who cannot adequately respond to this increased demand, diabetes (chronic hyperglycemia) eventually ensues. This dynamic was modeled by Topp and colleagues (J. Theor. Biol., 2000) by adding an equation for beta-cell mass (essentially, the number of beta cells), which was assumed to increase slowly (months, years). We and others have extended this groundbreaking idea to model in detail animal and clinical data. By adding equations for beta-cell function (secretion per cell), we could offer plausible explanations for why it is easier to prevent diabetes than to cure it. Here we present applications of the model to a variety of situations, including ethnic differences in diabetes risk and extracting extra information from oral glucose tolerance tests (OGTT). For example, we predicted, and clinical studies confirmed, that time to peak glucose during the OGTT can improve predictions of risk beyond the standard measures of baseline and final glucose level.

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MS8

The Role of F1fo-Atp Synthesis in Shaping Mitochondrial Cristae

Abstract not available at time of publication.

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MS8

Er Sheet Persistence is Coupled to Dynamic Actin Filament

Abstract not available at time of publication.

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MS8

Fluctuating-rate Model of Single-cell Dynamics and its Applications

Stochastic processes become more and more popular to model the mesoscopic biophysical dynamics, especially in single-cell biology. We proposed a fluctuating-rate model for the stochastic biochemical dynamics in a single cell, which is indeed piecewise deterministic Markov process. We also found that the fluctuating-rate model yields a nonequilibrium landscape function, which, similar to the energy function for equilibrium fluctuation, provides the leading orders of fluctuations around each phenotypic state, as well as the transition rates between the two phenotypic states. The rigorous proof needs to integrate the well-known Donsker-Varadhan theory and Feidlin-Wentzell theory in such an averaging case. We then apply this model to Lac operon system, and show how and why the stochastic gene-state switching can significantly broaden the environmental parameter ranges for the existence of bistability induced by positive feedback, which can be beneficial dealing with unpredictable environmental changes.

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MS8

The Role of Mass Balance and Surface Proteins in ER Dynamics

Proteins play a major role in reconfiguring the energetic structure of interfacial morphology. We propose a model that allows for free motion of surface proteins on an interface whose shape conforms to the density of surface proteins. Accurate models of membrane shape requires detailed control of local membrane stretching, essentially local mass conservation for the lipid constituents. This is afforded easily through the FCH free energy formulation, moreover we describe the impact of a model in which lipid mass is lost at high curvature areas.

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MS9

Interplay between Curvature-inducing Proteins and Intracellular Membrane Structures: Application to Biologically Relevant Minimal Surfaces

An astonishing variety of membrane structures can be observed in the cellular environment, both at the plasma membrane and at the organelles. These morphologies are intricately related to biological functions, enabling and regulating fundamental cellular processes. Yet the membrane composition in curvature-inducing proteins allowing to shape these structures remain challenging to assess. We ask, given a cellular membrane structure, what is the distribution and concentration of curvature inducing proteins necessary to maintain this shape? We propose a theoretical approach based on Helfrich model extended for lipid-protein interaction, that allows us to compute the field of spontaneous curvature that sustains a given membrane structure at mechanical equilibrium. We demonstrate this approach by investigating the role of spontaneous curvature in minimal surfaces, which include catenoids – relevant to vesicle trafficking, tubulation, and nuclear pores – and helicoids – relevant to endoplasmic reticulum ramps. In these cases, the shape equation reduces to a variable-coefficient Helmholtz equation for the spontaneous curvature, where the source term is proportional to the local Gaussian curvature. Importantly we show the existence of energy barriers associated with geometrical variations of the membrane structure, pointing out the need for a coordinated action of at least two distinct curvature-inducing proteins, in agreement with experimental observations of necking processes.

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MS9

Tuning Length Scales of Small Domains in Cell-derived and Synthetic Model Membranes

When a taut lipid membrane demixes into a liquid-ordered phase and a liquid-disordered phase, domains nucleate, diffuse, collide, and coalesce until only one domain of each phase remains. The length scale of these domains is limited only by the size of the system. In contrast, in a membrane with excess area, small domains can persist due to a modulated phase, a microemulsion, or hindered coarsening. Here, we tune the characteristic length scale of small features in membranes of cell-derived giant plasma membrane vesicles (GPMVs) and synthetic giant unilamellar vesicles (GUVs). We find that as the membranes temperature and excess area increase, the characteristic length scale decreases. We vary the ratio of lipids in the membranes and find that the resulting area fractions and fluorescence levels do not support a theory in which lipid compositions are anti-registered across a bilayer. We vary the chemical linkage between lipid head groups and tails and find small-scale membrane features; this result does not support the proposal that carbonyl dipoles in the ester-linkages give rise to a modulated phase. Our experiments support a theory in which mean bilayer spontaneous curvature is integral to the creation of small-scale membrane features.

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MS9

Topological Methods for Characterizing the Polymer Entanglement and Viscoelasticity

We explore how the microscopic interactions link to bulk macroscopic properties of materials. We study systems of polymer chains in a solvent and examine the effect of hydrodynamic and of bonded and excluded volume interactions. First, we investigate how the entanglement of polymeric chains relates to bulk viscoelastic responses in polymeric materials. We show how the structure of the material can be analyzed using results from topology to develop new tools for entanglements. Next, we investigate the hydrodynamic effect of thermal fluctuations to the macroscopic properties of the material using the Stochastic Eulerian Lagrangian Method. Our studies will lead to a better understanding of the viscoelastic properties of materials which involve different length scales and complex microscopic interactions, like the cytoskeleton.

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MS9

Curvature-driven Phase-separation of Spherical Vesicle Membranes: Insights from Single-bead Lipid Models

Motivated by the role of the collective dynamics of lipids in many biological processes, we explore the morphology and kinetics of phase separation in spherical lipid bilayer vesicles. We use single-bead implicit-solvent coarse-grained models based on anisotropic pair potentials to simulate coarsening dynamics and preferred curvatures. We find for molecular mixtures with different preferred curvatures that several interesting phenomena can arise, such as curvature-induced stalling of coarsening and for more extreme curvature variations even the occurrence of budding events of small vesicles. We report on our findings and related theory describing the kinetics of domain formation, coarsening arrest, and related phenomena as curvature is varied. We also explore and report on links between these curvature-composition effects and the mechanics of vesicles.

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MS11

Excitability in Cerebellar Stellate Cells: From Latency to Runup

Our recent work has recently shown that inhibitory cerebellar stellate cells, involved in motor control, alter their excitability over time after patch-clamping them. They do so by increasing their excitability over time (runup) and by exhibiting peculiar biphasic latency profile (latency to first spike). This is achieved through modifying the kinetics of certain ion channels expressed on the membrane of these neurons. Using mathematical modeling techniques, we identified what these ion channels are and how their kinetics are modified. In this talk, I will present the model that explains these outcomes and show that these neurons are type 1 oscillators possessing a SNIC bifurcation. I will also illustrate how we used dynamical systems approaches to explain the runup phenomenon in excitability, the biphasic profile in latency and the transient single spiking associated with the SNIC.

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MS11

Rivers in Dynamical Systems: How to Define Them, How to Find Them, and How They can Shape Dynamics

The properties of phase space geometry that give rise to excitability also naturally produce other interesting dynamic features, such as transitions to oscillations under parameter variations. One example of such a feature is a structure known as a river. Rivers are long-recognized but poorly understood trajectories that locally attract other orbits yet need not be related to invariant manifolds or other familiar phase space elements. We have developed a novel change of coordinates, *local orthogonal rectification* (LOR), that can be applied to any specified curve in the phase space of a dynamical system and can be used to find trajectories with specified properties. I will introduce LOR and will illustrate its utility in several neuroscience models. In particular, I will show how analysis with LOR yields a precise, natural definition for rivers and allows us to locate them and use them to analyze model dynamics.

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MS11

Modeling Astrocytic Modulation of Neuronal Dynamics

There has been a tremendous effort by the computational neuroscience community to develop and analyze models for neuronal firing patterns, which arise in a wide array of brain systems. However, very few of these studies considered how the firing patterns depend on astrocytic regulation of brain homeostasis. Recent experiments have

demonstrated that astrocytes may play a critical role in the modulation of neuronal network activity, including oscillations and synchronization, mainly through their role in ion homeostasis and uptake of the neurotransmitters GABA and glutamate. We use computational modeling and mathematical analysis to identify mechanisms and processes by which astrocytes modulate neuronal activity in both normal brain function and neurological disease.

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MS11

Modelling the Hypothalamic Network Driving Secretion of Reproductive Hormones

Reproduction critically depends on the pulsatile secretion of gonadotrophin-releasing hormone (GnRH) from the hypothalamus. This rhythm drives the secretion of gonadotrophic hormones from the pituitary gland, which are critical for gametogenesis and ovulation, and its frequency is regulated throughout the life course to maintain normal reproductive health. However, the precise mechanisms controlling the pulsatile GnRH dynamics are unknown. Here, we propose and study mathematical model of the population of neurones in the arcuate nucleus of the hypothalamus that co-expresses three key modulators of GnRH secretion: kisspeptin; neurokinin B (NKB); and dynorphin (Dyn). The model highlights that positive feedback in the population exerted by NKB and negative feedback mediated by Dyn are the two key components of the pulse generator, which operates as a relaxation oscillator. Furthermore, we use the model to study how external inputs modulate the frequency of the pulse generator, a prediction that can be readily tested in-vivo using optogenetically-driven stimulation. Finally, our model predicts the response of the system to various neuropharmacological perturbations and reconciles inconsistent experimental observations following such interventions in-vivo. We anticipate that our model in combination with cutting-edge, in-vivo techniques, allowing for neuronal stimulation and recording, will set the stage for a quantitative, system-level understanding of the GnRH pulse generator.

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MS12

Classical Result and New Avenues of Research for Stochastic Models in Biology

Stochastic reaction networks are mathematical models used to describe a biological system with low molecule counts. If few molecules are present, then the dynamics of the system is strongly affected by stochastic noise, and the changes of the molecules counts are described by means of a continuous time Markov chain. I will introduce stochastic reaction networks and give an overview of the main results concerning them. In particular, I will show the connections between stochastic reaction networks and deterministic reaction networks, which can be regarded as fluid limits of the stochastic models. I will introduce diffusive approximations as well. Finally, I will outline some results pertaining stationary distributions of stochastic reaction networks, and relate them to graphical equilibria. All these topics will be discussed with more details in the course of the minisymposium.

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MS12

Quasi-stationary Distributions in Reaction Networks

For the stochastic process corresponding to a reaction network, we consider the case of the state space having an absorbing set, which is reached almost surely. In this setting, the natural object of study is a so-called quasi-stationary distribution, which is the stationary measure when we condition on the process not going extinct. Indeed, if the system has been running for a long time, and has not yet reached extinction, then the quasi-stationary distribution is the likely distribution of the state variable, and may thus be seen as the counterpart to a stable stationary solution in the deterministically modeled system. We provide sufficient conditions for the existence and uniqueness of such quasi-stationary distributions and examine the relationship with the deterministic dynamics in the fluid limit.

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MS12

Positive Recurrence and Mixing Times of Stochastically Modeled Reaction Networks

One of the most challenging issues facing researchers who study biological systems is the often extraordinarily complicated structure of their interaction networks. Thus, how to characterize network structures that induce emergent phenotypes (characteristic behaviors) of the system dynamics is one of the major open questions in systems biology. In the deterministic modeling regime, a number of network conditions have been produced, each of which characterizes qualitative behaviors of system dynamics. Conversely, there are very few results relating the dynamics of stochastically modeled reaction networks with their associated network structure. In this talk, we will mainly focus on which underlying structure of the networks imply positive recurrence for the continuous-time Markov chain associated to the stochastically modeled reaction networks. I will also present results related to their mixing times, which give the time required for the distribution of the continuous-time Markov chain to get close to the stationary distribution.

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MS13

Three Dimensional Swarming Patterns in Viscous Fluids

Swarming patterns arising from self-propelled particles have been extensively studied in two-dimensions and in the absence of an embedding medium. We consider the dynamics of more realistic three-dimensional self-propelled particles interacting in a fluid medium. The fluid interaction terms generated by direct short-ranged pairwise interactions impart much longer-ranged hydrodynamic forces, effectively amplifying the coupling between individuals. We study two limiting cases of fluid interactions, a "clear fluid" where particles have direct knowledge of their own velocity, that of others and of the fluid, and an "opaque fluid" where particles are able to determine their velocity only in relation to the surrounding fluid flow. We discover a number of new collective three-dimensional patterns including flocks with prolate or oblate shapes, recirculating pelotonlike structures, and jet-like fluid flows that entrain particles mediating their escape from the center of mill-like structures. We also discuss how fluid flows may stabilize emergent patterns that would be short-lived in fluid free environments.

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MS13

A Probabilistic Analysis of Volume Transmission in the Brain

Volume transmission is a fundamental neural communication mechanism in which neurons in one brain nucleus modulate the neurotransmitter concentration in the extracellular space of a second nucleus. In this talk, we will describe a mathematical model of volume transmission involving the diffusion equation in a bounded three-dimensional domain with a set of interior holes that randomly switch between being either sources or sinks. The interior holes represent nerve varicosities that are sources of neurotransmitter when firing an action potential and are sinks otherwise. To analyze this random PDE, we will show that its solution can be represented as a certain local time of a Brownian particle in a random environment, and that this representation can be used to prove surprising properties of the solution. More broadly, we will explain how this probabilistic perspective on Brownian functionals relates to recent results on escape problems involving mean first passage times of diffusion and asymptotic analysis of PDEs.

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MS13

The Role of Receptor Clustering in Chemoreception

Cells interact with their environment and communicate with other agents through contact with diffusing signaling molecules at receptors sites distributed on the cellular surface. For this process of chemoreception to be effective in such a noisy environment, surface receptors must be numerous and widely distributed. The spatial organization or 'clustering' of these receptors has long been known to play a key biophysical role, however, mathematical analysis of this role is a challenging problem that, despite much attention, is not yet resolved. In this talk I will describe new theoretical results which give precise information of the role of clustering in scenarios where receptors occupy spherical surfaces or are periodically arranged on infinite planes. With these new results, optimizing configurations of receptors can be identified. In the case of a plane with a periodic arrangement of receptors, we find that a hexagonal configuration maximizes the sensing rate of the receptors. In addition, we will discuss a new suite of Kinetic Monte Carlo methods for diffusive signaling problems. These methods are able to verify theoretical results and in addition allow for efficient exploration of the space of receptor clustering configurations.

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MS13

Assessing Biological Models with Topological Data Analysis

We use topological data analysis as a tool to analyze the fit of mathematical models to experimental data. This study is built on data obtained from motion tracking groups of aphids in [Nilsen et al., PLOS One, 2013] and two random walk models which were proposed to describe the data. One model incorporates social interactions between the insects, and the second model is a control model which excludes these interactions. We use computational persistent homology to calculate topological signatures of the experimental data and of the models. Statistical tests on the distances between these topological signatures suggest that the interactive model better describes the data, whereas traditional order parameters used to summarize the experiments are not able to distinguish between the two models.

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MS14

Modeling Insights into the Mechanical Coordination in the Collective Locomotion of Heart Progenitor Cells

During embryonic development, cells often migrate in groups. The heart progenitors of the ascidian Ciona provide one of the simplest examples of collective migration whereby just two cells migrate with defined leader-trailer polarity. The cells are also capable of migrating individually, albeit by a shorter distance, with imperfect directionality, and with altered morphology. Thus, maintaining the leader-trailer polarity is important for directed migration to the destination. To understand the mechanics of this collective migration phenomenon, we develop a computational model to study the interplay of actomyosin contractility, cell-matrix adhesion, and the resulting leader-trailer polarity maintained for collective migration and combine modeling with imaging of the migrating cells. Two competing hypothesis are tested to understand the mechanical coupling and coordination between leader-trailer cells and the cells in the extracellular tissues: (1) cells act as a single unit in which the leader cell generates actin-driven protrusions while actin polymerization is down-regulated in the contractile trailer cell; (2) alternatively, contraction at the rear of the trailer cell leads to higher osmotic pressure pushing on leader cell. We present insights from modeling explorations of the mechanochemical coordination in this model system for collective locomotion.

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MS14

Cytoskeletal and Membrane Force Contributions to Cytokinesis: An in-Silico Approach

Cytokinesis, the final step of cell division, is a widely conserved process. Proper initiation, placement, and dynamics of cytokinesis are required in most dividing cells for successful development, and to evade disease states. The cytokinetic furrow is generated by a transient contractile ring rich in actin filaments, non-muscle myosin II (NMM II) and crosslinking proteins. Recent agent-based models have explored different aspects of how actomyosin cytoskeletal networks can generate contractile forces, however most of these ignore the contractile rings connection to the plasma membrane. Conversely, many models have detailed membrane and cytoplasmic contributions to cytokinesis, but reduce cytoskeletal elements to pure force contributions. In order to explore the universal molecular mechanisms behind contractile force generation, we thus set out to combine aspects of both modeling approaches to generate a hybrid model that explicitly simulates the actomyosin ring components tethered to an active membrane. Using this hybrid model, we begin to explore how different components contribute to the overall dynamics of cytokinesis. Specifically, we compare the contributions of cytoskeletal component densities during constriction, to the contributions of membrane deformation under constant or dynamic membrane tension. Together, our results will reveal the mechanistic importance of several components of the contractile ring as they affect structure and force transmission in the ring.

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MS14

Onset of Collective Dynamics in Active Biosystems

A novel modeling and computational approach is used to investigate the origin of self-organization in bacterial suspensions. The key feature of this approach is the incorporation of interbacterial interactions motivated by experimental observations while allowing for efficient computation for a large number of particles. The first part of the talk investigates the emergence of striking effective properties of a bacteria suspension in the collective state. The mathematical analysis leads to explicit formulas for the effective viscosity as well as the effective normal stress differences describing the complete rheological behavior of an active suspension in terms of known physical parameters. Next, numerical analysis of a corresponding thin film PDE model confirms the experimental observation that particle size and shape rather than the concentration of bacteria governs the size and duration of the collective state in bacterial suspensions. The results of the analysis exemplify the delicate balance between hydrodynamic interactions and collisions governing mesoscopic collective motion in bacterial suspensions.

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MS14

Osmotic Water Flow and Solute Diffusion in Moving Cells

Differences in solute concentration across a semipermeable membrane of cells generates transmembrane osmotic water flow. The interaction of such flows with membrane and flow mechanics may be crucial in many biological applications. Particularly, in recent studies, experimental evidence suggests that membrane ion channels and aquaporins (water channels), and thus, solute diffusion and osmosis, play an important role in cell movement. To clarify the role of osmosis in cell movement, one needs to understand the interplay between solute diffusion, osmosis and mechanical forces. In this presentation, we discuss a mathematical model that allows for studying the interplay between diffusive, osmotic and mechanical effects, and the numerical method for solving the model system. An osmotically active solute obeys a advection-diffusion equation in a region demarcated by a deformable membrane. The interfacial membrane allows transmembrane water flow which is determined by osmotic and mechanical pressure differences across the membrane. The numerical method is based on an immersed boundary method for fluid-structure interaction and a Cartesian grid embedded boundary method for the solute. We demonstrate our numerical algorithm with the test case of an osmotic engine, a recently proposed

mechanism for cell propulsion.

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MS15

The Parameter Houlihan: A Solution to High-throughput Identifiability for Brutally Ill-posed Problems

To make forward progress toward understanding complex physiology via model refinement and selection, and in many clinical situations that require an urgent solution, we do not always have the luxury of working with models with identifiable parameters or in situations that are not brutally ill-posed. In this circumstance much can still be gained by using data assimilation, but we need to have a way to coping with the lack of identifiability and the bewilderment when faced with choosing which parameters to estimate from among 10s to 1000s. Here we assume a situation that is brutally ill posed, where the models have far more parameters than we can hope to resolve, but where we need a solution. Moreover, we are assuming that we may have many potential models and we need to be able to choose what parameters to approximate in a more high-throughput way. In this talk I will discuss methods for creating a rank-ordered list of parameters to estimate to give the most useful forecast and help determine which models most faithfully represent a given system.

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MS15

A New Fitting Model for Evaluating Oral Glucose Tolerance Tests Predicts Future Glycemic Status

There has been a growing interest in extracting metabolic parameters from clinical data in diabetes. As such, mathematical models of glucose homeostasis have been used to identify those parameters that guide clinical practices for diabetic patients. We have developed a new algorithm to fit our mathematical model to Oral Glucose Tolerance Test data. The mathematical model was originally designed for understanding underlying mechanisms of progression to diabetes (Ha et al. Endo 2016). The current fitting algorithm has been developed to estimate three major metabolic parameters: peripheral insulin sensitivity, hepatic insulin sensitivity, and beta-cell function. Insulin sensitivity estimated by the fitting model is well correlated with insulin sensitivity measured by insulin clamp and intravenous glucose tolerance test, R2 = 0.5. Given two longitudinal OGTT data sets, the model can predict the response of future glycemic status to changes in insulin sensitivity.

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MS15

Bayesian Estimation and External Validation of Mechanistic Endocrine Parameters in Critically-ill Adults

Models of glucose-insulin regulation include parameters that represent physiologic processes, like kidney filtration rates and insulin sensitivity. Here, we use data collected from critically-ill adults in a Neural Intensive Care Unit (glucose measurements, insulin administration, and enteral nutrition delivery records) to estimate parameters from different endocrine models within a Bayesian Inverse framework. We compare parameter estimates to related laboratory measurements to determine the extent to which glucose-insulin models can provide insight into other physiologic processes.

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MS15

Methods of Analysis of a Gap Junctionally Connected Functional Network

Network theory is becoming more prevalent in mathematical physiology as clusters of cells can be represented as a graph, from which multiple measures such as network robustness, centralities, synchronization of activity and small worldness can be measured. Usually this is applied to neural networks, but recently functionally connected networks have also been the focus of this type of analysis. To investigate the performance of gap junctionally connected β cells in pancreatic islets, we used a model describing the electrical and calcium dynamics to build a connectivity map, where the cells were considered the nodes. By correlating the calcium traces between the individual cells, functional connections were mapped out, creating the edges of our graph. As islet performance can be measured as the synchronization of oscillatory activity of the islet, we tested multiple synchronization indices on our network to accurately capture the behavior of the islet. Recently there has an interesting hypothesis regarding the organization of cells within the islet. Rather than more or less equal input from each β cell, islets have been shown experimentally to be scale-free and have small-world networks. By calculating the efficiency and clustering of the functional networks, we have measured small worldness in the islets

depending on heterogeneous parameters. This work was initiated as part of the NSF-REU (#1460652) with Elise Falgout, Destiny Frett, Lorenzo Neil, and Ryan Schumm.

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MS16

Variational Approach of Coarse-grained Lipid Dynamics

Abstract not available at time of publication.

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MS16

3D Computational Modeling of Bleb Initiation Dynamics

Blebbing occurs in cells under high cortical tension when the membrane locally detaches from the actin cortex, resulting in pressure-driven flow of the cytosol and membrane expansion. Some cells use blebs as leading edge protrusions during cell migration, particularly in 3D environments. Blebs can be initiated through either a localized loss of membrane-cortex adhesion or ablation of the cortex in a region. Bleb shape resulting from different initiation mechanisms has not been studied in detail, either experimentally or with theoretical models. Results from experiments have suggested that cytoplasmic elasticity is important for limiting bleb size. A 3D dynamic computational model of the cell is presented that includes mechanics of and the interactions among the cytoplasm, the actin cortex, the cell membrane, and the cytoskeleton. The model is used to quantify bleb expansion dynamics and shapes that result from simulations using different initiation mechanisms. Results from model simulations with a viscous fluid cytoplasm model show much smaller and broader blebs when they are initiated via cortical ablation than when they are initiated by removing membrane-cortex adhesion. Simulation results using the poroelastic model of the cytoplasm provide qualitatively similar bleb morphology regardless of the initiation mechanism.

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MS16

Gating of a Mechanosensitive Channel due to Cellular Flows

Abstract not available at time of publication.

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MS16

A Numerical Analysis of the Functionalized Cahn-Hilliard Equation

Abstract not available at time of publication.

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MS17

Emergent Three-dimensional Sperm Motility Coupled to Calcium Dynamics

Sperm are navigating in a complex three-dimensional fluid environment in order to reach and to penetrate the egg. Changes in calcium concentration along the sperm flagellum regulate flagellar bend amplitude and beat asymmetry, enabling the sperm to achieve egg fertilization. However, the exact mechanisms of how calcium regulates the flagellar beat form are yet unknown and under investigation. We propose a fluid-structure interaction model that couples the three-dimensional motion of the flagellum in a Newtonian viscous fluid with the calcium dynamics in the flagellum. The flagellum is modeled as an elastic rod with preferred curvature and twist, using the Kirchhoff rod model. The calcium dynamics are represented as a one-dimensional reaction-diffusion model on the moving flagellum, accounting for calcium CatSper channels. The sperm motility and calcium dynamics are coupled assuming that the sperm flagellum preferred curvature depends on the local evolving calcium concentration in time. The model is used to investigate the calcium coupling effect on the three-dimensional emergent waveforms and trajectories, compared to the two-dimensional case. Model results are in agreement with experiments, and show that 1) the planar swimmer is faster than the helical one, and shows a clear turning motion if asymmetric calcium coupling is considered; 2) three-dimensional trajectories can be characterized as hypotrochoid curves.

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MS17

Single-flagellated Bacterial Swimming: Run, Reverse, and Flick

Single-flagellated bacteria propel themselves by rotating a flagellar motor, translating rotation to the filament through a compliant hook and subsequently driving the rotation of the flagellum. The flagellar motor alternates the direction of rotation between counterclockwise and clockwise, and this leads to the forward and backward directed swimming. Such bacteria can change the course of swimming as the hook experiences its buckling caused by the change of bending rigidity. In this paper, we present a comprehensive model of a monotrichous bacterium as a free swimmer in a

viscous fluid. We describe a cell body as a rigid body using the penalty method and a flagellum as an elastic rod using the Kirchhoff rod theory. The hydrodynamic interaction of the bacterium is described by the regularized Stokes formulation. Our model of a single-flagellated micro-organism is able to mimic the swimming pattern that is well matched with the experimental observation. Furthermore, we find the critical thresholds of the rotational frequency of the motor and the bending modulus of the hook for the buckling instability, and investigate the dependence of the buckling angle and the reorientation of the swimming cell after buckling on the physical and geometrical parameters of the model.

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MS17

Sperm Motility in Complex Environments

Sperm can swim in a variety of environments, interacting with chemicals and other proteins in the fluid. Some of these extra proteins or cells may act as friction, possibly preventing or enhancing forward progression of swimmers. The homogenized fluid flow is assumed to be governed by the incompressible Brinkman equation, where a friction term with a resistance parameter represents a sparse array of obstacles. Representing the swimmers with a centerline approximation, we employ regularized fundamental solutions to investigate swimming speeds, trajectories, and interactions of swimmers. Although attraction of two swimmers is more efficient in the Stokes regime, we find that attraction does not occur for larger resistance. Additionally, we study interactions of swimmers in a channel.

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MS17

Mixing and Pumping by Pairs of Helices in a Viscous Fluid

We study the fluid dynamics of a pair of rigid helices rotating at a constant velocity, tethered at their bases, in a viscous fluid. Utilizing the regularized Stokeslet and its image system, we analyze the flow both with and without a bounding plane. We are able to discern precisely what flow features are unaccounted for in studies that ignore the surface from which the helices emanate. Our results are helpful to examine how the spacing and phase difference between identical rotating helices affects their pumping ability, axial thrust, and power requirements. We also find that maximal thrust and optimal mixing of the fluid around two helices is achieved when they rotate in opposite phase.

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MS18

A Signal Processing Perspective on the Role of Receptive Field Structure in Encoding Natural Scenes and Illusory Images

The structure of receptive fields in the early visual system is hypothesized to be evolutionarily advantageous in image processing tasks. We address the potential functional benefits and shortcomings of the structural characteristics common in receptive fields in the context of an integrate-and-fire neuronal network model with visual stimulus inputs. Based on the sparsity of natural scenes, we utilize a compressive-sensing framework for reconstructing input images from measurements of the evoked neuronal firing rates, thereby giving a measure of how well the nonlinear network dynamics encode various classes of stimuli. Analyzing several receptive field models, we investigate how the accuracy of input encoding depends on the network architecture, and demonstrate that the center-surround structure common in receptive fields facilitates marked improvements in natural scene processing well beyond uniformly-random excitatory connectivity. However, we show that the spatial localization inherent in receptive fields combined with information loss introduced by nonlinear neuronal dynamics may underlie deficiencies in processing specific classes of non-natural stimuli, such as the Hermann grid, yielding a novel explanation for the manifestation of illusory effects. This computational framework provides a robust and generalizable means of relating sensory network structure to function, which we expect to yield future insights into stimulus encoding across sensory systems.

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MS18

Mice are not Cats: An (almost) Exact Proof

We study the connectivity principles underlying the emergence of orientation selectivity in primary visual cortex (V1) of mammals lacking an orientation map. We present a computational model in which random connectivity gives rise to orientation selectivity that matches experimental observations. It predicts that mouse V1 neurons should exhibit intricate receptive fields in the two-dimensional frequency domain, causing shift in orientation preferences with spatial frequency. We show evidence for such receptive fields in mouse V1 using calcium imaging and intracellular whole cell recordings.

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MS18

Architectural and Functional Connectivity in the Cerebral Cortex

The extent of the relation between architectural and functional connectivity in the cerebral cortex is a question which has attracted much attention in recent years. Neuroscientists frequently use the functional connectivity of neurons to infer the architectural connectivity of the network, which indicates the locations of synaptic connections between neurons. Architectural connectivity can be used in modeling neuronal processing and in forming conjectures about the nature of the neural code. These two types of connectivity are by no means identical. In particular, certain measures of functional connectivity, such as correlations, give rise to an undirected network, while synaptic architectural connectivity is always directed. Nevertheless, architectural connectivity can be inferred from functional connectivity, and this work is one attempt to determine how to do so. We begin by examining correlation, and examining how accurate a reconstruction of the neural structure can be derived. We avoid time spans which would be unfeasible in an experiment. Additional work will involve analyzing neuronal network structure, looking especially at incidence matrices representing both types of connectivity with the intention of establishing how one depends on the other. This can be achieved by studying the structure of these matrices through tools including low-rank decomposition and spectral properties.

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MS18

Sparse Representation of Pulse-coupled Networks by Maximum Entropy Principle

It has been a challenging issue to effectively characterize the distribution of pulse-coupled network states of nodes with binary dynamics. The number of possible network states exponentially grows as the node number increasing. Low order maximum entropy principle (MEP) analysis has been successful in effectively characterizing the distribution of network states of nodes with binary dynamics in many experiments, e.g., in neuroscience. However, it is still unclear whether the high order effective interactions in MEP analysis could accumulate to have a significant effect on a large network. It is either yet to study what role can the coupling structure of the network play to the effective interactions among nodes. Here, we discover a relationship between the effective interaction and the coupling structure to show that many high order effective interactions are zero in a sparsely connected network. Therefore, the MEP analysis potentially has an effective sparse representation of the distribution of network states of nodes with binary dynamics.

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MS19

Near-real-time Study of Complex Cardiac Models in Two and Three Dimensional Tissue using WebGL2.0

Statistics show that cardiac disease continues to be the leading cause of death in US and globally, therefore, cardiac studies are essential to provide deeper insight in diagnosis and treatment. Cardiac computational studies present their own challenges due to restrictions on time-stepping enforced by the steep upstroke of the cardiac action potential, and restrictions on the spatial discretization sizes imposed by the size of the cardiac cells. Additionally, complex cardiac models require solving tens of ordinary differential equations for each computational cell. Due to these challenges, solving cardiac models in tissue demand high-performance approaches. In this talk, we will present how WebGL2.0 can be used to carry out computation of complex models in near-real-time in a Web browser using a personal computers GPU. Specifically, we will showcase the computation of OHara-Rudy model and its behavior in multi-dimensions. We show how Early-After-Depolarizations (EADs) can form in this model under different parameters and regimes which cam lead to serious cardiac-arrhythmias.

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MS19

Defibrillation Shocks and Fibrillation in a Rabbit Heart

Fibrillation is an erratic electrical state of the heart, of rapid twitching rather than organized contractions. Ventricular fibrillation is fatal if not treated promptly. The standard treatment, defibrillation, is a strong electrical shock to reinitialize the electrical dynamics and allow a normal heart beat. We focus the defibrillation shock and the subsequent electrical phenomena it induces. Six partially overlapping causal factors for defibrillation success are identified from the literature. We present evidence in favor of five of these and against one of them. A major conclusion is that a dynamically growing wave front, starting at the heart surface appears to play a primary role during defibrillation by critically reducing the volume required to sustain the dynamic motion of scroll waves; in contrast, virtual electrode occurring at boundaries of small, isolated blood vessels only cause minor effects. As a consequence, we suggest that the size of the heart is an important defibrillation variable. Ongoing studies of the fibrillation state will be also presented.

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MS19

Exponential-based Methods for Cardiac Simulations: Extending Rush-Larsen to Markov-based Models and Beyond

Mathematical models of cardiac electrophysiology at the cellular level are usually cast as nonlinear systems of ordinary differential equations. Whereas traditional models are based on the Hodgkin-Huxley (HH) formalism introduced in their pioneering work on action potential genesis, modern models use new approaches to describe sub-cellular phenomena and components, such as Markov-Chains or generic non-linear equations. A common method to solve HH type equations is the Rush-Larsen (RL) method. Introduced in 1978, it consists of local linearizations to obtain analytical exponential-based formulas for each time step. RL method has good stability properties and together with its simplicity of implementation it has become very popular. However, as modern models adopt other formalisms than the HH one, different numerical methods are needed. In this talk we will present other exponential-based numerical methods that have been recently proposed for the solution of cardiac cell models. The methods can be taken as extensions or generalizations of the RL. We will compare the methods in terms of stability and computational efficiency. One of the methods is called Uniformization. Although it is traditionally used for performance analysis of computer systems, such as networks; our results suggest that the Uniformization technique can be very robust and efficient for the solution of the Markov-Chains that are found in many modern models of cardiac electrophysiology.

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MS19

High-order Operator-splitting Methods for Cardiac Tissue Simulations

Cardiac tissue simulations often use the bidomain and monodomain models to describe the electrophysiology of cardiac tissue. These models take the form of multi-scale reaction-diffusion partial differential equations that couple the dynamic behaviour on the cellular scale with that on the tissue scale. The systems of differential equations associated with these models are large and strongly non-linear, but they also have a distinct structure due to their multi-scale nature. Operator-splitting methods attempt to take advantage of this structure to efficiently produce numerical solutions. The focus of this presentation is on operator-splitting methods with order higher than two. Such methods require backward time integration in each operator and historically have been considered unstable for solving deterministic parabolic systems. The stability and performance of operator-splitting methods of up to order four to solve the bidomain and monodomain models are demonstrated on several examples arising in the field of cardiovascular modelling.

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MS20

Large Deviation Theory for Chemical Reaction Networks

At the microscopic level, the dynamics of networks of chemical reactions can be modeled through mass action kinetics as jump Markov processes whose sample paths converge, in the limit of large number of molecules, to the solutions of a set of algebraic ordinary differential equations. Fluctuations around these asymptotic trajectories can in principle be studied through large deviations theory in path space, also called Wentzell-Freidlin (W-F) theory. However, the specific form of the jump rates for this family of processes does not satisfy the standard regularity assumptions imposed by that theory, and weaker conditions need to be developed to deal with the framework at hand. In this talk, I will first review the class of models under investigation and the formulation of some relevant theorems in W-F theory. Using tools of Lyapunov stability theory I will then design sufficient conditions for the applicability of large deviations estimates to the asymptotics the Markov process at hand. Translating such conditions in terms of the topological structure of the chemical reaction network, I will finally define a large class of chemical reaction systems to which such estimates can automatically be applied, and conclude by outlining some of the proofs in the process above. This is joint work with Amir Dembo and Jean-Pierre Eckmann.

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MS20

Approximation of Stochastic Reaction Networks on Bounded Domains

Stochastic models of mass-action chemical kinetics often requires intensive simulations to be investigated. Their study can be simplified both theoretically and computationally by approximating the corresponding Markov Chains with a deterministic system of odes or with a diffusion process. Strong approximation results was found by Tom Kurtz in the seventies. Both such approximations however fails if the state space is bounded (at zero or at a constant maximum level due to the conservation of mass) and if the process visits the boundaries with non-negligible probability. We present an approximation in terms of a jump-diffusion process which is robust to this event.

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MS20

Quasi-steady-state Approximations in the Stochastic Models of Enzyme Kinetics

In this talk, I will introduce several quasi steady-state approximations (QSSAs) applied to the stochastic enzyme kinetics models. Different assumptions about chemical

species abundance and reaction rates lead to the standard QSSA (sQSSA), the total QSSA (tQSSA), and the reverse QSSA (rQSSA) approximations. These three QSSAs have been widely studied in the literature in deterministic ordinary differential equation (ODE) settings and several sets of conditions for their validity have been proposed. By using multiscaling techniques for stochastic chemical reaction networks, I will show that these conditions for deterministic QSSAs largely agree with the ones for QSSAs in the large volume limits of the underlying stochastic enzyme kinetic networks. This is joint work with Wasiur KhudaBukhsh, Heinz Koeppl, and Grzegorz Rempala.

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MS20

Reflected Diffusions and (Bio)-chemical Reaction Networks

Continuous-time Markov chain models are often used to describe the stochastic dynamics of networks of reacting chemical species, especially in the growing field of systems biology. Discrete-event stochastic simulation of these models rapidly becomes computationally intensive. Consequently, more tractable diffusion approximations are commonly used in numerical computation, even for modest-sized networks. However, existing approximations (e.g., linear noise and Langevin), do not respect the constraint that chemical concentrations are never negative. In this talk, we propose an approximation for such Markov chains, via reflected diffusion processes, that respects the fact that concentrations of chemical species are non-negative. This fixes a difficulty with Langevin approximations that they are frequently only valid until the boundary of the positive orthant is reached. Our approximation has the added advantage that it can be written down immediately from the chemical reactions. Some numerical examples illustrate the advantages of our approximation over direct simulation of the Markov chain or use of the linear noise approximation.

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MS21

Agent-based and Continuous Models of Locust Hopper Bands: The Role of Intermittent Motion, Alignment and Attraction

Locust swarms pose a major threat to agriculture, notably in North Africa and the Middle East. In the early stages of aggregation, locusts form hopper bands. These are coordinated groups that march in columnar structures that are often kilometers long and may contain millions of individuals. We propose a model for the formation of locust hopper bands that incorporates intermittent motion, alignment with neighbors, and social attraction, all behaviors that have been validated in experiments. Using a particle-in-cell computational method, we simulate swarms of up to a million individuals, which is several orders of magnitude larger than what has previously appeared in the locust modeling literature. We observe hopper bands in this model forming as a fingering instability. Our model also allows homogenization to yield a system of partial integro-differential evolution equations. We identify a bifurcation from a uniform marching state to columnar structures, suggestive of the formation of hopper bands.

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MS21

Dynamics of Social Interactions and Agent Spreading in Ant Colonies: Effects of Environmental Events and Spatial Heterogeneity

The flexible spatial behaviors of social ant colonies allow us to study information transmission, food distribution and contagious infection, all of which involve spatial behaviors and social interactions in different environments. To explore the effects of spatial heterogeneity and environmental factors on social contacts and agent-spreading dynamics in these colonies, we propose and study an agent-based model which incorporates: (1) Three different task groups with their own spatial zone; (2) Workers doing either random or preferential walks, which gives rise to the concept of spatial fidelity (the proportion of the ant population performing a preferential walk); and (3) the initial spatial distribution which is either random or aggregated. These three components generate spatial heterogeneity. Our study shows a strong linear relationship between social contacts and spatial heterogeneity degree. Larger spatial fidelity increases the social contact rate and the spatial heterogeneity degree (SHD) both of which follow logistic growth patterns. These results have biological implications on the dual-functionality of ants flexible spatial behavior related to how spatial fidelity inhibits or facilitates transmission rates. Our model reveals the potential functions of flexible spatial behavior and deepens our understanding on how ant colonies balance the transmission of agents with different attributes under the varied environments.

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MS21

Collective Mechanical Adaptation in Honeybee Swarms

Honeybee swarms form clusters made solely of bees attached to each other, forming pendant structures on tree branches. These clusters can be hundreds of times the size of a single organism. How these structures are stably maintained under the influence of static gravity and dynamic stimuli (e.g. wind) is unknown. To address this, we created pendant conical clusters attached to a board that was shaken with varying amplitude, frequency and total duration. Our observations show that horizontally shaken clusters spread out to form wider, flatter cones, i.e. the cluster adapts to the dynamic loading conditions, but in a reversible manner - when the loading is removed, the cluster recovers its original shape, slowly. We use agent-based simulations to suggest a behavioral hypothesis that individual bees respond to local variations in strain. This behavioral response improves the collective stability of the cluster as a whole at the expense of increasing the average mechanical burden experienced by the individual. Altogether, our results show how an active, functional super-organism structure can respond adaptively to dynamic mechanical loading by changing its morphology to achieve better load sharing.

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MS21

Linking Altered Cell Interactions to Mutated Skin Patterns on Zebrafish

Zebrafish (Danio rerio) is a widely-studied animal model, partly because many of its genes have human counterparts. A rich vary of color patterns form on zebrafish and other Danio fish due to the collective behavior of pigment cells. This makes zebrafish a model organism for elucidating the impact of genome on phenome by linking genetic mutations to functional differences in cell behavior. Working closely with the biological data, we develop an agent-based model of pattern formation on zebrafish, coupling deterministic migration by ODEs with stochastic rules for updating cell population size on growing domains. Our model suggests that redundancy in wild-type cell interactions may be responsible for robust stripe formation, and it identifies cell behaviors that may be altered to produce patterns on mutations and close relatives of zebrafish. We also consider a continuum limit and explore stripe formation on the tailfin, where bone rays and epithelial growth may help direct pigment cell placement.

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MS22

3D Stochastic Simulations of Cargo Transport Reveal the Influence of Cargo and Environment

Active transport of subcellular cargos along microtubules is essential for organization and function of eukaryotic cells. While we understand much about how single motors are able to generate force to accomplish this transport, little is understood about how properties of the cargo itself and properties of its environment can influence how cargos are transported. To investigate how these properties may influence transport in the cell, we developed a 3D Brownian dynamics simulator of cargo transport which includes cargo shape and motor location on the cargo. We present results describing how cargos navigate microtubule intersections in vitro. These results suggest that tuning intersection geometry may allow the cell to sort cargos based on several properties. We also present simulations which investigate the effects of surface-fluid properties of vesicular cargo and lipid droplets, which have previously been challenging to simulate. Simulations in which motors are free to diffuse in the cargo membrane suggest the possibility that this freedom may allow cargos to both bind rapidly to the microtubule and make efficient use of several motors, a combination which is difficult to achieve when motors are anchored rigidly. The end goal of the simulator is to reveal how changes in cargo or environment properties can drive cargos toward distinct transport outcomes, opening the way for environment-based cargo sorting and, ultimately, navigation and cell-scale spatial organization.

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MS22

Dynamic Models of the Stochastic Intracellular Transport of Cargoes on Networks of Microtubules

Molecular motors such as kinesins walk along microtubules (MTs) and undergo a mechano-chemical cycle where their heads move to neighboring binding sites, resulting in mechanical transport of cargoes. This motion is the result of a cyclic conformational change in the kinesin molecule and the diffusion of its heads. In certain cases, binding sites on MTs are unavailable because they are occupied or mechanically blocked by other molecules such as tau proteins. In other cases, MTs are organized in bundles or in networks that create intersections leading to mechanical blocking of binding sites. In this presentation, we explore

the effects of obstacles and MT intersections on the motion of cargoes transported by individual kinesins or teams of multiple kinesins. Models are discussed for capturing the mechano-chemical cycle while also accounting for the stochasticity on the dynamics and the mechanical interference between kinesins and obstacles, and between intersecting MTs. Stochastic studies on the kinesin motion are performed by considering the binding and unbinding of kinesins to MTs and their dependence on the force acting on kinesin molecules. Four types of motion: passing, pausing, switching, and dissociating are captured at MT intersections. This modeling approach provides a physical understanding of the effects of MT topology on kinesin-mediated transport and can be used to address other unanswered questions regarding degraded transport caused by obstacles on MTs.

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MS22

Modeling Challenges for Motors and Microtubules

This presentation will review some of the prevalent methods for representing the dynamics of molecular motor proteins on a single microtubule from the biomolecular to the cellular scale. Focus will then be given to how these models might be adapted or extended to more complex microtubule arrangements or structures in order to interpret or understand recent experimental observations, with particular reference to issues being addressed by the speakers contributing to this session.

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MS22

Assessing the Impact of Electrostatic Drag on Processive Molecular Motor Transport

The bidirectional movement of intracellular cargo is usually described as a tug-of-war among opposite-directed families of molecular motors. While tug-of-war models have enjoyed some success, recent evidence suggests underlying motor interactions are more complex than previously understood. For example, these tug-of-war models fail to predict the counter-intuitive phenomenon that inhibiting one family of motors can decrease the functionality of opposite-directed transport. We use a stochastic differential equations modeling framework to explore one proposed physical mechanism called microtubule tethering, that could play a role in this "co-dependence' among antagonistic motors. This hypothesis includes the possibility of a trade-off: weakly-bound trailing molecular motors can serve as tethers for cargoes and processing motors, thereby enhancing motor-cargo run lengths along microtubules; however, this introduces a cost of processing at a lower mean velocity. By computing the small- and large-time mean-squared displacement of the theoretical model and comparing the results to experimental observations of dynein and its "helper protein' dynactin, we find some positive evidence for microtubule tethering interactions.

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MS23

The Role of Microenvironment in Regulation of Cell Infiltration and Bortezomib-Ov Therapy in Glioblastoma

In the present paper we investigated the role of NK cells in combination therapy with oncolytic virus (OV) and bortezomib. NK cells display rapid and potent immunity to metastasis and hematological cancers, and they overcome immunosuppressive effects of tumor microenvironment. We developed a mathematical model in order to address the question of how the density of NK cells affects the growth of the tumor. We found that the anti-tumor efficacy increases when the endogenous NKs are depleted, and also when exogenous NK cells are injected into the tumor. These predictions were validated by our in vivo and in vitro experiments.

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MS23

Ductal Microinvasions: Integrating Histology, Mechanobiology and Computational Modeling

Progression from a ductal carcinoma in situ (DCIS) to an invasive tumor is a major step initiating a devastating and often lethal metastatic cascade. One of the first steps in this process is the development of ductal microinvasions, i.e., small cohorts of tumor cells that breach the basement membrane surrounding the duct, and migrate through the extracellular matrix (ECM). At this point, for the first time, the epithelially-derived tumor cells engage in a direct physical contact with the extracellular matrix and the stroma. We combined single cell-based model of the tumor-ECM interactions and ECM remodeling, and image-based analysis of the cellular biophysico-chemical features as determined from patients histology samples of DCIS. Using this model we showed how changes in the local microenvironmental niche near the DCIS edge enable initiation and progression of ductal microinvasions. Of particular interest are the biomechanical interactions between the cells and the ECM fiber structure, and microenvironmental features that define tumor niche prone to microinvasions. These findings can be compared to the patient histology samples and help define criteria for future development of new prognostic methods and therapeutic interventions by targeting the tumor niche.

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MS23

A Mathematical Model of Cell / Extracellular Ma-

trix Fiber Interaction

One strategy used by tumor cells to enhance their proliferation is the secretion of proteases, which break down the surrounding extracellular matrix (ECM), allowing the cell to recruit integrins, make strong attachments with the ECM, and induce motility. Upon inhibition of proteases, tumor cells have the ability to switch from this mesenchymal mode of motility, to amoeboid motility, in which tumor cells make weaker attachments with the ECM and squeeze through preexisting gaps in the ECM. It has been extensively shown that ECM rigidity affects motility and proliferation of various cell types, including tumor cells, and the mechanical interaction of a tumor cell with the ECM plays a particularly important role in amoeboid motility. In this talk I present a two-dimensional model of a cell undergoing amoeboid movement and interacting with ECM fibers. The evolution of the cell membrane is dependent on active forces, membrane tension, cell volume conservation, and contact forces with ECM fibers, which are modeled as one-dimensional elastica with a fixed thickness. The positions of the cell membrane and surface of each ECM fiber are tracked using the level set method. Using this model, we will explore how the mechanical properties of the cell and the ECM affect cell deformation and cell speed through the ECM network.

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MS23

Getting in Shape and Swimming: The Role of Cortical Forces and Membrane Heterogeneity in Eukaryotic Cells

Recent research has shown that motile cells can adapt their mode of propulsion to the mechanical properties of the environment in which they find themselves - crawling in some environments while swimming in others. The latter can involve movement by blebbing or other cyclic shape changes, and both highly-simplified and more realistic models of these modes have been studied previously. Herein we study swimming that is driven by membrane tension gradients that arise from flows in the actin cortex underlying the membrane, and does not involve imposed cyclic shape changes. Such gradients can lead to a number of different characteristic cell shapes, and our first objective is to understand how different distributions of membrane tension influence the shape of cells in a quiescent fluid. We then analyze the effects of spatial variation in other membrane properties, and how they interact with tension gradients to determine the shape. We also study the effect of fluid-cell interactions and show how tension leads to cell movement, how the balance between tension gradients and a variable bending modulus determine the shape and direction of movement, and how the efficiency of movement depends on the properties of the fluid and the distribution of tension and bending modulus in the membrane.

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MS24

Mechanics of the Cell Cortex: Simulations and Experiments

Cell shape changes are vital for many physiological processes such as cell proliferation, cell migration and morphogenesis. They emerge from an orchestrated interplay of cellular force generation and cellular force response, both mainly dictated by the actin cytoskeleton. To understand cellular force response from a mechanistic point of view, we describe cells as incompressible viscoelastic bulk domains surrounded by an impermeable elastic surface (the cortex) under active tension. A comparison of simulated and experimental shapes of cells in a flow channel, permits extraction of cell mechanical parameters. As the cell cortex is found to be the dominant mechanical element, we investigate the cortical force response of cells which are clamped between two plates. We compare simulation results to cell-mechanical measurements. The results corroborate the idea of the cortex as a thin, isotropic, incompressible material and enable us to extract the Young's surface modulus and the surface Poisson ratio of the cortex.

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MS24

Hydrodynamics of Transient Cell-cell Contact in T Cell Receptor Triggering

In many biological settings, two or more cells come into physical contact to form a cell-cell interface. In some cases, the contact is transient, lasting only seconds. One example is offered by the T Cell, an immune cell which must attach to the surface of other cells in order to decipher information about disease. The aspect ratio of these interfaces (10 nanometers thick and 10 micrometers in diameter) puts them into the thin-layer limit or "lubrication limit' of fluid dynamics. A key question is how the molecules on the two cells (receptors and ligands) come into contact. What are the roles of thermal undulations of the membrane and deterministic forces from active filopodia? We present a computational fluid dynamics algorithm capable of simulating fluid-structure interactions with thermal fluctuations on seconds- and microns-scales. We simulate two apposing membranes, including thermal fluctuations, active forces, and membrane permeability. Our results demonstrate that the force required will increase for smaller cell-cell distances (where the thin-layer effect is strongest) leading to an optimal "attack range' that might explain the geometry of filopodia. The results also suggest a role for membrane permeability; Factors that influence permeability, such as aquaporins, are dynamically controlled by the cell, and have been shown to impact cell processes including cancer angiogenesis, raising the possibility that cell-cell contacts can be regulated in this way.

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MS24

Modeling and Computation of a Multicomponent Vesicle in Stokes Flow

Abstract not available at time of publication.

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MS24

The Importance of Mechanical Constraints for Proper Polarization and Psuedo Cleavage Furrow Generation in the Early C. Elegans Embryo

Abstract not available at time of publication.

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MS25

Self-assembly of Protein Clusters in Lipid Bilayer Membranes: Role of Hydrodynamic Coupling and Curvature

We develop fluctuating hydrodynamics approaches to extend Saffman-Delbruck theory to capture the collective drift-diffusion dynamics of proteins within curved lipid bilayer membranes. Our approach is at the level of fluid interfaces having any curved radial manifold shape. We take into account the two dimensional hydrodynamics of the two curved leaflets of the bilayer coupled with the three dimensional hydrodynamics of the surrounding bulk fluid. Using analytic and computational approaches, we show how Gaussian curvature can significantly impact dissipation within the curved two dimensional membrane fluid to augment the collective drift-diffusion dynamics of protein inclusions. We further show for the self-assembly of protein clusters that these effects contribute significant kinetic contributions giving differences with widely used non-hydrodynamic theories. We demonstrate with theory and simulation results some possible biological ways for regulating self-assembled protein cluster size and kinetics within lipid bilayer membranes.

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MS25

Multi-scale Model for Tissue Engineered Articular Cartilage

Articular cartilage (AC) is a connective tissue that covers articular joints to provide a surface that allows bones to slide over each other, and absorb shocks. AC has a complex structure composed of a dense extracellular matrix (ECM), including fluid, a collagen network, and proteins, and chondrocytes (cells). Nutrients and oxygen are provided via diffusion through the ECM. Pathologies, injuries and normal wear and tear cause the erosion and damage of AC. Cartilage is produced in vitro to be implanted at the site of the damage to restore normal functionality. To guarantee a successful outcome, tissue-engineered AC must have specific structural and mechanical properties. A hybrid multi-scale mathematical model is used to investigate the phenomena of AC growth in a tissue-engineered construct to elucidate the influence of different biological factors, such as scaffold porosity and cell velocity. This hybrid model couples a discrete modeling approach for the chondrocytes, with a continuous approach for the other components of the matrix. Two different timescales regulate the model components. The chondrocytes are described using an off-lattice cellular automata model that accounts for biased movement, division, contact inhibition and death. The continuous components of the model, nutrients and porosity, are modeled consistently with the literature. The insight provided by the model are used to elucidate the outcomes of laboratory experiments involving tissue-engineered AC.

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MS25

A Mathematical Model of Extravascular Platelet Aggregation

Platelet aggregation is an essential part of hemostasis, the process to stop bleeding in response to a vascular injury. The local hemodynamics and the nature of the injury can affect size, structure and formation time of a platelet aggregate. Our previous models were restricted to study intravascular clot formation, which is confined to the interior of a single vessel. Here, we develop a mathematical model of extravascular platelet aggregation that has been iteratively developed with an experimental microfluidic device. Our previous model of platelet aggregation is extended to include a transiently bound platelet species and a new description for the limited transport of platelet densities using the finite element method. The setup includes two channels in parallel, a blood and a wash channel, connected by an extravascular injury channel. Separate flow rates are imposed at the inlets of the two parallel channels to force blood through the injury channel and exit through the outlet of the wash channel. The injury channel is coated with small proteins that initiate platelet aggregation. Under various shear rates, hematocrits and platelet counts, computational estimates of occlusion times, flow fields, and platelet aggregate porosities are compared to experimental measurements. We find that the timing and spatial distribution of extravascular platelet aggregates are sensitive to these variations.

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MS25

Computational Multiscale Modeling of Coordinated Behavior in Lamprey Swimming

The lamprey is a model organism for locomotion and neurophysiology research. Lampreys use a neural network, a central pattern generator (CPG), to produce rhythmic signals which drive the animal's basic swimming mode. Mechano-sensors called edge cells provide sensory feedback

to the organism based on the bending of the body. In previous work, we constructed a multiscale integrative model of a flexible swimmer consisting of a CPG, calcium dynamics, muscle mechanics, body dynamics and fluid-structure interactions, then closed the physiological loop with a basic model of sensory feedback. The CPG is modeled as two chains of coupled oscillators which are capable of receiving information from the bending dynamics of the body. The functional form of such sensory feedback from edge cells in the lamprey is not known. Using experimental information from natural organisms, we construct proposed functional forms and examine their effects on swimming stability and energetics in the computational model.

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MS26

Gap Junctions Between Pyramidal Cells in Cortical Neuronal Networks

Neuronal activity in the brain underlies several processes from vision and movement, to learning and memory. This activity results from the interaction of neurons through both chemical synapses, a space between two cells where chemical signaling takes place, and electrical synapses, or gap junctions, a direct connection between the interior of two cells. Pyramidal cells, whose activity comprises the main output signal in the cortex, have been shown to be transiently connected via gap junctions, with a peak in number and strength during the first postnatal week, and decaying in both as the brain develops. In contrast, gap-junction coupling among interneurons increases during development to reach a high steady state connectivity probability. Though the effect of gap-junction coupling among interneurons have been widely studied, the role of gap-junction coupling among the pyramidal cells has not been elucidated. Through simulations of a realistic model neuronal network, we investigate the effect gap-junction connectivity between pyramidal cells on synchronous activity on both the neuron and population level.

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MS26

Dynamics of Excitation and Inhibition in a Model of the Rodent Barrel Cortex

The spiking of barrel regular-spiking (RS) cells is tuned for both whisker deflection direction and velocity. Velocity tuning arises due to thalamocortical (TC) synchrony (but not spike quantity) varying with deflection velocity, coupled with feedforward inhibition, while direction selectivity is not fully understood, though may be due partly to direction tuning of TC spiking. As deflection direction deviates from the preferred direction of an RS cell, excitatory input to the RS cell diminishes minimally, but temporally shifts to coincide with the time-lagged inhibitory input. This work constructs a realistic large-scale model of a barrel; model RS cells exhibit velocity and direction selectivity due to TC input dynamics. The model puts forth the novel proposal that RS-RS synapses can naturally and simply account for the unexplained direction dependence of RS cell inputs as deflection direction deviates from the preferred direction of an RS cell, and TC input declines, RS-RS synaptic transmission buffers the decline in total excitatory input and causes a shift in timing of the excitatory input peak from the peak in TC input to the delayed peak in RS input. The model also provides several experimentally testable predictions on the velocity dependence of RS cell inputs. This model is the first, to my knowledge, to study the interaction of direction and velocity and propose physiological mechanisms for the stimulus dependence in the timing and amplitude of RS cell inputs.

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MS26

Inferring Information Transfer from Experimentally Recorded Spike-train Data Sets

Understanding information processing in the brain requires the ability to determine the functional connectivity between the different regions of the brain. We present a method using transfer entropy to extract this flow of information between brain regions from spike-train data commonly taken in neurological experiments. Transfer entropy is a statistical measure based in information theory that attempts to quantify the information flow from one process to another, and has been applied to find connectivity in simulated spike train data. Due to statistical error in the estimator, inferring functional connectivity requires a method for determining significance in the transfer entropy values. We discuss the issues with numerical estimation of transfer entropy and resulting challenges in determining significance before presenting the trial-shuffle method as a viable option. The trial-shuffle method, for spike train data that is split into multiple trials, determines significant transfer entropy values independently for each individual pair of neurons, rather than globally comparing all neuron transfer entropy values. We establish the viability of this method by showing that it performs comparably or better to a previous approach in the literature based on the false positive detection rate. We then investigate the performance of the trial-shuffle method in terms of information flow within a network as we vary model parameters.

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MS26

Sparse Neuronal Network Leads to Sparse Time Delayed Precision Matrix

In networks of the brain, neuron structural connectivity is generally sparse. e.g. for a human, there are roughly 10^{11} neurons while each neuron has only 10^4 synaptic connections to other neurons on average. The dynamical and functional consequences of sparsity for neuronal networks are yet to be fully investigated. In this work, we show that in the Leaky Integrate-and-Fire and Hodgkin-Huxley neu-

ronal network models, the sparsity of connectivity will lead to sparsity of the time delayed precision matrix (inverse of covariance matrix between neurons in different time delays). Applications relying on the precision matrix could benefit from this sparsity.

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MS27

Sensitivity Analysis for Stochastic Reaction Networks

We consider the problem of estimating infinitesimal parameter sensitivities for stochastic models of reaction networks, where the dynamics is described as a continuous-time Markov chain with states representing the molecular counts of various species. These sensitivity values are very important for analyzing the stochastic model, inferring the model parameters and understanding network design. In particular, sensitivity analysis can reveal information about robustness properties of networks and shed light on the underlying control mechanisms that are crucial for a cells functioning and survival. The aim of this talk is to present several approaches for estimating parameter sensitivities that are all based on a simple formula that expresses the sensitivity value as the expectation of a random variable whose realizations can be obtained by simulating paths of the stochastic dynamics. We will discuss how simulation techniques, such as tau-leap approximations, multi-level methods etc. can be easily integrated with our approach and how one can incorporate model reductions to deal with multiscale networks. We will illustrate these ideas through many examples.

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MS27

Graphically Balanced Equilibria and Stationary Measures of Reaction Networks

The graph-related symmetries of a reaction network give rise to certain special equilibria (such as complex balanced equilibria) in deterministic models of dynamics of the reaction network. Correspondingly, in the stochastic setting, when modeled as a continuous-time Markov chain, these symmetries give rise to certain special stationary measures. Previous work by Anderson, Craciun and Kurtz identified stationary distributions of a complex balanced network; later Cappelletti and Wiuf developed the notion of complex balancing for stochastic systems. We define and establish the relations between reaction balanced measure, complex balanced measure, reaction vector balanced measure, and cycle balanced measure and prove that with mild additional hypotheses, the former two are stationary distributions. Furthermore, in spirit of earlier work by Joshi, we give sufficient conditions under which detailed balance of the stationary distribution of Markov chain models implies the existence of positive detailed balance equilibria for the related deterministic reaction network model. Finally, we provide a complete map of the implications between balancing properties of deterministic and corresponding stochastic reaction systems, such as complex balance, reaction balance, reaction vector balance and cycle balance. This is joint work with Daniele Cappelletti.

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MS27

Results on Stochastic Reaction Networks with Non-mass Action Kinetics

In 2010, Anderson, Craciun, and Kurtz showed that if a deterministically modeled reaction network with mass action kinetics is complex balanced, then the associated stochastic model admits a stationary distribution that is a product of Poissons. That work spurred a number of follow-up analyses. In 2015, Anderson, Craciun, Gopalkrishnan, and Wiuf considered a particular scaling limit of a stationary distribution for such reaction network, and proved it is a well-known Lyapunov function. In 2016, Cappelletti and Wiuf showed the converse of the main result of Anderson, Craciun and Kurtz in 2010. Specifically, if a reaction network with stochastic mass action kinetics admits a stationary distribution that is a product of Poissons, then the deterministic model is complex balanced. In 2017, Anderson, Koyama, Cappelletti, and Kurtz proved that if a deterministically modeled reaction network with mass action kinetics is complex balanced, then the associated stochastic model is non-explosive (so the stationary distribution characterizes the limiting behavior). In this paper, we generalize each of the three follow-up results detailed above to the case when the stochastic model has a particular form of non-mass action kinetics.

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MS27

The Reaction-network Complexity of Discrete Distributions

A cell and its environment exchange information by means of their interactions and part of this information guides the cell's decision making process. Many molecules in a cell exist at quantities low enough to be comparable to the magnitude of thermal fluctuations. This means that we can better understand the behavior of cells by means of probabilistic models. Information theory tells us that a probability distribution can contain information so it is likely that a cell will make use of this information to its advantage. This places demands on a cell's ability to efficiently coordinate probabilistic behaviors. We are therefore interested in the question of how good cells are at generating probability distributions. Before we can answer this question we need a mathematical framework in which we can give it a rigorous formulation. Stochastic chemical reaction networks (SCRN) model well-stirred chemical reactions as stochastic processes and they are useful for reasoning about the probabilistic behavior of cells. We show that SCRN can program arbitrarily precise approximations to any discrete distribution. Furthermore, we formalize a notion of complexity of probability distributions generated by SCRN and use it to study the efficiency of our programs. We show that some programs have optimal asymptotic complexity when

compared to the information content of the distributions they generate.

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MS28

Multiscale Modeling of Cardiovascular Disease

Atherosclerosis, the leading cause of death in the United State, is a disease in which a plaque builds up inside the arteries. The LDL and HDL concentrations in the blood are commonly used to predict the risk factor for plaque growth. In this talk, I will describe a recent mathematical model that predicts the plaque formation by using the combined levels of (LDL, HDL) in the blood. The model is given by a system of partial differential equations within the plaque with a free boundary. This model is used to explore some drugs of regression of a plaque in mice, and suggest that such drugs as used for mice may also slow plaque growth in humans. Some mathematical questions, inspired by this model, will also be discussed. I will also mention briefly some related projects about abdominal aortic aneurysm (AAA) and red blood cell aggregation, which would have some potential blood biomarkers for diagnosis of AAA.

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MS28

A Multi-scale Computational Frame Work to Study Cell and Tissue Mechanics

How individual cells coordinate tissue-scale processes is still poorly understood topic due to the inherent complexity of emergent tissue level behavior of cells. Recent studies have shown that besides chemical signaling, mechanical interaction between cells also plays a major role in this regard. Testing hypothetical novel biophysical mechanisms across spatial scales require computational models that can span subcellular to tissue levels. However, the task of including detailed descriptions of mechanical interactions between cells is challenging due to the prohibitively high computational costs and complexity of intercellular mechanical interaction. In here, we have developed a multi-scale modeling for simulating cell and tissue mechanics based on the Subcellular Element (SCE) modeling approach. Computational implementation of the model is based on an efficient parallelization algorithm that utilizes Graphical Processing Units (GPUs) for simulating large numbers of cells within a reasonable computational time. As a demonstration of the predictive power of the model, epithelial cells growth and division during development are simulated and polygon class distribution of cells is compared with experimental data. Furthermore, regulation of mechanical properties of cells during mitotic rounding is simulated and contribution of each mechanical property on the expansion and roundness of the cells before division of cells is quantified.

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MS28

Control of Cell Fraction and Population Recovery During Tissue Regeneration in Stem Cell Lineages

Multicellular tissues are continually turning over, and homeostasis is maintained through regulated proliferation and differentiation of stem cells and progenitors. Following tissue injury, a dramatic increase in cell proliferation is commonly observed, resulting in rapid restoration of tissue size. This regulation is thought to occur via multiple feedback loops acting on cell self-renewal or differentiation. Models of ordinary differential equations have been widely used to study the cell lineage system. Prior modeling studies have suggested that loss of homeostasis and initiation of tumorigenesis can be contributed to the loss of control of these processes, and the rate of symmetric versus asymmetric division of the stem cells may also be altered. In this work, we compare three variants of hierarchical stem cell lineage tissue models with different combinations of negative feedbacks and use sensitivity analysis to examine what are the possible strategies for the cells to achieve certain performance objectives. Our results suggest that multiple negative feedback loops must be present in the stem cell lineage to keep the fractions of stem cells to differentiated cells in the total population as robust as possible to variations in cell division parameters, and to minimize the time for tissue recovery in a non-oscillatory manner.

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MS28

An Operator Splitting Scheme for Solving Fluid and Massive Interface Interaction Problem

A few study focused on problems involving interaction of fluid with an elastic interface with mass. In this talk, we present an operator splitting scheme for simulating an elastic and massive interface moving in viscous, incompressible flows. We utilize a continuous description of the interface and Helfrich bending elasticity energy for representing its elasticity. An energy approach is employed to derive the fluid-interface coupling condition. To this end, the dynamic evolution of the interface is defined by a geometric partial differential equation, which involve computing curvatures of the surface and surface Laplacian of the mean curvature. We introduce a robust finite difference scheme for solving the geometric partial differential equation. The Lie's scheme then is used to define the operator splitting for solving the fluid-interface interaction problem. Examples will be presented to demonstrate the applicability of the proposed scheme for numerical studying biological problems.

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MS29

Axonal Transport with Attachment and Detachment to Parallel Microtubule Network

We present a mathematical framework to analyze the intracellular transport inside an axon. Our model captures the spatial dynamics and interactions of motor and cargo through a system of coupled stochastic differential equations. Using the techniques of asymptotic analysis, the first passage time for the reattachment of a tethered motor is computed. Through the application of renewal-reward theory we are able to derive the key quantities of interest for the transport processes spanning over multiple attached and detached phases of a single molecular motor and cargo complex.

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MS29

Insights from Including the Microtubule Cytoskeleton in Modeling mRNA Localization

The cellular cytoskeleton ensures the dynamic transport, localization and anchoring of various proteins and vesicles. In the development of egg cells into embryos, messenger RNA (mRNA) is transported along microtubule filaments and must accumulate at the cortex of the egg cell on a certain time and spatial scale. Using dynamical systems modeling and analysis, we show that models including the cytoskeleton structure better predict the spread of the particles, and can be used to investigate the contribution of an anchoring mechanism to the timescale of localization. Our numerical studies using model microtubule structures predict that anchoring of mRNA-molecular motor complexes may be most effective in keeping mRNA localized near the cortex and therefore in healthy development of oocytes into embryos.

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MS29

Minimal Ingredients for Coupled Spindle Assembly and Chromosome Bi-orientation in a Computational Model of Fission Yeast Mitosis

Mitosis ensures the proper segregation of chromosomes into daughter cells, which is accomplished by the mitotic spindle. During fission-yeast mitosis, chromosomes establish bi-orientation as the bipolar spindle assembles, meaning that sister kinetochores become attached to microtubules whose growth was initiated by sister poles. This process must also correct erroneous attachments made by the kinetochores during the attachment process. Our goal is to build a 3D computational model of spindle assembly based on a realistic description of microtubule, kinetochore, and chromosome dynamics, in order to interrogate the role of specific mechanisms in these chromosome bi-orientation and error correction processes. We have added chromosomes to our previous computational model of spindle assembly [R. Blackwell et al., *Science Advances* **3**, e1601603 (2017)], which included microtubules, a spherical nuclear envelope, motor proteins, crosslinking proteins, and spindle pole bodies (centrosomes). In the new model, each chromosome is represented by a pair of sister chromatids, and sister kinetochores are represented as chromatid-associated discs. In preliminary work, we have explored the mechanical properties of kinetochores and their interactions with microtubules that achieve amphitelic spindle attachments at high frequency. A plausible set of minimal assumptions yields simulations that generate chromosome attachment errors, but resolve them, much as normal chromosomes do.

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MS29

Local Geometry Dictates How Teams of Myosin Va Motors Move Fluid Vesicles through a 3D Actin Network

Inside a cell, material must be transported large distances to specific targets. Passive diffusion is too slow and imprecise, so eukaryotic cells employ molecular motors like myosin Va, which use chemical energy to 'walk' along the 3D network of protein filaments, like actin, of the cytoskeleton. To understand this process, we performed experiments on actin meshes. In the first actin mesh, the random mesh, actin filaments were oriented randomly in 3D. The second actin mesh, the Arp2/3 mesh, was identical to the first, except that the protein Arp2/3 was added, which induces local directionality by causing actin filaments to branch at 70°. In each mesh, we tracked $\sim$ 500 myosin Va bound vesicles. These trajectories, analyzed with mean squared displacement and a changepoint analysis, were divided into times when the vesicle was stationary, diffusing or undergoing active transport. Vesicles were more likely to undergo active transport on the Arp2/3 network, and more likely to be stationary on the random network. Remarkably, a mathematical model of myosin Va, the fluid vesicle, and the actin filaments reproduces these results. Further, in the random network, on local actin geometries where we measured stuck trajectories, model simulations produce more stuck trajectories than on local actin geometries where we measured active transport. These results suggest that, in our experiments, local actin geometry dictates how myosin Va motors move their cargo.

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MS30

Modeling Collective Invasion in Cancer

A major reason for cancer treatment failure and disease progression is a heterogeneous composition of tumor cells at the genetic, epigenetic, and phenotypic levels. While tremendous efforts have been made to characterize the makeups of single cells, much less is known about interactions between heterogeneous cancer cells and between cancer cells and the microenvironment, especially in the context of cancer invasion. Indeed,clinical studies show that invasion predominantly occurs via collective invasion packs (heterogeneous populations of interacting cancer cells), which invade more aggressively and result in worse outcomes. Many fundamental questions remain:What is the division of within the heterogeneous invasion pack? How do the invasion packs remodel the extracellular space? How does the 3D ECM environment modify the social interaction network within the pack? Can this interaction network be exploited to devise novel treatment strategies? In this talk, I will present our recent experimental and modeling efforts that address these questions. Using non-small cell lung cancer spheroids in collagen, we show that the invasion packs consist of at least two distinct cell types: the leaders and the followers. In vitro and in silico experiments show that leaders and followers engage in mutualistic social interactions during collective invasion. Analyzing this social interaction network can potentially reveal theweak-links, which when perturbed can disrupt collective invasion.

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MS30

Coupling Biochemistry and Biophysics in a 3D Cell Based Model of Breast Cancer Invasion

Collective cell migration requires cells to communicate with each other and with the micro-environment. It is a key process in cancer cell invasion and intravasation. I will present my research on cell-clusters in a 3D experimental setup with a specific focus on how migration and proliferation influence cluster-morphologies. Specifically, I investigate the role of an anti-adhesive transmembrane molecule, podocalyxin (podo). Podo localization is an indicator of poor prognosis in breast cancer patients. My experimental collaborators in the Roskelley lab at the University of British Columbia have shown that by inserting clusters of podo-expressing cells in various extracellular matrices (ECM) drastically alters the cluster morphologies. The properties of a tumor ECM can vary temporally and spatially. Therefore, I ask how the invasive potential of cancer cells is affected when the cell-ECM interactions change. I developed a cell-based computational model, which couples the biochemical pathway, responsible for podo localization, to the biophysical properties of the cells. I will show that the model can capture cluster morphologies observed experimentally and the distribution of podo within the cluster. Furthermore, the model predicts that the axis of cell division greatly influences the morphologies.

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MS30

3-D Computational Modeling of Coordinated Phenotypic Switching and Persistence in Cancer Invasion

In breast cancer, hypoxia is known to contribute to invasion and metastasis. Experiments have shown that hypoxic cells can switch to an invasive phenotype: more glycolytic, more motile, less proliferative, and often less adhesive. It is unclear where these phenotypic traits are acquired, and whether invasive phenotypes are temporary or permanent. For invasive cells to successfully metastasize, they must not only leave a primary tumor and arrive at a new site, but also *colonize* it by reverting to a non-motile, proliferative phenotype. Other experiments have demonstrated that not all hypoxic cells are motile; instead, 'leader' cells may coordinate with 'follower' cells (through unknown chemical and mechanical signaling) to collectively invade tissues. In this talk, we will present an open source agent-based modeling framework—PhysiCell—and adapt it to investigate the role of hypoxia-driven motility, and how the persistence of phenotypic switching drives successful tissue invasion and colonization. We will incorporate cell-cell communication through secreted factors, extracellular matrix remodeling (realigned matrix fibers bias cell motility), and contact. We will compare a variety of cell-scale hypotheses against experimental data, and close with recent progress on **high-throughput hypothesis testing**, where hundreds or thousands of hypothesis sets are simultaneously simulated on a supercomputer and evaluated against an error metric.

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MS30

Cell-matrix Interactions in Fibrosis and Cancer: Multiscale Mechano-chemical Models

In the current study, we sought to determine the mechanical mechanism underlying the effect of the ECM on the stability of the cell spheroids, and developed a computational model to mimic the tumor spheroid-matrix system. The model consists of a closely-packed spheroidal cluster of contractile cells embedded in a non-linear fibrous material representing the ECM. The cells are treated using a combination of passive mechanical and active chemo-mechanical elements. Cell contractility varies depending on the stiffness of the surrounding matrix, via the activation of mechanosensory molecular pathways such as Rho-pathway. The ECM is also modeled by using a non-linear element which accounts for the alignment of the fibers and strain-stiffening. The model is incorporated to obtain the response of the spheroid embedded in matrix with the elastic modulus ranging from 0.01-0.5 KPa. The soft matrix, does not show any resistance toward the deformations caused by the contractility of the spheroid and realign in the radial direction. In this case due to the strong intercellular adh esions, the spheroid remains stable. Alternatively, by increasing the stiffness of the ECM, large tensile stresses are exerted to the cells, which in turn trigger the cellular feedback mechanisms and increase the concentration of the recruited myosin within the cells. Consequently, the cells elongate in the radial direction and break the intercellular

bonds, leading to the migration of the cells in the matrix.

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MS31

Accurate Gradient and Force Computation for Elliptic Interface Problems

The matched interface and boundary (MIB) method is a 2nd order numerical method for elliptic interface problems with piecewise variable coefficients, finite jump across a smooth interface, and singular sources. In this talk, we extend the MIB method by developing second order scheme to compute gradient from each side of the interface and on irregular points of the MIB discretization, particularly when singular sources are regularized using Green's function based decomposition. Furthermore, schemes for computing gradient can be conveniently applied to compute the electrostatic solvation force of the elliptic Poisson-Boltzmann model, which is very significant and useful in biophysics and biochemistry. Numerical examples at various level of complexity are provided to validate the schemes for gradient and force computations.

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MS31

Modeling of the Interaction Between a Transmembrane Protein and a Lipid Bilayer Membrane

Abstract not available at time of publication.

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MS31

Hy Membrane Oligomers Reach a Finite Size? Reticulons and Dynamin as Case Studies

Abstract not available at time of publication.

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MS31

Curvature Driven Translational and Rotational Diffusion of Membrane Proteins

Abstract not available at time of publication.

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MS32

A Phase-field Approach in Modeling Implicit Solvation System with Electrostatics

Abstract not available at time of publication.

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MS32

A Multiphasic Complex Fluids Model for Cytokinesis of Eukaryotes

Cell Mitosis is a fundamental process in eukaryotic cell reproduction, during which parent cells nucleus first dissembles leading to DNA and chromosome replication, then chromosomes migrate to new locations within the parent cell to form offspring nuclei which trigger cytokinesis leading to the formation of two offspring cells eventually. In this presentation, we develop a full 3D multiphase hydrodynamic model to study the fundamental mitotic mechanism in cytokinesis, the final stage of mitosis. The model describes the cortical layer, a cytoplasmic layer next to the cell membrane rich in F-actins and myosins, as an active liquid crystal system and integrates the extracellular matrix material and the nucleus into a multiphase complex fluid mixture. With the novel active matter model built in the system, our 3D simulations show very good qualitative agreement with the experimentally obtained images. The hydrodynamical model together with the GPU-based numerical solver provides an effective tool for studying cell mitosis theoretically and computationally.

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MS32

Bubble Assemblies in Ternary Systems with Long Range Interaction

A nonlocal diffuse interface model, based on the Nakazawa-Ohta density functional theory for triblock copolymers, is used to study bubble assemblies in ternary systems. The model has three parameters weighing three types of long range interaction and two parameters that fix the total area of each constituent. As the parameters vary, a large number of morphological phases appear as stable stationary states. One open question related to the polarity direction of double bubble assemblies is answered numerically. Moreover, it is shown that the average size of bubbles in a single bubble assembly depends on the sum of the minority constituent areas and the long range interaction coefficients. One further identifies the ranges for area fractions and the

long range interaction coefficients for double bubble assemblies.

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MS33

Modeling Single-neuron Dynamics and Dendritic Computation

A neuron with dendrites is believed to be the fundamental computational unit in the brain. To understand information processing in the brain, mathematical modeling of single-neuron dynamics has proven to be an effective approach. In this talk, by using asymptotic analysis, I will derive a class of single-compartment neuron models, consisting of one ordinary differential equation, from the corresponding multi-compartment models consisting of a set of partial differential equations, and further verify the derived model in realistic neuron simulations and biological experiments. In contrast to the existing single-compartment models, our derived model is capable of performing detailed dendritic computations such as direction selectivity and coincidence detection, and may greatly reduce the computational cost in large-scale neuronal network simulations without the loss of dendritic functions.

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MS33

Oscillations in Model Neuronal Networks

Synchronous neuronal network oscillations are a ubiquitous phenomenon, occurring in diverse areas of the brain. We describe synchronous behavior in model networks of noisy integrate-and-fire neurons. Starting with just excitatory neurons, we probabilistically describe synchrony by quantifying the competing effects of coupling and noise. Adding inhibitory neurons, stable PING oscillations arise, described by a mean-field model. An even more realistic model including a direct voltage connection via gap junctions creates networks with fast oscillations and tight synchrony.

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MS33

Firing Rate Models for Gamma Oscillations

Gamma oscillations (30-100 Hz) are widely observed in the mammalian brain and are important markers for cognition, attention, and response to stimuli. Models typically involve networks of excitatory and inhibitory spiking neuron models. The time scale of inhibition, τ_{inh}, strongly affects the oscillation frequency. The models involve many dynamical variables and typically are studied by simulation. Mean field (firing rate) models of the Wilson-Cowan type, while tractable mathematically, do not include synaptic currents or τ_{inh} explicitly. We developed rate models that include synaptic dynamics as well as firing rate, and in some cases mean voltage. Our models can be analyzed with bifurcation, phase plane, fast/slow dissection methods and with simulations. We applied our framework to account for observations of multiple gamma rhythms (fast and slow) in the hippocampus – sometimes fast or slow frequency gamma oscillations are seen or even alternations between the two types at different moments in time. Our model with one excitatory unit and two inhibitory units (having different τ_{inh}) that compete through mutual inhibition can mimic various features of the data. Bistability between fast and slow oscillations can occur for a range of relative drive to the inhibitory units. Noise-induced switching accounts for the momentary random appearance of fast or slow gamma cycles.

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MS33

A Coarse-graining Framework for Spiking Neuronal Networks: From Strongly-coupled Integrate-and-Fire Neurons to Augmented Systems of ODEs

Homogeneously structured, fluctuation-driven networks of spiking neurons can exhibit a wide variety of dynamical behaviors, ranging from homogeneity to synchrony. We here extend our partitioned-ensemble average (PEA) formalism to systematically coarse-grain the heterogeneous dynamics of strongly coupled, conductance-based integrate-and-fire neuronal networks. The population dynamics models derived successfully capture the so-called multiple-firing events (MFEs), which emerge naturally in fluctuation-driven networks of strongly coupled neurons. Although these MFEs likely play a crucial role in the generation of the neuronal avalanches observed in vitro and in vivo, the

mechanisms underlying these MFEs cannot easily be understood using standard population dynamic models. Using our PEA formalism, we systematically generate a sequence of model reductions, going from Master equations, to Fokker-Planck equations, and finally, to an augmented system of ordinary differential equations. Furthermore, we show that these reductions can faithfully describe the heterogeneous dynamic regimes underlying the generation of MFEs in strongly coupled conductance-based integrate-and-fire neuronal networks.

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MS34

Evaluation of Cardiac Pacemaking Activity and Parametric Stability Analysis of the Biopacemaker Patch

The biological pacemaker approach has been proposed as a possible alternative to the electronic pacemaker with the creation of a new multicellular pacemaking substrate. While biopacemaker patches can be a promising approach, the biopacemaker stability and function could depend on the variability of the cell dynamics and complex electrical coupling to the heart. The linear stability of the fixed points and detailed bifurcation analysis of the model is unclear for a discrete model with and without coupling to cardiac excitable tissue. The stability of the pacemaker cells in a heterogeneous network of excitable cardiomyocytes is studied using a discrete network of Luo-Rudy I mathematical model of ventricular cardiomyocytes. Here, we investigated multicellular stability analysis of heterogeneous populations of cardiac cells where automaticity is controlled through a bias constant current parameter. The fixed points were determined using a local reduction from the cellular 8-dimensional dynamical system to a simplified 1-dimensional system. Global linear stability of the fixed points was evaluated using the global Jacobian. Validation of the approach was done on multicellular stochastically distributed spontaneous cells where the effect of electrical coupling between cells was evaluated. Preliminary results of coupling the biopacemaker to cardiac tissue highlight the role of restricted coupling between the biopacemaker and tissue in favoring biopacemaker function.

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MS34

Mechanisms Underlying Pro-arrhythmic Effects of State-specific Ion Channel Blockers

It is well documented that many drugs designed to be anti-arrhythmic can sometimes increase the propensity for cardiac arrhythmias. The effects of antiarrhythmic drugs usually result from binding to ion channels and altering channel kinetics, and therefore, a better understanding of how drug effects on ion channel kinetics influence tissue level dynamics would be greatly beneficial to the drug development and drug screening processes. While several experimental and modeling studies have examined how drug-ion channel interactions of specific drugs translate to effects on tissue level dynamics, no unifying principles have been identified. Using a modified Hodgkin-Huxley formalism, we have begun developing a framework that connects common drug-ion channel binding motifs to pro-arrhythmic effects at the tissue level.

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MS34

Not all Heartbreak is the Same: A Cross-species Comparison of Cardiac Arrhythmias

Much research has been devoted to investigating the initiation of cardiac arrhythmias by alternans, a period doubling bifurcation in the duration of cardiac action potentials which is strongly correlated with the onset of sudden cardiac death. Alternans results from a cellular level instability in the bidirectionally coupled voltage and calcium dynamics. Although the formation and maintenance of alternans has been studied extensively in animal models such as rabbit, rat, and zebrafish, surprisingly little attention has been given to the discrepancies observed across species. Even when the hearts of two species are anatomically similar, the electrophysiology can behave quite differently. In this talk I will present high spatiotemporal resolution experimental data from optically mapped fluorescent recordings of simultaneous transmembrane voltage and intracellular calcium transients from the surfaces of Langendorff-perfused whole hearts of a variety of species including rabbit, porcine, canine, cat, rat, zebrafish, alligator, and snake, and I will discuss the variety of alternans observed in these species and the different driving mechanisms behind them.

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MS34

Computational Approaches to Atrial Fibrillation-selective Pharmacological Therapy

A significant limitation in the management of atrial fibrillation (AF), the most common cardiac arrhythmia, is the

lack of safe and effective pharmacological treatments. Current approaches have limited efficacy, due at least in part to an incomplete understanding of the molecular and cellular basis of AF initiation and maintenance, and are associated with increased risk for ventricular arrhythmias. One strategy to avoid these malignant adverse effects is to target ion channels primarily expressed in atria. We developed new mathematical models of the atrial-specific ultra-rapid delayed-rectifier and the small-conductance Ca-activated K currents (IKur and IK,Ca) based on experimental data collected in patients in normal sinus rhythm (nSR) and chronic AF (cAF) conditions. Using our framework for human atrial myocyte simulations and a population-based approach, we (a) assessed the role of IKur and IK,Ca in action potential regulation and arrhythmogenesis; (b) identified optimal channel-drug interaction properties conferring anti-AF selectivity to IKur and IK,Ca modulators; and (c) studied how inter-subject variability and various degrees of AF-induced ionic remodeling affect the response to anti-AF therapy. By identifying the main factors responsible for atrial arrhythmogenesis (or for its prevention), our computational investigation provides potentially useful insight for developing new mechanism-based therapeutic approaches to treat AF.

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MS35

An Asymptotic Model for Biofilm Growth

Current continuum models are designed for typical length scales around 1mm. Direct comparison to experiments are very difficult because the typical dimensions of the flow cells are larger, and it is difficult or currently impossible to estimate the environmental conditions for the biofilm where the measurements are taken due to incomplete information from upstream. To address these constraints, we present an asymptotic solution for the biofilm growth where the small parameter is based on the depth of substrate penetration within the biofilm. Lubrication theory is used to estimate fluid flow, which in turn allows us to measure surface shear stress leading to erosion, and to estimate substrate concentrations in the flow. We compare our asymptotic model to a fully resolved continuum model and also compare to full flow-cell experiments to show that our model is capable of capturing bulk characteristics of the domain as well as estimate the biofilm growth over much larger length scales.

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MS35

A Multi-scale One-dimensional Biofilm Growth Model that Accounts for Detachment and Attachment

We derive a multi-scale model for biofilm formation in a porous medium reactor. The starting point is the traditional mesoscopic one-dimensional Wanner-Gujer biofilm model. Mesoscopic processes included in the model are hydrodynamics and transport of substrates in the reactor, biofilm and suspended bacteria growth in the pore space through consumption of a single, non-reproducing growth limiting substrate, attachment of suspended cells to the biofilm, detachment of biofilm cells, and cell lysis. The mesoscopic equations are up-scaled from the biofilm scale to the reactor scale, yielding a stiff system of quasilinear hyperbolic balance laws, which are studied numerically. We investigate the role of suspended bacteria and the effect attachment has on reactor performance.

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MS35

Flow Conditions Underlie the Evolutionary Dynamics of Biofilm Formation

Bacteria often live in biofilms, which are microbial communities surrounded by a secreted extracellular matrix. Here, we demonstrate that hydrodynamic flow and matrix organization interact to shape competitive dynamics in Pseudomonas aeruginosa biofilms. In competition with cells that cannot make matrix material, wild-type cells always increase in relative abundance in planar microfluidic devices under simple flow regimes. By contrast, in microenvironments with complex, irregular flow profiles which are common in natural environments wild-type matrix-producing and isogenic non-producing strains are found to coexist. This result stems from local obstruction of flow by wild-type matrix producers, which generates regions of near-zero shear that allow matrix mutants to locally accumulate. Our findings connect the evolutionary stability of matrix production with the hydrodynamics and spatial structure of the surrounding environment, providing a potential explanation for the variation in biofilm matrix secretion observed among bacteria in natural environments.

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MS35

Physical Determinants of Bacterial Biofilm Architecture

In many situations bacteria aggregate to form biofilms: dense, surface-associated, three-dimensional structures populated by cells embedded in matrix. Biofilm architectures are sculpted by mechanical processes including cell growth, cell-cell interactions and external forces. Using single-cell live imaging in combination with simulations we characterize the cell-cell interactions that generate Vibrio cholerae biofilm morphologies. Fluid shear is shown to affect biofilm shape through the growth rate and orientation of cells, despite spatial differences in shear stress being balanced by cell-cell adhesion. Our results demonstrate the

importance of cell dynamics mediated by adhesion proteins and matrix generation in determining the global architecture of biofilm structures.

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MS36

Mathematical Modeling of Rapid Decisions Involving Changes of Information

In the real world, people integrate non-stationary information that changes while the decision is in progress. Although theories / mathematical models of decision-making developed in psychology and cognitive neuroscience have traditionally been applied to paradigms with stationary information, changing stimuli are becoming of increasing interest due to their probative value. Building mathematical models of the decision making process when information changes over time however presents a number of both modeling and methodological challenges that must be overcome to gain insights using real data. I will describe joint modeling / experimental work aimed at utilizing computational models in conjunction with perceptual experiments to probe how the decision process responds to changes of evidence and investigate how those changes impact decisions.

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MS36

Decision-making and Evidence Accumulation in Complex Environments

In a constantly changing world, animals must account for fluctuations and changes in their environment when making decisions. They must make use of recent information, and appropriately discount older, irrelevant information. But to do so they need to learn the rate at which the environment changes. In addition, animals may have available social information based on their neighbor's actions that can help guide their own decisions. Developing normative models of evidence accumulation is a first step in quantifying such decision-making processes. While optimal, these algorithms are computationally intensive. To address this problem we can develop approximations of normative inference processes, and show how these approximate computation can be implemented in neural circuits.

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MS36

Rats Optimally Accumulate and Discount Evidence in a Dynamic Environment

Real-world environments have statistics that change over time. Decision-making in this context requires discounting old evidence that may no longer inform the current state of the world. Previous work derived the optimal inference process for decision-making in a dynamic environment, and analyzed the case of Gaussian distributed evidence samples (Veliz-Cuba et al, 2016). We developed a rat auditory behavioral task with a dynamic environment, where evidence is delivered in discrete pulses from two independent Poisson processes. Using discrete evidence pulses, we can exactly compute the optimal inference process for our task. Critically, the optimal timescale for evidence discounting depends on both the stimulus statistics and noise in sensory processing. When both of these components are taken into account, rats accumulate and discount evidence optimally. Current work is focused on investigating the neural mechanisms underlying evidence accumulation. To facilitate neural investigations, we have developed a parametric model which quantifies several sources of error in the optimal inference process, and predicts a moment-by-moment estimate of the rat's accumulated evidence. The resulting model takes the form of a single stochastic differential equation, which can be solved explicitly, and we will demonstrate how to validate its predictions using neural data.

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MS36

A Normative Theory of Decision-making From Multiple Stimuli

The dynamics of simple two-alternative decisions in humans and animals is well captured by the drift-diffusion model. The drift-diffusion model unifies the connectionist approach and the Bayesian optimality-based approach to decision-making. However, most real-life decisions include a dynamically-changing influence of additional contextual stimuli. We adopt a Bayesian framework to develop a computational model for decision-making using multiple stimuli. We show how this model reduces to a two dimensional DDM under continuum limit, which we show can also be derived from spectral reduction of an appropriate connectionist model. We also explore the optimal decision-making in the paradigm of multiple stimuli and compare it with the heuristic fixed-threshold policy that is known to be optimal for the DDM. Our model can be applied to diverse tasks of longstanding interest in psychology, including the Flanker, AX-CPT, Stop-Signal, and Posner Cueing. We show empirically that our model can infer differences in attention allocation from data collected from humans performing AX-CPT.

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MS37

Pattern Formation Mechanism for Homeostatic Control of Synapse Density During C. Elegans Growth

We propose a novel mechanism for Turing pattern formation that provides a possible explanation for the regular spacing of synapses along the ventral cord of C. elegans during development. The model consists of two interacting chemical species, where one is passively diffusing and the other is actively trafficked by molecular motors; we identify the former as the kinase CaMKII and the latter as the glutamate receptor GLR-1. We use linear stability analysis to derive conditions on the associated nonlinear interaction functions for which a Turing instability can occur. We find that the dimensionless quantity γ, the ratio of switching rate and diffusion coefficient to motor transport velocity, must be sufficiently small for patterns to emerge. One consequence is that patterns emerge outside the parameter regime of fast switching where the model effectively reduces to a two component reaction-diffusion system. Furthermore, these patterns are also maintained during domain growth. We discuss selection and stability of patterns for this mechanism in both 1- and 2-dimensional domains.

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MS37

On Final Transition Probabilities for Intersecting Microtubules

A cell's cytoskeleton contains of a dense network of intersecting microtubules. Directed transport of cargo occurs along these microtubules through molecular motors, with experiments showing that motors occasionally change their direction at microtubule intersections. Previous computational results demonstrate that transition probabilities of motor systems depend upon such factors as total motor number and microtubule spacing. In this talk, we incorporate these features into a Markov switching model to calculate final transition probabilities of motor systems, determining which microtubule a motor system is ultimately attached.

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MS37

Understanding the Emergence of Contractility in Acto-Myosin Networks

We investigate the emergence of contractile behaviors in disordered non-muscle actomyosin networks, whose non-equilibrium dynamics remain largely unexplored when containing reversibly-bound passive cross-linkers and active myosin II motor filaments. Current understanding of how contractility emerges in disordered actomyosin networks of non-muscle cells is still largely based on the intuition derived from earlier works on muscle contractility. In addition, in disordered networks, passive cross-linkers have been hypothesized to percolate force chains in the network, hence, establishing large-scale connectivity between local contractile clusters. Our work, based both on analytical theory and detailed molecular simulations, shows that cross-linker binding dynamics plays a crucial role even at the level of elementary force generating elements in contractile actin networks. In particular, our results shed light on the non-equilibrium effects of transiently binding proteins in biological active matter, as observed in the non-muscle actin cytoskeleton, showing that highly efficient contractile force dipoles result from synergy of passive cross-linker and active motor dynamics. These findings begin to elucidate the tools available to this biological active matter to dramatically alter their micro-structural morphologies and generate active cellular forces.

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MS37

Motion of Intermediate Filaments in Cells

Recently, the intracellular transport of intermediate filaments has been identified as a key process for their dynamics. Their regulated interactions with motors and structural linkers result in different modes of motility for assembled intermediate filaments proteins in cells. Based on experimental data, mathematical models of the spatiotemporal distribution of intermediate filaments in cells are developed to investigate the contributions of different types of transport such as retrograde flow of actin and motor proteins. Furthermore, models for the motion of single fibres driven by motor proteins are also proposed.

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MS38

Parallel Integrated Models of Neurovascular Coupling and Bold Signals

The neurovascular coupling (NVC) mechanism, the cerebral metabolic rate of oxygen consumption, and the cerebral blood volume (CBV) are known to contribute to the fMRI BOLD response, however a thorough understanding

of these factors has yet to be fully established. The NVC response, the ability to locally adjust vascular resistance as a function of neuronal activity, is believed to be mediated by a number of different signalling mechanisms. The talk will describe the integrated model of neurovascular coupling and the BOLD response with the ability to simulate the fMRI BOLD responses due to continuous neuronal spiking, bursting and cortical spreading depression (CSD) along with the underlying complex vascular coupling and the astrocytic syncytium allowing spatial buffering through gap junction protein connexins. Bursting phenomena provides relatively clear BOLD signals as long as the time between bursts is not too short. For short burst periods the BOLD signal remains constant even though the neuron is in a predominantly bursting mode. Simulation of CSD exhibits large negative BOLD signals. The comparison with experimental cerebral blood flow (CBF) data indicates the possible existence of multiple neural pathways influencing the vascular response. Initial negative BOLD signals occur for all simulations due to the rate at which the metabolic oxygen consumption occurs relative to the dilation of the perfusing cerebro-vasculature.

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MS38

Global Sensitivity for Neurovascular Coupling Models

We describe global sensitivity techniques appropriate for the study of large neuro-vascular coupling models. Challenges attached to the size of the models (number of states), the number ofparameters, the dynamics of the models and possible correlations between parameters are also discussed. The properties of the proposed variance-based approach are illustrated on specific models where one seeks to not only assess the relative importance of the involved parameters but also of the various compartments entering into the models. Joint work with J. Hart and T. David.

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MS38

Reduced Model for the Fontan Circulation

The Fontan physiology results from surgical intervention in patients with congenital heart defects. Several variants of this physiology are used in clinical practice. In this work, we describe a mathematical framework for modeling global hemodynamics in different variants of the Fontan physiology. Blood flow in the major vessels are described by a network of hyperbolic conservation laws, while the organ beds and the heart are described by ODE models.

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MS38

Patient-specific Predictions of Control and Abnormal Baroreflex Responses

The baroreceptor reflex (baroreflex) is the response of the autonomic nervous system to changes in system blood volume and blood pressure (BP). Particularly, the baroreflex can be triggered when either the BP rises or drops suddenly. One clinical test to evaluate the efficacy of the baroreflex is the Valsalva maneuver (VM), which is the process associated with forced expiration against a closed airway. The VM elicits a distinctive curve in both BP and heart rate, and deviations from this curve signify autonomic nervous dysfunction.
Humans are inherently complex and varied, so mathematical modeling of the baroreflex and its systemic effects poses many challenges, both from design and computational standpoints. Furthermore, increasing emphasis has been placed on offering patient-specificity of the model to aid clinicians in the development of treatment plans for abnormal subjects. This talk will focus on the ability of a phenomenological mathematical model to predict both control and abnormal responses of a patient to the Valsalva maneuver. We will discuss the characteristics of an abnormal baroreflex response versus a control response. Furthermore, we will delve into computational difficulties in parameter estimation of a system with a large parameter space.

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MS39

Fluctuating Hydrodynamics Methods for Drift-diffusion Dynamics of Particles within Curved Fluid Interfaces: Applications to Lipid Bilayer Membranes and Cellular Mechanics

Motivated by kinetics within lipid bilayer membranes and cell mechanics, we introduce fluctuating hydrodynamics methods to capture the drift-diffusion dynamics of particles and spatially extended microstructures immersed within curved fluid interfaces. We account for the interfacial hy-

drodynamic coupling, traction coupling with the surrounding bulk fluid, and thermal fluctuations. We demonstrate our approaches by investigating the role of hydrodynamic coupling and diffusive kinetics in the self-assembly of protein clusters. We then show how active particle systems can be studied by modeling microswimmers using Golestanian motions to gain insights into the role of confined hydrodynamics within spherical fluid interfaces. We next study a fluctuating polymeric network to investigate the role of hydrodynamic coupling on collective motions within structures such as the spectrin network. Our introduced fluctuating hydrodynamics methods aim to provide a few new modeling and simulation approaches for capturing some of the rich phenomena that can arise in curved fluid interfaces for further investigations of biological processes.

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MS39

Equilibrium Shapes of Compound Vesicles

Many biological structures have a fine internal structure in which a membrane is geometrically confined by another membrane. Here we investigate how the equilibrium shape of a double membrane system changes as the length of the internal membrane is increased. A repulsive pressure is introduced between the membranes to prevent the membranes from intersecting. Large repulsive pressures yield complex response diagrams with bifurcation points where modal identities may changes. The effect of membrane tension on the shapes will be discussed. Regions in parameter space where such behavior occurs are then mapped.

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MS39

Multicomponent Vesicles in Electric Fields

Recent work has demonstrated the interesting dynamics which occur when multicomponent vesicles are exposed to electric fields. In this work, the dynamics of three-dimensional vesicles in the presence of electric fields will be considered. The results show a rich variety of dynamics, which strongly depend on the material properties of the underlying lipid species.

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MS39

A Two-phase Flow Model for a Poroelastic Drop in Linear Flows

In this work a two-phase flow model is constructed to study the combined effects of interfacial slip, permeability and elasticity of the porous skeleton inside a viscous drop under simple linear flows. This two-phase flow model describes a viscous fluid filling a deformable elastic skeleton inside a drop whose interface deforms according to the balance of traction on the interface. When the viscous dissipation of the interior porous flow is negligible (compared to the friction between the fluid and the skeleton), the two-phase flow is reduced to a poroelastic Darcy fluid instead. At the interface between such an interior poroelastic fluid and an exterior Stokesian fluid, both slip and permeability are taken into account. The permeating flow induces dissipation that depends on the elastic stress of the interior solid. Small-deformation analysis leads to a set of linear ODE's of which the eigenvalues can be used to find parameter regimes where small-deformation is reasonable. By exploring the interfacial slip, permeability and interior elasticity various flow patterns are found at equilibrium of these slightly deformed poroelastic drops. These results shed light on the rheology of a suspension of poroelastic spherical particles, and give insight to possible flow patterns of a system of self-propelling swimmers with porous flow (such as intracellular cytosol) inside.

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MS40

Unconditionally Energy Stable Dg-Fe Schemes for Diffuse Interface Models

Cahn-Hilliard type equations coupled with fluid flow inspired from modeling tumor growth, biofilms, wound healing and other complex biological processes will be introduced and numerically solved. Discontinuous Galerkin Finite Element Methods for the numerical solution of the equations will be presented. For the underline schemes: solvability, energy stability, convergence and error estimates will be established where possible. Simulation results will be provided.

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MS40

Intra-Droplet Patterning of RNA-protein Bodies (RNPs) in Phase Separated Systems

Intracellular phase transitions are an emerging mechanism for cell organization. These membrane-less compartments are formed via liquid-liquid demixing and subsequent concentration of cellular components. By undergoing these localized phase separations, cells are able to create dynamic compartments that help maintain the regulation of biomolecular interactions and localize factors such as RNAs and proteins. In most cases, intrinsically disordered proteins with low complexity sequences promote phase separation and frequently these disordered domains are coupled to multiple RNA binding domains. Additionally, the RNA partners in these RNA/protein (RNP) bodies can contain multiple binding sites, allowing for multiple proteins to attach to a single RNA. These multiple binding sites could allow for an unlimited number of interactions between protein and RNA that are capable of driving phase separation. We examine how protein and RNA interactions

influence phase separation. By employing phase field modeling techniques that combines a modified double-well free energy with mass action kinetics, this model explores how the multivalent behavior of protein and RNA can influence phase separation. We show that it is the shared need and competition for free protein that creates a shell and core intra-droplet pattern. The existence of this pattern in biological droplets could ultimately dictate protein and RNA accessibility for required interactions both inside and outside the droplets.

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MS40

Unconditionally Energy Stable Numerical Schemes for Phase-field Vesicle Membrane Model

Numerical schemes to simulate the deformation of vesicles membranes via minimizing the bending energy have been widely studied in recent times due to its connection with many biological motivated problems. In this talk I will introduce a new unconditionally energy stable numerical scheme for a vesicle membrane model that satisfies exactly the conservation of volume constraint and penalizes the surface area constraint. Moreover, we extend these ideas to present an unconditionally energy stable splitting scheme decoupling the interaction of the vesicle with a surrounding fluid. Finally, the well behavior of the proposed schemes are illustrated through several computational experiments.

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MS41

Orientation Selectivity in V1, Mouse Vs Macaque

Recent experiments have revealed vast difference between mouse and macaque V1 in connectivity and anatomical structures. However despite of not having the same pinwheel structure as macaque, they have sharper orientation selectivity in V1 neurons than expected. In addition, some experiments have found their orientation selectivity is contrast-dependent rather contrast-invariant as what is found in macaque (and other animals). Excitatory neurons of mouse V1 exhibit contrast-sharping tuning curve of firing rate, while inhibitory neurons show contrast-broadening ones. To understand the various underlying mechanisms and how they contribute to the tuning curve sharpness, we built a large-scale comprehensive V1 input layer model for mouse, with a experimental constrained setup from LGN to V1 connection as well as cortical connections. We show that, both a high level of feedback inhibition and orientation specific coupling within the excitatory neurons are important to the contrast-sharpening effect, while orientation specific inhibitory input to excitatory neurons have a secondary effect. And the inhibtory neurons' broadening can be explained by its orientation nonspecific and large connection strength from the excitatory neurons, and a elongated LGN connection pattern can help to enhance this effect. A similar inhibition dominated network has also been used to explain contrast-invariance in macaque, suggesting a soft boundary between the two.

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MS41

Balanced Core in Heterogeneous Neuronal Networks

The balance between excitatory and inhibitory current inputs is crucial for neuronal computation and has been observed in many experiments. Theoretical studies have mainly focused on the analysis of homogeneous networks. However, neuronal networks in the brain are usually inhomogeneous. Here we show that the balanced state can exist even in inhomogeneous neuronal networks because that embedded in the original network there is a homogeneous-like core that underlies origin of the balanced state.

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MS41

Dynamic Bifurcations in a Firing Rate Model of Insect Olfaction

This talk will present a coarse-grained mathematical description of the dynamics present in insect, in particular locust, olfaction. When a locust detects an odor, the neuronal network in its antennal lobe begins oscillating. These oscillations then subside, and are replaced by slow modulations of the individual neuronal firing rates. Modeling the effects of a white-smell-type odor using an integrate-and-fire network and a firing-rate model, both with fast excitatory and inhibitory and slow inhibitory currents, we propose a possible mechanism for generating this dynamical sequence to be a slow passage through a saddle-node-on-a-circle bifurcation

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MS41

Network Connectivity Reconstruction from Dynamics in Neuronal Systems

Abstract not available at time of publication.

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MS42

Intercellular Ephaptic Coupling in the Heart: Myth or Reality?

Cardiac action potential propagation is rendered possible by gap junctions connecting adjacent cells. However, a controversial mechanism has been proposed, called ephaptic coupling, which may serve as a backup process when gap junctional coupling is reduced. Ephaptic coupling involves extracellular potentials (V_e) in intercalated discs, where the intercellular cleft is very narrow. During excitation, the Na^+ current (I_{Na}) on one side of the cleft produces a large negative V_e which acts to depolarize the membrane on the other side of the cleft, leading to I_{Na} activation and excitation of the next cell. We conducted proof-of-principle patch clamp experiments demonstrating ephaptic effects on I_{Na} and developed a high-resolution numerical model based on the finite element method to investigate the significance of the recently reported Na^+ channel clustering in intercalated discs. In HEK cells stably expressing human cardiac Na^+ channels, restricting the extracellular space modulated I_{Na} as predicted by simulations. In the intercalated disc model, aggregating Na^+ channels into a cluster potentiated this modulation, and action potential transmission from one cell to another was facilitated by Na^+ channel clusters facing each other across the intercellular cleft when gap junctional coupling was reduced. Our results support the existence of cardiac ephaptic coupling and reveal the role of Na^+ channel clusters in intercalated discs.

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MS42

Tuning Critical Excitations in Stiff Cardiac Models

Excitable models of cardiac tissue typically couple dynamical features on wildly disparate spatial and temporal scales, leading to patterns which resist classical methods of analysis. Semi-analytical techniques [Bezekci B, Idris I, Simitev RD, Biktashev VN. Semi-analytical approach to criteria for ignition of excitation waves. Opera Medica et Physiologica. 2016(S1).] may address this difficulty and characterize excitability properties of cardiac models, for which stiff models present a numerical challenge. An essential ingredient of these techniques is the stability spectrum of the simplest coherent structures produced by these models. I will discuss techniques for computing these solutions in several stiff models of cardiac tissue dynamics and use their stability characteristics to predict excitability properties of the model. Additionally, I explore how the same techniques are applied to models with non-Tikhonov features and are used to understand conduction block.

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MS42

Controllability Analysis of a Cardiac Cell Model

Sudden cardiac arrest is a leading cause of death in the industrialized world. Most cases of sudden cardiac arrest are due to ventricular fibrillation (VF), a lethal heart arrhythmia. Alternans, a beat-to-beat alternation in action potential duration, has been suspected to contribute to the onset of VF. Other groups have investigated the mechanisms behind alternans, and have found situations in which alternans is predominantly associated with instabilities in the transmembrane ion-channel dynamics, or with instabilities in the intracellular calcium-handling subsystem. Furthermore, it has been noted that the effectiveness of a given alternans suppression method may be affected by the underlying alternans mechanism. To help gain insight into these results, we conducted the present study, in which we examined the Luo-Rudy dynamic (LRd) model, a nonlinear ODE model of the action-potential dynamics of a cardiac cell. To determine whether different methods of affecting the cell (i.e., different control inputs) could succeed in suppressing alternans, we used a numerical linearization approach to analyze a model property called controllability, which was characterized under a range of cycle-length conditions. The controllability results indicated that while alternans could be suppressed through a variety of interventions, that the magnitude of the controllability measure was largest for control inputs that represent making direct adjustments to the intracellular calcium dynamics.

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MS42

Fast Propagation Regions of a Specific Geometry can Cause Reentry in Excitable Media

Many theoretical and experimental studies indicate that a propagation block represents an important factor in spiral wave initiation in excitable media. The analytical and numerical results we obtained for a generic two-component reaction-diffusion system demonstrate quantitative conditions for the propagation block in a one-dimensional and a two-dimensional medium due to a sharp spatial increase of the medium's excitability or the coupling strength above a certain critical value [V. Zykov, A. Krekhov, and E. Bodenschatz, Proc. Natl. Acad. Sci. U.S.A., 114(6), 1281 (2017),V. Zykov, A. Krekhov, and E. Bodenschatz, Chaos, 27, 093923 (2017)]. Here we prove that this critical value strongly depends on the medium parameters and the geometry of the inhomogeneity. For an exemplary two-dimensional medium we show how the propagation block can be used to initiate spiral waves by a specific choice of the size and shape of the medium's inhomogeneity.

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MS43

Parameter Regions for Multistationarity

Polynomial Ordinary Differential Equations are an important tool in many areas of quantitative biology. Due to high measurement uncertainty, few experimental repetitions and a limited number of measurable components, parameters are subject to high uncertainty and can vary in large intervals. One therefore effectively has to study families of parametrized polynomial ODEs. Multistationarity (i.e. the existence of at least two distinct positive steady states) has been recognized as an important feature of these ODEs. As parameter values are confined to large intervals one is generally interested in parameter conditions that guarantee multistationarity and further constrain the parameter values. The focus of this talk are mass action ODEs that admit a monomial parameterization of positive steady states. For such systems it is straightforward to derive a parameterization of rate constants where multistationarity exists. To this class belong, for example, multisite phosphorylation systems, key players in intracellular signaling and regulation.

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MS43

Rational Parametrizations of Steady State Manifolds for a Class of Mass-action Systems

Classical results give structural conditions under which the steady state set of a (bio)chemical reaction system has a monomial parametrization. This property has been studied extensively in the context of characterizing a mechanism's capacity for mono- and multi-stationarity. In this talk, we generalize the existing structural framework and derive sufficient conditions for guaranteeing that the steady states have a rational parametrization. Applications include the EnvZ-OmpR osmoregularity pathway and the Shuttled WNT signaling pathway.

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MS43

Dynamics of the Selkov Model of Glycolysis

The Selkov model is a two-dimensional system of ODE which was introduced to describe glycolytic oscillations. We discuss the existence, uniqueness and stability of periodic solutions of this system. We also treat the issue of the existence of solutions which are unbounded at late times, either in a monotone or oscillatory way. Among the techniques used in this analysis are the Poincaré compactification and blow-up of degenerate steady states.

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MS43

Absolute Concentration Robustness: An Algebraic Perspective

How do cells maintain homeostasis in fluctuating environments? Investigations into this question led Shinar and Feinberg to introduce in 2010 the concept of absolute concentration robustness (ACR). A biochemical system exhibits ACR in some species if the steady-state value of that species does not depend on initial conditions. Thus, a system with ACR can maintain a constant level of one species even as the environment changes. Despite a great deal of interest in ACR in recent years, the following basic question remains open: How can we determine quickly whether a given biochemical system has ACR? Although various approaches to this problem have been proposed, we show in this talk that they are incomplete. Accordingly, we present a new method for deciding ACR, which uses computational algebra. We illustrate our results on several biochemical signaling networks.

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MS44

Optimizing Flexibility in the Collective Decisions of Honeybees

Honeybees make decisions as a group while searching for a new home site or foraging. The quality of each choice influences the rate at which scout bees recruit others via a waggle dance. In addition, decided bees can influence those with opposing opinions to change their minds via stop-signals. Most previous experimental studies have assumed bee swarms make decisions in static environments, but most natural environments are dynamic. In such cases, bees should adapt to new evidence as the environment constantly changes. One way of adapting is to abandon ones current opinion and restart the evidence-accumulation and decision process (Seeley et al 2012). Incorporating such individual behavior into a dynamical model leads to a collective decision-making process that discounts previous evidence and weights newer information more strongly. We show that properly tuning this forgetting process can improve a swarms performance on a foraging task in a dynamic environment. Individual forgetfulness allows the group to change its mind, and move to a higher yielding foraging site. The rate at which bees forget should be increased as the rate of environmental change increases. Our analysis explores parameter-dependent changes in the foraging yield using bifurcation theory and fast/slow analysis in a mean field version of the collective decision-making model. We also study the impact of finite-size effects, a source of stochasticity that can also lead the group to change its mind.

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MS44

Evidence Accumulation and Decision-making on Networks

A central question in neuroscience is how organisms use sensory and social information to make decisions. Yet few models of decision making account for both types of information. Popular models describe an ideal observer using a sequence of sensory measurements to choose among alternatives. However, these models describe an observer in isolation, whereas animals often make decisions in groups. It is natural to ask how an observer should combine private measurements with social information to make decisions. While heuristic models of this type have been proposed, few normative models exist. We develop a normative model for collective decision making on a network of agents performing a two-alternative forced choice (TAFC) task. We assume each agent is rational (Bayesian) and accumulates evidence privately until it makes a choice. All of its network neighbors observe this choice. Thus the flow of information is described by a directed network, and each deciding agent communicates its decision to those observing it. In this setup the computations of agents can be intuitively explained, but can become extremely complex. We describe how the absence of a decision of a neighboring agent communicates information, and how an agent must marginalize over the decision states of all agents it does not observe directly. We also show how decision thresholds and network connectivity affect group evidence accumulation, and give a full description of decision-making dynamics in cliques.

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MS44

Optimal Confidence-weighted Collective Decisions

Theory shows that where individuals vary in their decision-making accuracy, and can measure or estimate their own accuracy, optimal collective decisions make use of a simple rule for weighting individual votes by confidence. However, this theory does not make explicit how confidence-weighted votes should be aggregated in a decentralised way. In this talk I will show how optimal local evidence integration can propagate confidence weights through a network of decision-makers, achieving group accuracy near the theoretical limit in a short time, without parameterisation based on network structure. I will compare this against an existing proposal for decision integration, belief-consensus. I will also discuss links between statistically-optimal individual decisions, and optimal confidence weighting.

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MS44

Intertrial Correlations in Sequential Decision-making Tasks

Understanding how organisms can learn the probabilistic structure of the environmental to improve decisions is of central interest in neuroscience and psychology. Binary choice tasks have been used extensively to identify strategies humans and other animals use to make decisions. Experiments demonstrated that subjects can learn the latent probabilistic structure of their environment, improving decision performance. For instance, humans can learn to account for dependencies between trials when the correct choice has a greater than chance probability of being repeated. We study normative probabilistic models of evidence accumulation in such situations. Within each trial, the belief of an observer is described by a drift-diffusion process. We show that optimal observers account for the probability that their action (choice) may change the environment by adjusting their belief according to the probability of this change. Observer performance is measured using reward rate (RR), which is tuned by changing the evidence threshold needed to make a decision. For fixed thresholds we find closed form expressions for the mean decision times, and probabilities of correct choices. We use these to show that RR increases from the first to the second trial in nontrivial environments, but remain constant afterward. We also show how gradually increasing the threshold from one trial to the next can improve performance, as it

accounts for the information transferred between trials.

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MS45

Simulating Prostate Cancer Stem Cell Dynamics to Predict Patient-specific Response to Intermittent Androgen Deprivation Therapy

Intermittent androgen suppression is an attractive treatment approach for biochemically recurrent locally advanced prostate cancer to delay evolution of treatment resistance. We developed a mathematical model of prostate cancer stem cell dynamics during therapy as a plausible mechanism of resistance evolution. We simulate division dynamics of cancer stem cells, non-stem cancer cells, and PSA concentration and generate highly accurate model fits to the longitudinal data of 55 patients undergoing 2-4 cycles of intermittent androgen suppression. We analyze model dynamics to identify cancer stem cell proliferation patterns that correlate with patient outcomes and use this to forecast evolution of resistance in individual patients. The presented framework may contribute to identifying patients that do and do not develop resistance to intermittent androgen suppression.

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MS45

Complex Dynamic Inflammatory Processes: An Overview of Modeling and Effective Control Strategies

From pathogenic insults to sterile transplant procedures, similar host inflammatory processes are involved in the host's attempt to respond to perceived threats and restore homeostasis. This talk will discuss some fundamental principles of the host response and the modeling techniques used to understand their dynamics. In addition, a comparison of intervention strategies to systematically control the response to a desired outcome will be discussed with respect to a diverse virtual patient population.

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MS45

The Effect of Metabolic Remodeling on Heart Mechanical Performance

The energetic status of the myocardium is compromised in decompensated hypertrophy in the failing heart, with the chemical energy (in the form of the ATP hydrolysis potential) available for the heart to do work diminished compared to normal. However, mechanistic relationships underlying observed relationships between energetic state and mechanical function are not well understood. We hypothesize that metabolic/energetic dysfunction directly causes contractile dysfunction of the myocardium in heart failure. This hypothesis is supported by experimental rodent models and associated multi-scale computer models, through which we have developed computer models that predict how the depletion of cytoplasmic metabolite pools and decrease of mitochondrial oxidative capacity in the myocardium affects energetic state in heart failure. Similar associations between myocardial metabolic state and mechanical function of the heart have been observed with normal human aging. Preliminary patient-specific analysis have been conducted to investigate if there is a causal link between the changes in myocardial energetic status and heart mechanical function with normal aging. The analysis with multi-scale computer models is based on patient-specific measurements (e.g. heart geometry, mechanical function, and PCr/ATP) obtained with different cardiac imaging approaches.

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MS45

The Contribution of Macrophages to Disease Progression

The immune response plays an essential role in many diseases and physiological processes. A sequential response of immune cells is triggered in most inflammatory responses and typically begins with infiltration of neutrophils and progresses to macrophage infiltration with varying phenotypes. Understanding the dynamics of these key cell types and how their response varies between individuals is necessary to optimizing patient outcome. Therefore, we have worked with various models and used parameter estimation and parameter sampling to explore marcophage dynamics in wound healing and during an inflammatory response to an infection. We were able to identify relationships between parameters that give rise to normal dynamics. We then focused on those parameters that when modulated are linked with significant changes in dynamics to identify potential targets for treatments.

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MS46

Simulating Membrane Physics with a Polynomial

Atlas

We propose a new computational method for the simulation of flexible biological membranes in low Reynolds number flows. We explore the idea of representing a surface using a collection of chart functions, each of which constitutes a local parameterization for a portion of the surface. We call the overall surface discretization a polynomial atlas because the charts are bivariate Chebyshev polynomials of low rank. This discretization scheme is capable of representing surfaces of arbitrary topology, and it affords spectrally accurate computations of differential geometry quantities (curvature, normal vectors, et cetera). We describe the form of the boundary integral method in the absence of a global surface parameterization and we solve several example problems illustrating the method. Suitable time integration schemes are also discussed.

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MS46

Electrohydrodynamics of Surfactant-laden Drops and Vesicles

Electrohydrodynamics (EHD) of viscous drops and vesicles is of great relevance in biomedical, engineering and industrial applications. In this talk I will focus on results on this subject from my collaborations with various groups over the years. We present modeling results from investigating the EHD of vesicle and viscous drop under an electric field. In the case of viscous drops, we illustrate how inertia can play an important role, especially when the drop undergoes extreme deformation; we found that electrical stresses can be used to predict drop break-up under strong electric field. Surfactants (surface active agents) may also lead to different drop EHD, for both dielectric or conducting drops. We discuss preliminary results that show important differences in shape outcomes, depending on the strength of the Péclet number. Throughout the lecture, we present various comparisons with previous results. We found that in general, under an electric field of moderate strength steady drop and vesicle shapes in our model compare well with numerical simulation results, both in good agreement with experimental results.

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MS46

A Rigorous Error Analysis Framework for Slender Body Theory

Slender body theory facilitates computational simulations of thin fibers immersed in a viscous fluid by approximating each fiber as a one-dimensional curve of point forces. We develop a PDE framework for analyzing the error introduced by approximating a truly three-dimensional object in Stokes flow by a one-dimensional curve. In particular, given a 1D force specified along the fiber centerline, we define a notion of 'true' solution to the full 3D slender body problem and obtain an error estimate for the slender body approximation in terms of the fiber radius.

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MS46

The Role of Adhesion in Vesicle Suspensions

Vesicle suspensions are an example of a complex Stokesian fluid that is often used to study capillary flow. In addition to the hydrodynamics, other physics that are important to incorporate include adhesion. I will propose an adhesion model and describe the related numerical methods.

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MS47

Locally Conservative Parameter-Robust Finite Element Methods For Poroelasticity

We consider finite element methods for the total pressure formulation of Biot's consolidation model with local mass conservation and discuss the a priori error analysis. For computational efficiency, we also discuss an operator splitting approach which obtains numerical solutions with sequential solves of subproblems.

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MS47

An Implicit Discontinuous Galerkin Method for Modeling Intestinal Edema

Edema refers to fluid collection in the regions between cells as a result of the usual homeostasis between Starling forces, and lymphatic mechanisms, being disrupted. Edema can arise alongside other clinical issues across a variety of tissue beds and often complicates treatment; examples include, hydrocephalus, and acute respiratory distress syndrome, among others. Edema in the small intestine can be triggered by traumatic injury in addition to clinical processes, such as packing a wound, related to surgical treatment. Edema in the small bowel can stiffen tissue fibers, and increase the distance between synapses responsible for contractile function; inducing ileus. In medical practice, edema is often studied in the context of compartmental models, using Starling's equation, and modeled via a simple ODE; as a result, many common medical models neglect the coupled interaction of the poroelastic tissue. In this talk, Biot's equations of linear poroelasticity are used

to model severe edema in the small intestine. The proposed numerical method is based on a novel mixed formulation of Biot's equations of linear poroelasticity and discretization by discontinuous Galerkin finite elements. We briefly discuss the numerical method, and the link to edema phenomena via the Starling-Landis and Drake-Laine physiological fluid balance model. Numerical simulations of a recent experiment, in the clinical literature of gut motility, will be presented.

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MS47

Stokes-Biot Stability and a Mixed Formulation For Generalized Poroelasticity

The Biot equations, describing fluid flow through a poroelastic medium, were generalized to multiple fluid network poroelasticity (MPET) by Barenblatt and Aifantis. In the quasi-static case, these equations read as: for a set of N fluid networks, find the displacement u and the network pressures p_n such that $-\nabla \cdot (2\mu\varepsilon(u) + \lambda\nabla \cdot u) + \sum_n \alpha_n \nabla p_n = f$ and $c_n \partial_t p_n + \alpha_n \nabla \cdot \partial_t u - \kappa_n \Delta p_n + S_n = g_n$ for each $n = 1, \ldots, N$. The Biot-Willis coefficient α_n, the storage coefficient $c_n \geq 0$, the hydraulic conductivity tensor κ_n, and network transfer terms S_n parametrize each fluid network. The MPET equations have gained the attention of the biomechanics community as the framework can aptly describe elastic media permeated by multiple fluid networks; e.g. such as the vasculature, paravasculature, and cerebrospinal fluid networks encountered in brain-tissue models. We present an $H(div)$-based conformal mixed method for MPET satisfying Stokes-Biot stability; the method is based on a 3-field formulation via a fluid flux for each permeable fluid network. We discuss robustness properties of the approach, when κ_n and $c_n \to 0$, with numerical demonstrations relevant to cerebral interstitial and paravascular fluid flows.

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MS47

Convergence and Stability of Lowest Order Discretizations for Biot's Model

We consider the linear Biots model in poroelasticity discretized with stabilized piece-wise linear finite elements (conforming and non-conforming). In the conforming case we consider the piece-wise linear space for the displacement field enhanced with face bubbles and piece-wise constants for the pressure field. In both nonconforming and the conforming case we show stability and approximation of the corresponding schemes. In particular in the conforming case we show how the face bubbles can be eliminated to obtain new discrete system and we further use this technique to derive a stable discretization for Stokes equation with minimum number of degrees of freedom. We also extend this construction to obtain a three field discretization for the Biots model. We prove that the resulting scheme is stable in case of low permeabilities and/or small time steps and derive several error estimates for the fully discrete model.

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MS48

Synchronization in Oscillator Networks with Coupling Delay and Symmetry

We consider a general model for a network of biophysical neurons with time delayed connections. We study the existence and stability of cluster solutions, i.e., periodic solutions where the neurons divide into groups. Neurons within a group are synchronized, while neurons in different groups are phase-locked with a fixed phase difference. We study and compare the situations when the neurons are inherently oscillatory and when they are not.

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MS48

Spike Statistics During Olfactory Stimulation via Orthonasal and Retronasal Inhalation

Electrophysiological experiments are fundamental in advancing our understanding of neural processing of information. Currently, however, experiments can only do so much in telling us about circuit details; for example, accessing dynamics of connection strengths amongst different cell types and across multiple layers is currently elusive. I will present some recent work detailing how theoretical and computational methods can be useful in these efforts. We present a data-driven framework to predict relative connection strengths in multilayered populations, applied to the rodent olfactory system under orthonasal (normal breathing) and retronasal (odors originating from the back of nasal cavity) inhalation. Our modeling work provides novel experimental predictions about how the spike train statistics change with pharmacological manipulations. This work can serve as a guide to further investigations into the relationships of various neural attributes within and across different regions during sensory processing.

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MS48

: Intrinsic Cellular Properties Determine Variable Clustering Patterns in Randomly Connected Inhibitory Neural Networks

The plethora of inhibitory interneurons throughout the brain play a pivotal role in generating rhythmic neural activity. Our work demonstrates that the intrinsic cellular properties of these neurons affect the characteristics of clustered dynamics in randomly connected, heterogeneous inhibitory networks. We quantify these properties by the neuron's current-frequency relation (IF curve) and Phase Response Curve (PRC), and analyze network bursting properties of networks of neurons with Type I or Type II properties in both IF and PRC profile. Type II neurons whose properties arise with or without an M-type adaptation current are considered. Importantly, many of the dynamics exhibited by these networks diverge from the predictions of the interneuron network gamma (ING) mechanism. Our results show that randomly connected networks of Type I neurons synchronize into a single cluster of active neurons while networks of Type II neurons organize into two mutually exclusive clusters. Networks of Type II neurons containing the adaptation current behave similarly to networks of either Type I or Type II neurons depending on network parameters; however, the adaptation current imbues these dynamics with additional, unique features. To understand these results, we compute neuronal PRCs calculated with a perturbation matching the profile of the synaptic current in our networks. Differences in these PRCs across the neuron models reveal mechanisms underlying the divergent network dynamics.

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MS49

Electricity is Different: It Follows Universal Rules

Maxwell wrote $\mathbf{curl}\left(\mathbf{B}\left(x,t\right)/\mu_0\right) = \widehat{\mathbf{J}}\left(x,t\right) + \varepsilon_r\varepsilon_0\frac{\partial \mathbf{E}(x,t)}{\partial t}$ and showed light was electromagnetic. Physicists now know that ε_r is not the positive real constant that Maxwell assumed: current should be redefined to include all movement of charge (with mass) including classical dielectric polarization, but also currents driven by fields not mentioned in electrodynamics at all. Then $\mathbf{curl}\left(\mathbf{B}\left(x,t\right)/\mu_0\right) = \mathbf{J}\left(x,t\right) + \varepsilon_0\frac{\partial \mathbf{E}(x,t)}{\partial t}$ is as universal as electrodynamics. $\mathbf{div}\left(\mathbf{J}\left(x,t\right) + \varepsilon_0\frac{\partial \mathbf{E}(x,t)}{\partial t}\right) = \mathbf{0}$ shows that current is conserved perfectly everywhere and at every time that Maxwell's equations are valid. In a series circuit, current is equal in every element no matter what the microphysics of conduction because $\varepsilon_0\frac{\partial \mathbf{E}(x,t)}{\partial t}$ is different in each element, taking on the value needed to make total current equal everywhere.

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MS49

Charge Transport in Biological Environments: the Energetic Variational Approaches

Almost all biological activities involve transport of charged ions. Ion channels play critical roles in biological systems including heart and nerves. The study of the dynamic properties of these systems provide formidable challenges and exciting opportunities for interdisciplinary researches and collaborations. In this talk, I will discuss a unified energetic variational approach developed specifically for these multiscale-multiphysics FFSI (field-fluid-structure interaction) problems. I will present some relevant theories, approaches and methods developed in the area.

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MS49

An Electrodiffusion Model of Cortical Spreading Depression

Cortical spreading depression (SD) is a local disruption in ionic homeostasis in the brain that propagates at a rate of 2-5mm/min. SD is associated with migraine headache as well as many other brain pathologies including stroke and brain trauma. The massive redistribution of ionic concentration in brain tissue necessitates the use of electrodiffusion modeling. We present a multidomain model of tissue-level electrodiffusion to describe SD. Neural tissue is treated as a triphasic continuum consisting of the neuronal, glial and extracellular compartments. The system of equations consists of a highly coupled nonlinear partial differential algebraic system whose unknowns are the ionic concentrations, voltages and volume fractions of each compartment. Simulation results will be presented in both 1 and 2 spatial dimensions.

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MS49

A Super-Gaussian Poisson-Boltzmann Model for Electrostatic Solvation Energy Calculation

Calculations of electrostatic potential and solvation energy of macromolecules are essential for understanding the mechanism of many biological processes. In the classical implicit solvent Poisson-Boltzmann (PB) model, the macromolecule and water are modelled as two-dielectric media with a sharp border. However, the dielectric property of interior cavities and ion-channels is difficult to model realistically in a two-dielectric setting. In fact, whether there are water molecules or cavity-fluid inside a protein cavity remains to be an experimental challenge. In order to compensate this uncertainty, a novel super-Gaussian dielectric PB model is introduced, which devices an inhomogeneous dielectric distribution to represent the compactness of atoms and characterize empty cavities via a gap dielectric value. Moreover, the minimal molecular surface level set function is adopted so that the dielectric profile remains to be smooth when the protein is transfer from water phase to vacuum. As the order approaches the infinity, the super-Gaussian dielectric function reduces to a piecewise constant of the two-dielectric model. Free energy calculations of various proteins are carried out to validate the new model. A macromolecule with both cavity-fluids and empty cavities is employed to demonstrate how the cavity uncertainty in protein structure can be bypassed through dielectric modelling in biomolecular electrostatic analysis.

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MS50

Planar S-systems: Global Stability and the Center Problem

S-systems are simple examples of power-law dynamical systems (polynomial systems with real exponents). For planar S-systems, we study global stability of the unique positive equilibrium and solve the center problem. Further, we construct a planar S-system with two limit cycles.

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MS50

Persistence and Global Stability in Biological Interaction Models

Abstract not available at time of publication.

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MS50

Approximation and Stability Analysis of Delayed Reaction Networks

In this contribution we analyze a class of delayed kinetic systems derived from mass action type reaction network models. The delayed models are approximated using the chain method known from the theory of differential equations. The structural and dynamical properties of the approximating CRNs are studied. Using the approximation, we can define the time delayed positive stoichiometric compatibility classes. The semistability of the equilibrium solutions for complex balanced systems with arbitrary time delays can be shown using an appropriate Lyapunov-Krasovskii functional and LaSalle's invariance principle. As a consequence, it is proved that every positive complex balanced equilibrium solution is locally asymptotically stable relative to its positive stoichiometric compatibility class.

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MS50

Multistationarity in Mass-action Systems: Injectivity and the Species-reaction Graph

A dynamical system is multistationary if there are multiple steady states. Some mass-action systems, designed to model chemical and biochemical reaction networks, may be multistationary; however, whether a given reaction network exhibit multistationarity may not be obvious. Craciun and Feinberg defined the notion of an injective reaction network, which cannot be multistationary for any choice of rate constants. Moreover, they introduced the species-reaction graph for a reaction network, and provided sufficient conditions on the species-reaction graph that guarantees the reaction network is injective; thus the mass-action system cannot be multistationary. We are interested in the converse of this result: what are the necessary conditions on the species-reaction graph for injectivity?

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MS51

A Kinetic Contagion Model for Fearful Crowds

Abstract not available at time of publication.

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MS51

A Convection-diffusion Model for Gang Territori-

ality

Abstract not available at time of publication.

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MS51

Behavioral Contagion in Virtual Environments

The mimicking of behavior exhibited by neighboring individuals, called behavioral contagion, plays a fundamental role in how groups of organisms respond to new information. In humans, behavioral contagion is prevalent in situations ranging from normal to high stress. Though important to understand, stressful situations are impractical to reproduce in an experimental setting. Here, virtual reality presents an opportunity, however, the ability of virtual environments to elicit behavioral contagion response remains to be tested. In this study, we adapt a real-world experiment from literature for virtual environments and use it to reproduce behavioral contagion. Specifically, we create a virtual environment that consists of an interactive crowd of sixty virtual characters whose movement is determined by two established pedestrian motion models. The stimulus group comprised a subset of characters, who look up as the participants explore the virtual environment. Our results show that the probability of looking up by a participant depends on the size of the stimulus group, with this probability approaching near certainty when three or more characters look up. The strength of contagion is also affected by the stimulus group size, with larger groups resulting in more time spent looking up. Results from this study provide evidence that behavioral contagion can be triggered in virtual environments, and sets the stage for testing complex hypotheses in a variety of scenarios.

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MS51

Modeling and simulation of Multiscale Crowd Dynamics with Emotional Contagion

We developed a hierarchy of models to study the crowd dynamics coupled with emotion. The model involves movement with a speed proportional to a fear variable that undergoes a temporal consensus averaging based on distance to other agents. In the continuum limit, we observe a threshold for the the interaction distance vs. interaction timescale that produce qualitatively different behavior for the system - in one case particle paths do not cross and there is a natural Eulerian limit involving nonlocal interactions and in the other case particle paths can cross and one may consider only a kinetic model in the continuum limit. We also designed efficient numerical methods to couple the kinetic and continuum models in a multiscale setting.

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MS52

Combination Therapy in Cancer

Most clinical trials for cancer therapy fail: 70% fail in Phase 1, and 60% fail in phase 2. This is particularly the case in combination therapy, with two drugs. Mathematical models can be used to explore the correlation between the two drugs, namely, are the two drugs positively correlated at any dose amounts, or do they develop antagonism at certain amounts. Such a study will have implications in designing clinical trial more effectively. In this talk I will consider combination therapy where one of the drugs is one of the recently FDA-approved checkpoint inhibitors, anti-PD-1, or anti-CTLA-4. I will show, for several choices of a second drug, that there are zones of antagonism in the combination therapy, e.g., an increase in the drug anti-PD-1 has the effect of increasing the cancer volume. Such zones of antagonism should be avoided in clinical trials. The mathematical models are represented by systems of PDEs and the tumor boundary is a free boundary. This work is joint with Dr. Xiulan Lai.

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MS52

Analysing Aspects of Sperm Swimming Mechanics

Mammalian sperm adapt to numerous microenvironments in their function as DNA payload carriers and such responses are often physical rather than biological given, unlike most cells, sperm are generally incapable of gene expression. Furthermore, given a fertile human sample has on the scale of 100 million cells, population effects also arise. Consequently, we utilise previously published sperm microscopy, together with theoretical models and numerical simulations, with the aim of examining how the mechanics of sperm swimming can inform our understanding of how the surrounding microenvironment and population effects influence sperm behaviour.

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MS52

Modeling Heterogeneity in Solid Tumors: Emergent Patterns of Metabolism in Colon Cancer

Many solid tumors exhibit a striking phenotypic diversity that helps the tumor survive harsh circumstances such as the limited availability of nutrients, an attacking immune system or chemotherapy treatment. Here, we use multiscale mathematical modeling to investigate the emergence and consequences of non-genetic heterogeneity, focusing on colon cancer as an example. We report on a self-organizing pattern of metabolism in xenograft colon tumors where clusters of highly glycolytic cells are arranged in a regular, spotted array. To explore the basis for this pattern, we develop Turing-like reaction-diffusion equations describing the interactions between different metabolic cell types, nutrients, and growth factors. A key component of the model is Wnt signaling, a pathway known to upregulate glycolysis, which is highly active in colon cancer. The model

predicts that partial inhibition of Wnt signaling alters the patterning and the expression of factors that increase the range of Wnt ligand diffusion. These predictions are validated in xenograft tumors and are consistent with expression data in primary human colon cancer. The model also predicts that inhibitors that target glycolysis and/or Wnt signaling are not so effective as single therapies for cancer as they are in combination for synergistic reduction of tumor growth. We validated this prediction in experiments in vitro using 3D colon tumor spheroids and vascularized colon micro-tumors.

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MS52

Phase Field Modeling of Cell Polarity and Cell Delamination

Control of cellular behaviors plays a critical role in pattern formation, growth regulation and regeneration. Numerous developmental processes have been extensively studied from a mechanistic perspective, but only recently have serious efforts been directed toward systems biology approach. In this talk, I will present two biological systems to study pattern formation by using phase field model. First, we present a mathematical model that incorporates the interplays between Rac, filamentous actin (F-actin), and membrane tension for the formation of cell polarity. Second, I present a phase field approach to study the neuroblast delamination in Drosophila. Dynamics of cell ingression and role of actin-myosin network in apical constriction reveal that the myosin signaling drives neuroblast delaminiation in such rare event. The joint work with Feng Liu (PKU), Yan Yan (HKUST).

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MS53

Optimal Control Strategies for Meningitis C in Nigeria

I this talk, I will present a deterministic model for *Neisseria meningitidis*, a bacterium that causes meningitis. Data from the 2017 meningitis outbreak in Nigeria was used to parameterize the model. Optimal control theory was then applied to investigate the optimal strategy for curtailing the spread of the diseases using personal-protection such as the use of facial masks, and vaccination as control variables to the model system. The results show that the two controls avert more infections at low costs. Furthermore, there exists a reciprocal relationship between the cost of facial masks and the use of vaccine. As the cost of facial masks increases, the use of vaccine increases. Cost-effective analysis was applied to investigate the most cost-effective strategy from various combination of control strategies using three approaches, the infection averted ratio (IAR), the average cost-effectiveness ratio (ACER) and incremental cost-effectiveness ratio (ICER). The results show that personal-protection-only strategy is the most cost-effective control strategy followed by the strategy combining all the time-dependent control variables, the vaccination-only strategy performed the least. The results further suggest that governments of communities with limited resources should consider complementing the use of vaccine with the use of facial mask particularly in hard-to-reach places in their communities.

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MS53

Neighborhood Control of Vector-borne Disease

Outbreaks of vector-borne disease such as Zika virus can occur when an infected individual introduces to virus to a residential neighborhood after traveling. Vector control strategies typically involve application of larvicide or adulticide by truck or plane, as well as door-to-door control efforts that require obtaining permission to access private property. The efficacy of the latter efforts depend on the compliance of local residents. We present a model for vector-borne disease transmission in a neighborhood, considering a network of houses connected via mosquito dispersal. We use this model to compare the effectiveness of various control strategies and determine the level of compliance at which door-to-door control becomes more cost effective than aerial spraying of larvicide and adulticide.

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MS53

Spatial Dynamics of Vector Borne Diseases

Vector-borne diseases affects approximately 1 billion people and accounts for 17% of all infectious diseases. With travel becoming more frequent across the global, it is important to understand the spatial dynamics of vector-borne diseases. Host movement plays a key part on how a disease can be distributed as it enables a pathogen to invade a new environment, and helps the persistence of a disease in locations that would otherwise be isolated. In this talk, we will explore how spatial heterogeneity combines with mobility network structure to influence vector-borne disease dynamics.

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MS53

Coupled Infectious Disease Models via Asymmetric

Movements

Many recent outbreaks and spatial spread of infectious diseases have been influenced by human movement over air, sea and land transport networks, and/or anthropogenic-induced pathogen/vector movement. These spatial movements in heterogeneous environments and networks are often asymmetric (biased). The effects of asymmetric movement versus symmetric movement will be investigated using several epidemiological models from the literature. These investigations provide a better understanding of disease transmission and control in the real life application.

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MS54

Coarse-grained Membrane Dynamics in the Integral Formulation

In macroscopic model, the well-known Helfrich membrane model has been extensively studied in both physical properties and membrane dynamics well. However, some phenomena such as membrane fusion and micelle formation are not able to be reproduced in this framework due to the geometry changes. Therefore, in order to include as much as known molecular details, we study the dynamics of coarse-grained lipid bilayer membrane using Janus particle configurations to represent collections of lipids sharing same orientations. The main idea is to solve an action field due to the hydrophobic tail-tail interactions and to obtain the energy variation of the system. We also examine the amphiphilic lipid dynamics by forming force and torque in terms of integral formulations. In this talk, we will present a schematic of the proposed lipid model and the large system simulations performed by the integral equation method.

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MS54

Membrane Rotors: From Euler Vorticity Dynamics to Quasi-geostrophic Flows

Membrane hydrodynamics is intriguing due to an interplay of dimensionalities; momentum travels in the plane of the membrane at short distances, but moves through the outer fluid at larger ones, showing a crossover from 2D to 3D like behavior. Chemical reactions on the surface of a cell, therefore, require a special treatment. While it is possible to perform a Smoluchowski-like calculation in 2D to predict reaction rates in membranes, we will see that the expected rates are reduced by an order of magnitude when accounting for hydrodynamic interactions between reactants and targets. A biomembrane, however, is more than just a passive medium. ATP synthase and other proteins produce a great deal of hydrodynamic traffic. In the second part of the talk, we will explore the dynamics of active rotors embedded in a membrane. We will see a power law transition — from Euler flows at small distances ($1/r$), to quasi-geostrophic flows at large distances ($1/r^2$). We will derive a Hamiltonian for a discrete system of rotors, find the conserved quantities, and describe a coarse-grained density field of rotors. We will present theory and simulations for both the discrete and the continuous cases.

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MS54

Multiscale Modeling of Red Blood Cells Passing through the Spleen

We developed a high-efficiency multiscale modeling method to predict the stress and deformation of cells during the interactions with their microenvironments in microcirculation and microfluidics, including red blood cells (RBCs) and circulating tumor cells (CTCs). There are more than 1 billion people in the world suffering from RBC diseases. The mechanical properties of RBCs are changed in these diseases due to molecular structure alternations, which is not only important for understanding the disease pathology but also provides an opportunity for diagnostics. On the other hand, the mechanical properties of cancer cells are also altered compared to healthy cells. This can lead to acquired ability to cross the narrow capillary networks and endothelial gaps, which is crucial for metastasis, the leading cause of cancer mortality. Therefore, it is important to predict the deformation and stress of RBCs and CTCs in microcirculations. We develop a high-efficiency multiscale model of cell-fluid interaction. We pass the information from our molecular scale models to the cell scale to study the effect of molecular mutations. Using our high-efficiency boundary element methods of fluids, we will be able to run 3D simulations using a single CPU within several hours, which will enable us to run extensive parametric studies and optimization.

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MS54

Seamless Multiscale Modeling of Blood Coagulation in Thrombosis

We propose a new multiscale framework that seamlessly integrates four key components of blood clotting namely, blood rheology, cell mechanics, coagulation kinetics and

transport of species and platelet adhesive dynamics. We use transport dissipative particle dynamics (tDPD), which is the extended form of original DPD, as the base solver, while a coarse-grained representation of blood cell's membrane accounts for its mechanics. This new multiscale particle-based methodology helps us probe synergistic mechanisms of thrombus formation, and can open new directions in addressing other biological processes from subcellular to macroscopic scales.

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MS55

Using Porous Media to Bridge Multiple Scales and Guide Clinical Experiments

Modelling biological systems with the purpose of guiding and ultimately reducing clinical experiments brings a number of challenges. Crucially, biological flow processes, such as cerebral fluid dynamics, occur over multiple scales. In this talk I present the development of a model of interstitial fluid dynamics within the very narrow (200 nm) basement membranes (BM) inside the wall of cerebral arteries coupled with blood flow in the cerebral vasculature (up to mm diameter). This process is termed intramural periarterial drainage (IPAD) and experiments have shown that it constitutes a crucial part of the brain's waste disposal system. The model uses Darcy's law to represent the BM's complex protein mesh and exploits the permeability parameter K to develop a macroscopic representation of nano-scale physiological features such as a valve mechanism. First, the model was used to show that, although regarded as the most likely candidate by clinicians, arterial pulsations are not a suitable driving mechanism for IPAD. It was further applied to develop an alternative hypothesis that aligns better with clinical observations, demonstrating the usefulness of such models to evaluate and refine clinical hypotheses.

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MS55

Robust Preconditioners for the Biots Model

Poroelasticity models the processes of coupled deformable porous media flow which is crucial in many applications. An essential component, and usually the most time-consuming part of simulating coupled PDEs, is solving the large-scale and ill-conditioned linear systems of equations arising from the discretization of the Biots model. In this work, we generalize the traditional framework of block preconditioners on saddle point systems for the poroelasticity and develop effective preconditioners that are robust with respect to the physical and discretization parameters. Preliminary numerical experiments are presented to support the theory and demonstrate the robustness of our preconditioners.

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MS55

Solvers for Nonlinear Boundary Integral Equations in Bioelectrostatics

The recently introduced solvation-layer interface condition (SLIC) is a modification of the popular dielectric continuum model capable of predicting, with high accuracy, ion solvation thermodynamics (Gibbs free energies, entropies, and heat capacities) in numerous polar solvents, as well as ion solvation free energies in water–co-solvent mixtures over available concentration series. SLIC changes the classical dielectric Poisson model by adding a the macroscopic dielectric-flux interface condition at the solute–solvent interface and a microscopic interface potential (static potential). The resulting model exhibits high accuracy without the need for fitting solute atom radii in a state-dependent fashion. Our results indicate that the interface potential is essential to reproduce entropies and heat capacities. We discuss the existence and uniqueness of solutions for this nonlinear boundary integral equation, as well as applicable nonlinear solvers.

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MS55

A Biomechanistic Framework For Exploring the Risk Factors Associated with the Early Stages of Alzheimers Disease

Brain disorders such as developmental and neurodegenerative diseases represent an enormous disease burden, not only in terms of human distress, but also economic cost. Technological advances offer the prospect of improved, clinically relevant predictive information for diseases of old age. Modelling the transport of fluid within the brain, in a personalised manner and from first principles, is essential to help decipher some of the underlying mechanisms that are currently being investigated. Multiple-Network Poroelastic Theory (MPET) is used to develop a 3D spatio-temporal model of perfused cerebral tissue. It will be shown that the MPET based model, coupled with an image-based model personalisation workflow and a blood flow variabil-

ity model, can provide valuable insight into the underlying mechanisms of Alzheimers Disease (AD). AD is the most common form of dementia, a clinical syndrome of progressive deterioration of cognitive abilities and ordinary daily functioning. In its early stages, AD presents itself as mild cognitive impairment (MCI), a state between normal ageing and dementia. In this work, 35 subject-specific datasets were used (n = 20 controls, and n = 15 MCI cases) to conduct simulations using the consolidated poroelastic pipeline. Subsequently, 28 regions of the brain parenchyma were analysed. This workflow can provide novel insight into the region-specific complexity of the solution fields allied to waste clearance, swelling and blood perfusion.

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MS56

Symmetries Constrain Dynamics in a Family of Balanced Neural Networks

We examine a family of balanced excitatory/inhibitory firing-rate neural networks, and find that this system may be described as a perturbation from a system with non-trivial symmetries. We analyze the system using the tools of equivariant bifurcation theory and demonstrate that symmetry-implied structures remain evident in the perturbed system. Finally, we show that something similar can happen in networks with excitatory clusters and global inhibition.

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MS56

Cholinergic Modulation of Synchronization in Excitatory-inhibitory Neural Networks

The characteristics of neural network activity depend on intrinsic neural properties and synaptic connectivity in the network. In brain networks, both of these properties are critically affected by the type and levels of neuromodulators present. The expression of many of the most powerful neuromodulators, including acetylcholine (ACh), varies tonically and phasically with behavioral state, leading to dynamic, heterogeneous changes in intrinsic neural properties and synaptic connectivity properties. At the cellular level, ACh significantly alters neural excitability and firing properties as measured by the phase response curve (PRC) in a manner that has been shown to alter the propensity for network synchronization. In this talk, Ill discuss our investigations into the interaction of cellular ACh modulation and network connectivity structure in excitatory and inhibitory neural networks. Our results analyze the influence of this interaction on determining spatio-temporal network activity patterns and potential functional effects of network activity pattern modulation.

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MS56

Geometric Analysis of Synchronization in Neuronal Networks with Global Inhibition and Coupling Delays

We study synaptically coupled neuronal networks to identify the role of coupling delays in network's synchronized behaviors. We consider a network of excitable, relaxation oscillator neurons where two distinct populations, one excitatory and one inhibitory, are coupled and interact with each other. The excitatory population is uncoupled, while the inhibitory population is tightly coupled. A geometric singular perturbation analysis yields existence and stability conditions for synchronization states under different firing patterns between the two populations, along with formulas for the periods of such synchronous solutions. Our results demonstrate that the presence of coupling delays in the network promotes synchronization. Numerical simulations are conducted to supplement and validate analytical results. We show the results carry over to a model for spindle sleep rhythms in thalamocortical networks, one of the biological systems which motivated our study. The analysis helps to explain how coupling delays in either excitatory or inhibitory synapses contribute to producing synchronized rhythms.

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MS57

Development of an Expression-based Mathematical Model of Human iPSC-derived Cardiomyocytes Electrophysiology and Ion Handling to Evaluate Drug-induced Arrhythmia Sensitivity

The Comprehensive in vitro Proarrhythmia Assay (CiPA) initiative, sponsored by an international consortium, promotes the coupling of in vitro experimental assays with theoretical models of cardiomyocyte electrophysiology and ion handling to assist in the prediction of cardiac torsadogenic drug risk. The mathematical model of the cardiomyocyte currently selected by CiPA, the OHara-Rudy model (ORd), was developed to simulate electrophysiology and ion handling of human adult ventricular cardiomyocytes (hAVCMs) and not explicitly for human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CMs). To reconcile differences between these similar yet different cell types, we have developed a model of the hiPSC-CM by incorporating differences in gene expression of selected ion channels, exchangers, receptors and pumps in iPSC-CMs against those found in hAVCMs. This expression-based hiPSC-CM model developed recapitulates many of the differences seen experimentally in hiPSC-CMs. Even more importantly this expression-based model can be tuned to easily capture variability between cell lines and even batches within a line. This is critical for the evaluation

of drug-induced torsadogenic risk based on results from hiPSC-CM testing. We will show how this expression-based hiPSC-CM model is optimized for a given experiment and how these tuned models can then be used to reproduce electrophysiological and ion handling changes when exposed to dofetilide, a known pro-arrhythmic drug.

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MS57

Computation of Electrostatic Binding Energy of Solvated Protein Complexes

The Poisson-Boltzmann (PB) implicit solvent model is a popular approach to studying the electrostatics of proteins surrounded by water with dissolved salt. Here we apply the treecode-accelerated boundary integral (TABI) PB solver to compute the electrostatic binding energy of solvated protein complexes. Results using the MSMS and NanoShaper molecular surface triangulation codes are compared. Extrapolation is used to improve the accuracy of the computed binding energy. The boundary integral results are benchmarked by comparison with the high-order finite-difference Matched Interface and Boundary (MIB) solver.

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MS57

New Nonlocal Poisson-Fermi Double Layer Models for Mixtures of Multiple Ion Species

In this talk, I will report a new nonuniform ionic size nonlocal Poisson-Fermi double layer model (nuNPF) and a new uniform ionic size Poisson-Fermi double layer model (uNPF) for electrolyte mixtures of multiple ionic species, variable voltages on electrodes, and variable induced charges on boundary segments. I then will introduce their fast finite element solvers for typical double layer problems defined on a rectangular box, a hollow sphere, and a hollow rectangle with a charged post. Numerical results show that nuNPF can significantly improve the quality of the ionic concentrations and electric fields generated from uNPF, implying that the effect of nonuniform ion sizes is a key consideration in modeling the double layer structure.

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MS57

Phase Field Model for Cell Motion in Vessel

A model derived by using the Energetic Variational Approach and the phase field method, is developed for simulating deformation and detachment of red blood cell passing through a narrow channel. The general slip boundary condition is used to simulated the interaction between red blood cell and blood vessel wall. An effcient energy stable numerical method is proposed to solved the obtained system. Effects of smoothness and adhesion of channel on red blood cell deformation and movement are studied. Red blood cells with different mechanical property are also used to explain the pathological risk for patient with sickle cell.

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MS58

Finding Identifiable Reparametrizations of Monomolecular Networks using Scaling Symmetry

Structural identifiability deals with the question of whether or not it is possible to uniquely determine values of unknown parameters of a model from given data. Monomolecular networks, or linear compartmental models, are linear ODE models used in pharmacokinetics and are encoded in a labelled directed graph. Many such models are unidentifiable: parameters can take on an infinite number of values and yet yield the same input-output data. In this work, we generalize previous work of Meshkat and Sullivant using techniques of Hubert and Labahn. For a certain class of unidentifiable linear compartmental models, we show how an identifiable reparametrization can be found using scaling symmetries. More generally, even when an identifiable reparametrization is not possible, using scaling symmetries leads to reparametrizations that are one step closer to being identifiable.

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MS58

Identifiability from a Few Variables in Biochemical Reaction Networks

Under mass-action kinetics, biochemical reaction networks induce a polynomial autonomous system of differential equations. The problem of identifiabilty of the parameters of the system has been broadly studied under different approaches. We define the concept of identifiability from a reduced set of variables and analyze a family of biochemical networks where we are able to identify all the reaction constants from a few biologically relevant variables. In particular, we prove that all the parameters in a signaling cascade system can be identified from one variable, corresponding to the last product of the last layer.

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MS58

Investigating Multistationarity in Structured Reaction Networks

Many dynamical systems arising in applications exhibit multistationarity (two or more positive steady states), but it is often difficult to determine whether a given system is multistationary, and if so to identify a witness to multistationarity, that is, specific parameter values for which the system exhibits multiple steady states. Here we investigate both problems. We prove two new sufficient conditions for multistationarity: (1) when there are binomial steady states and a certain critical function changes sign, and (2) when the steady-state equations can be replaced by equivalent triangular-form equations. We also investigate the mathematical structure of this critical function, and give conditions that guarantee that triangular-form equations exist.

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MS58

Revisiting a Synthetic Intracellular Regulatory Network that Exhibits Oscillations

In 2000, Elowitz and Leibler introduced the *repressilator* – a synthetic gene circuit with three genes that cyclically repress transcription of the next – as well as a mathematical model describing it. In 2006, Müller et al. generalized the model for an arbitrary number of genes and analyzed the possible steady states, the stability of the steady states, and the possible asymptotic behavior. These previous models assume first-order transcription, translation, and degradation, with rates equivalent among genes, mRNAs, and proteins, respectively. This assumption, however, is not consistent with current biological knowledge. Accordingly, we propose a new repressilator model allowing for differing transcription, translation, and degradation terms. We show that, under conditions on these new functions, there is still a unique steady state when an odd number of genes are in the network. We also show that, with an odd number of genes, either the model converges to the steady state or to a periodic orbit. Finally, we compare fits of current repressilator data under the old and the new models. Fitting the data with the new model leads to key insights into the dynamics of repression and degradation and helps answer questions such as: How many repressors are necessary to inhibit transcription? How are certain proteins degraded?

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MS59

Competitive Advantages of Three-dimensional Structure and Mechanical Robustness for Biofilms

Biofilms are communities of microbes that are bound to each other, and frequently to surfaces, by a matrix of polymers and proteins. As a result, biofilms have mechanical properties, of adhesion and cohesion, and structural properties in the form of fixed spatial arrangements of microbes in three dimensions, that are not present for the same types of microbes in their non-biofilm state. Recent work from our lab shows that cohesive forces between constituent microbes help biofilms resist clearance by the immune system (unpublished). Other work, by ourselves and collaborators, shows that three-dimensional spatial structure can help biofilms out-compete single cells (2016 mBio). I will present a brief sketch on both of these results and indicate how we anticipate that mathematical modeling could help guide the development of new types of approaches to combating biofilms. These approaches would target mechanical and structural properties, and therefore would be orthogonal to extant approaches to preventing and remediating biofilms. Standard molecular and genetic mechanisms for antibiotic resistance will not impinge on the mechanical anti-biofilm approaches we propose, which therefore will provide no selective pressure promoting the evolutionary development of antibiotic resistance.

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MS59

Building Microbial Communities from the Bottom Up

Microbes exist in complex, multi-species communities with

diverse interactions that play an essential role in both human health as well as the health of the planet. Over the last decade tremendous progress has been made in characterizing these communities, but the lack of experimentally tractable model systems has made it difficult to discern the rules governing microbial community assembly and function. In this talk I will describe our recent experimental efforts to develop a bottom-up approach to understanding the dynamics of these communities. We have begun by quantifying the network of pairwise competitive outcomes among species within a model microbial community. We find that simple assembly rules incorporating just these pairwise competitive outcomes are surprisingly successful in predicting the outcome of multi-species competition in multiple environments as well as within the gut of the worm, indicating that higher-order interactions among species can often be neglected. Guided by simple mathematical models, we now have a predictive understanding of how pairwise competitive outcomes change as the environment deteriorates. Given that these pairwise outcomes are typically predictive of multispecies outcomes, we are in a position to predict how multispecies community composition changes as the environment changes. These results are a first step towards a bottom-up approach of predicting the emergent behavior within complex multi-species communities.

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MS59

Dynamics of Viral Evolution and Mutation

We study a model of viral evolution, in which viruses have a barrier to cell entry, mediated by their match to cell "key", followed by a viral-type dependent immune response by the cell, and finally a probability to reproduce and mutate. These mutated viruses then go on to attack other cells in the model. Previously we found steady state behavior, featuring a phase transition as a function of temperature and immunity [Barbara A. Jones , Justin Lessler, Simone Bianco, and James H. Kaufman, "Statistical Mechanics and Thermodynamics of Viral Evolution," PLOS One 0137482 (2015)]. Here we describe our computational studies of the behavior of this model as a dynamical system, and the nonequilibrium evolution of the quasispecies distribution including metastable states and other unexpected features. The states on either side of the phase transition can be considered to represent viruses with different survival strategies. We have found evidence of this competition between strategies as well in the dynamical properties including growth rate.

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MS59

Designing Novel Antivirals using Viral Defective Interfering Particles

Defective interfering particles (DIPs) are viral deletion mutants lacking essential elements to complete their cycle. They need to co-infect cells with the wild-type (WT) virus to steal its essential elements, complete their cycle and further propagate. Because they hinder WT virus, engineered DIPs have been proposed as therapies for a number of diseases. Here we will focus on WT poliovirus and associated DIPs lacking genes encoding for capsid proteins. We use a combination of mathematical modeling and competition experiments to understand the mechanisms of action of DIPs and identify critical parameters to drive the design of efficient DIPs against WT infection. At the intracellular level, competition between DIPs and WT was found to rely on capsid proteins produced by WT and limiting resources necessary for replication. At the intercellular level, a Susceptible-Infected based model relying on intracellular parameters helped us identify intracellular competition as the most important process for the success of DIP at this higher level. Poliovirus studies are important as emerging strains have appeared following massive vaccination. Poliovirus was extensively studied in the last decades and thus represents a model for positive-sense single-stranded RNA viruses (e.g. Dengue, Zika). Accordingly, we would like to generalize the developed models to additional viral species, and build models for the host and epidemiological levels.

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MS60

Study of how Regulation of Mechanical Properties of Stem Cells in Plants Determines Shape of a Developing Tissue

One of the central problems in animal and plant developmental biology is deciphering how chemical and mechanical signals interact at the cellular and tissue level to regulate cell behavior within a tissue and produce the final shape, size and function of an organ. To address this problem, a novel, multi-scale, cell-based computational model of the stem cells of the shoot apical meristem (SAM) of Arabidopsis thaliana is developed and calibrated using experimental data. Novel biologically relevant features of the model include separate representations of the cell wall and cytoplasm as well as a detailed description of cell growth, cell wall extensibility and average internal cellular pressure. Model predictive simulations reveal relative impacts of cell wall mechanical properties and chemical signals controlling growth rates on overall shape of SAM as well as corresponding distribution of internal pressure across stem cells. Model simulations also show how distributions of mechanical properties of cell walls across the SAM cross-section contribute to the generation of curvature and relate cell growth rates and distribution of pressure across different layers to the magnitude and duration of asymmetric wall softening. This suggests a possible novel SAM growth mechanism to be tested in experiments. (Joint work with Mikahl Banwarth-Kuhn and Ali Nematbakhsh.)

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MS60

Microscopic and Macroscopic Descriptions of Transport in Epithelial Tissues

Morphogens such as Dpp and Wg in Drosophila or Shh in vertebrates play significant roles in cell fate determination and pattern formation during development. How morphogens that are produced in a restricted region of a tissue are transported to form a concentra-

tion gradient is still controversial. In the Drosophila wing disc, for instance, various mechanisms have been proposed to explain Dpp morphogen transport, including free diffusion, restricted diffusion, planar transcytosis and cytoneme-mediated transport. Here we investigate various microscale-level mechanisms to determine how the observed macroscale transportation rates depend on microscale mechanisms. The motivation for this is to understand the vast discrepancy between values of transport parameters measured in tissues using different experimental techniques.

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MS60

Multi-scale Models for Hair Follicle Regeneration and Embryo Development

Many biological processes in developmental systems require an intricate and well-coordinated regulation of spatial-temporal dynamics at multi-scales. How to incorporate the dynamics at different scales in one system is a big challenge in modeling of developmental systems. We developed several multi-scale models for different systems to study the dynamics in system development and pattern formation, which include: 1) a 3D agent-based model for hair follicle development and wave propagation, where follicle growth is regulated by the coupling of activator/inhibitor signaling that is described by stochastic PDE, and we show that the co-option of these signals into skin macro-environment produces wave-like coupled hair growth; 2) a model for single hair follicle growth dynamics with cellular resolution, where we explore a more detailed signaling network regulating the follicle cell lineage dynamics and the follicle structure development; 3) hybrid models for pattern formation during embryo development, with gene regulation network described by stochastic PDEs/ODEs and cells modeled by sub-cellular element method, where we explore how global information incorporated chemical signaling directs cell fate decision making and guides cell movement.

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MS60

The Role of Intracellular Signaling in the Stripe Formation in Engineered E. Coli Populations

Recent experiments showed that engineered Escherichia coli colonies grow and self-organize into periodic stripes with high and low cell densities in semi-solid agar. The stripes establish sequentially behind a radially propagating colony front, similar to the formation of many other periodic patterns in nature. These bacteria were created by genetically coupling the intracellular chemotaxis pathway of wild-type cells with a quorum sensing module through the chemotaxis protein CheZ. In this paper, we developed multiscale models to investigate how the intracellular pathway affects the stripe formation. We first developed a detailed hybrid model that treats each cell as an individual particle and incorporates intracellular signaling via an internal ODE system. To overcome the computational cost of the hybrid model due to the large number of cells involved, we next derived a mean-field PDE model from the hybrid model using asymptotic analysis. The analysis is justified by the tight agreement between the PDE model and the hybrid model in 1D simulations. Numerical simulations of the PDE model in 2D with radial symmetry agree with experimental data semi-quantitatively. Finally, we used the PDE model to make a number of testable predictions on how the stripe patterns depend on cell-level parameters, including cell speed, cell doubling time and the turn-over rate of intracellular CheZ. (Joint work with Min Tang and Xiaoru Xue)

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MS61

Modeling of Leptospirosis in Cattle

As one of the most widespread zoonotic diseases, Leptospirosis became endemic particularly in tropical and subtropical regions where the environment provides favorable conditions for propagation of the disease. It causes large economic loss in the livestock industry. In this talk, we introduce a SVIR dynamical system of ordinary differential equations with impulse action of vaccination at certain times in order to investigate whether the disease can be controlled with current vaccine schedules. Some analytical and numerical results will be presented.

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MS61

How Should we Model Environmental Transmission?

Many pathogens are able to infect hosts via the abiotic environment without direct contact between hosts. Existing mathematical models that include environmental reservoirs and environment-to-host transmission have model formulations that vary extensively without a clear scaling with respect to the environment or connection to the underlying mechanisms. Model insights on the ecology and evolution of pathogens and recommendations regarding disease control and surveillance are sensitive to underlying model assumptions. Therefore, there is a critical need to better characterize the appropriateness of environmental transmission formulations to accurately represent disease dynamics for pathogens with different natural histories and survival strategies in the environment. We discuss the role that non-host environments play on various pathogens life cycles and the implications of different transmission functions in modeling environment-to-host transmission. Some guidelines for deciding how to model environmental transmission are presented.

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MS61

Identifiability and Parameter Estimation of Multiple Transmission Pathways

Connecting dynamic models with data to yield predictive results often requires a variety of parameter estimation, identifiability, and uncertainty quantification techniques.

Here, we will examine how parameter estimation and disease forecasting are affected when examining disease transmission via multiple types or pathways of transmission, using polio and cholera as examples. We will examine how different pathways affect spatial transmission of infection, and illustrate some of the potential difficulties in estimating the relative contributions of different transmission pathways. We will also show how alternative data collection may help resolve this unidentifiability.

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MS61

Preemptive Intervention Strategies on Disease Networks

The risk of disease outbreaks on a network is important when considering where intervention strategies should be focused. The problem is intensified when considering uncertainty among regions within a network. We investigate questions of disease intervention, given uncertainty about the regions and where an outbreak occurs. We seek answers to the the problem of minimizing the costs while also lowering the expected network reproduction number below some desired threshold. We compare results to outbreak scenarios with intervention. This problem is relevant due to the current debate on the oral cholera vaccine global stockpile, how many doses should be requested, and how vaccines should be deployed.

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PP1

Mathematical Model for Cell Motility in the Unicellular Dictyostelium Discoideum Amoeba

Dictyostelium Discoideum is a soil-living amoeba which moves by making pressure driven protrusions of its plasma membrane, referred to as blebs. The location along the cell membrane where blebs form is influenced by membrane curvature, strength and distribution of membrane-cortex linker proteins as well as local pressure differentials. In this work, we extend an existing membrane energy model to include local pressure variation along the cell membrane and use it to study the characteristics of bleb nucleation sites.

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PP1

Testing Animal Motility Estimation Methods Using Simulations

The availability of land classification data sets and GPS location data has greatly impacted ecological studies. However, incorporating this data into meaningful spatial models can be challenging. Ecological diffusion models connect animal movement to heterogeneous landscapes through motility parameters (constants with units of area/time). Combining ideas from resource selection analysis and a homogenization technique for ecological diffusion, we devise a way to estimate motilities from land cover and GPS location data. With simulated landscapes and animal movement paths we test these methods. Motilities can then be incorporated into spatial models dealing with invasive spread, spread of disease, habitat use or population dynamics.

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PP1

A Boundary Integral Approach for Protein Electrostatics with Polarizable Force Fields

Using a continuum electrostatic description, a dissolved biomolecule can be represented as a cavity immersed in an infinite dielectric. Mathematically, this yields a coupled system of the Poisson equation inside the cavity, and the Poisson-Boltzmann equation in the solvent, interfaced by the molecular surface. This system of partial differential equations can be rewritten as a set of integral equations on the solute-solvent interface, reducing the dimensionality of the problem, and we solve it with a boundary element method. The charge distribution inside the biomolecule is obtained by means of a force field, which usually places point charges at the location of the atoms. However, more advanced force fields have emerged lately, that consider higher order multipoles and polarizability. One popular polarizable force field is AMOEBA. In this work, we will show that a boundary integral approach is ideal for point-multipolar descriptions, due to the analytical treatment of the charge distribution. Moreover, we will present an implementation of the boundary integral Poisson-Boltzmann solver PyGBe that is compatible with the AMOEBA force field, demonstrating validation results and tests for medium to large sized biomolecules.

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PP1

Spatial Modeling of Intracellular Calcium Dynamics in Branched Astrocyte Processes

Several contemporary studies show that astrocytes, a type of glial cell, are fundamental to a variety neural functions ranging from metabolic support to higher cognition such as recollection memory. This has led to the introduction of astrocytic dynamics into neural modeling. Most cellular functions in astrocytes are triggered by an increase or decrease in calcium concentration within the cytosol. Previous work treated astrocytic dynamics by representing calcium concentration as a point source or a completely spatial model in the cell. We now know that the role of the astrocyte takes many different perspectives. This work,

which is inspired by in vivo recordings of astrocytes in the ferret visual cortex, models the different levels of astrocytic calcium activity in the astro-neural system. In the model, we create a framework to enable the exploration of spatial calcium dynamics in astrocytes. Astrocyte processes are modeled as one-dimensional branches, over which we solve a system of reaction-diffusion equations for intracellular calcium dynamics. A branching structure, while not as general as a full 2D or 3D spatial simulation allows the study of astrocytes cellular properties over extended regions of space. Studying a spatial representation of the processes will help investigate the role of astrocyte morphology in calcium signal propagation as well as developing intuition on the functional relationship between different levels of activity in the cell.

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PP1

The Lorenz Attractor, a Model for Pigeon Flocking (with Constraints)-the Computer Program "BOIDS"

The Lorenz Attractor, first studied by Edward Lorenz, consists of a system of three (3) ordinary differential equations, which represents a simplified model of atmospheric convection. Under certain conditions (if the pigeons fly inside a hollow cube the size of a two-story building), the Lorenz Attractor can model pigeon flocking adequately. However, bird flocking has been modelled also by the computer program "Boids," first developed by Craig Reynolds. "Boids" operates under three (3) constraints: separation, alignment, and cohesion. We will attempt to show how the three (3) differential equations of the Lorenz Attractor correspond roughly to the three (3) constraints of the program "Boids." This constitutes a specific example of how a process in nature can be modelled by chaos theory, simply using computer graphics routines. This method is simpler than the various numerical methods which may be used to solve a given Lorenz system–in the absence of exact, analytic solutions.

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PP1

The Role of Viral Advection and Diffusion in Lower Respiratory Tract Infections

Lower respiratory infections (LRI) can cause longer infections, lingering respiratory problems, and higher incidence of hospitalization, and are particularly common in young children and the elderly. There are two viral transport mechanisms within the respiratory tract (RT): diffusion moves the virus both up and down the RT while advection via the mucociliary escalator drives virus upward. We use a model of viral dynamics in the respiratory tract to study the role of transport mechanisms in the occurrence of LRI. We find that a range of diffusion and advection values lead to long-lasting infections in the LRT, elucidating a possible mechanism for the severe LRI infections observed in humans.

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PP1

Predictive Effectiveness of On-demand Pre-exposure Prophylaxis to Prevent HIV

An important strategy for preventing HIV infection involves taking a drug in case of exposure. Continuous, daily dosing, with the first dose administered a full month before the initial high-risk incident, is the current CDC recommendation for preventing infection. However, the IPERGAY study showed that taking only three doses - one before and two following exposure to HIV - may prevent HIV infection almost as effectively as continuous dosing, with the added benefit of smaller quantity of drugs being administered. This is called on-demand PrEP. For this latter strategy, uncertainty exists around the optimum time to start treatment as well as how many doses to take. To address this question, we developed and analyzed a mathematical model of early infection and pre-exposure prophylaxis of HIV infection based on virus dynamics and the pharmacokinetics of existing HIV drugs. We ran simulations and analyzed the results in order to come up with testable predictions and recommendations on the best strategies for disease prevention with regards to when to start and stop treatment and the frequency and size of doses, within the range one is safely permitted to take.

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PP1

Incentivizing Hospital Infection Control

The emergence of antimicrobial resistance (AMR) is a serious danger to global public health and significantly affects our ability to prevent and treat a wide variety of infections. Of particular importance is transmission within hospitals, where AMR infections are most prevalent despite various hospital infection control (HIC) measures. A large investment in HIC within one hospital may be fruitless if none of the surrounding hospitals are also reducing transmission within their respective wards. While globally, all hospitals in a region benefit by coordinating infection control, it may be economically optimal to free-ride on others infection control efforts. It can be difficult to encourage hospitals or HMOs to cooperate with one another. Since autonomous hospitals (or similarly segregated populations) may choose a level of infection control lower than that recommended globally by a public health authority, governments can offer subsidies or other funding support as incentives to encourage spending. Given that funding may change behavior, how should subsidies be allocated between hospitals? Here we develop coupled mathematical models of epidemiology and hospital behavior in a game theoretic framework to investigate how hospitals change spending behavior in re-

sponse to subsidies.

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PP1

Modeling the Role of Feedback in the Adaptive Response of Bacterial Quorum Sensing

Bacterial Quorum Sensing (QS) is a form of intercellular communication that relies on the production and detection of diffusive signaling molecules called auotinducers. Such a mechanism allows the bacteria to track their cell density, in order to regulate group behavior, such as biofilm formation and bioluminescence. In a number of bacterial QS systems, including *V. harveyi*, multiple signaling pathways are integrated into a single phosphorylation-dephosphorylation cycle. In this paper, we propose a weight control mechanism, in which QS uses feedback loops to 'decode' the integrated signals by actively changing the sensitivity in different pathways. This allows bacteria to have a finer discrimination of their social and physical environment.

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PP1

Inferring Interacting Dynamics of Molecular Motors on the Curved Surface of a Microtubule

Molecular motors actively transport cargo along microtubules through the cytoplasm to where the are needed within cells. More than one type of motor can be attached to a single cargo, such as a kinesin which moves towards the plus end of the microtubule and dynein which moves towards the negative end. Why are there contra-directional motors simultaneously attached, and how are they regulated? To study this system, gold nanoparticles are attached to DNA origami, which functions as a type of artificial cargo with a fixed number of binding site specified for kinesin and dynein, and then tracked as the motors move the DNA origami on the microtubule. The high spatial and temporal sampling rates possible with gold nanoparticles means that movements around the curved surface of the microtubule must be taken into account in addition to the movement along the axis. A stochastic model along with tracking protocols and statistical inference techniques will be presented for this system.

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PP1

Childhood Obesity Trends in South Carolinas Beaufort, Hampton, and Jasper Counties

Obesity is a growing health hazard in the United States where more than one in three adults are obese, according to the National Health and Nutrition Examination Survey. Also, about one in three children and teenagers are considered to be overweight or obese in the country. In South Carolina, according to The State of Obesity, for 10-17 year olds, the combined overweight and obesity rate as of 2016, is 32.9%, which is ranked 17 (out of 51). It was also reported that South Carolina is the 12th most obese state in the US. For our research, data has been collected from South Carolinas Beaufort, Hampton and Jasper County schools consisting of 3rd, 5th, and 8th grade students body mass index (BMI) starting from 2006. These counties have a high percentage of obese or overweight students and when analyzing this data further into race, gender and socioeconomic status between the students, the proportions of obese and overweight students differ greatly. Using mathematical modeling with ordinary differential equations may help us quantify these key differences and possibly deter sustained high percentages of childhood obesity locally. Further understanding these existing differences will allow us to have a more knowledgeable base on where to start when working towards declining the high rate of childhood obesity in our Lowcountry schools, which will hopefully lead towards nationwide change.

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PP1

Extreme-value Approximation to a Multi-scale Model of Cargo Transport by Multiple Molecular Motors

We present a system of stochastic differential equations that model cargo transport by multiple molecular motors. Exploiting separation of scales renders an analytical approximation using extreme-value theory. In the microscopic level, free heads of motors are undergoing tethered diffusion as a stationary Gaussian process and have a chance to bind when they are near a binding site. Within biological-relevant parameter regions, it is approximately a level crossing problem, for which extreme-value theory gives distribution of time between upcrossing and time above the level. Combined with the functional central limit theorem, stepping of a single motor can be characterized. Finally those information is used in the mesoscopic level to study cargo dynamics. This approximation is then compared to numerical simulation. The connection with classical Kramers approximation for chemical reactions is drawn.

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PP1

Influence of Receptor Recharge on the Statistics of Captured Particles

We consider a setup in which n particles are initially released into a domain and diffuse freely. Part of the boundary consists of absorbing "escape" regions, where the particles can escape the domain, and reflecting regions. The rest of boundary consists of "capture" regions (receptors), that can switch between being reflecting and absorbing. Specifically, after capturing a particle, the capture region becomes reflecting for an exponentially distributed amount of time (recharge time). We are interested in the distribution of the number of particles that are captured before they escape. Our mathematical results are derived from considering our system in several ways: as a full spatial diffusion process with recharging traps on the boundary; as a continuous-time Markov process approximating the original system; and lastly as a system of ODEs in a mean-field approximation. We prove that the total expected number of the captured particles has an upper-bound of the order of (log n). We also find that the amount of variation observed in the total number of captured particles varies non-monotonically with the mean recharge time. Further, we investigate the average number and variance of captured particles as a function of time over a range of parameters, which allows us to predict distributions of intracellular signals resulting from receptor activation. Lastly, we discuss implications of our findings in some applications such as neuronal synapses and ambush predators.

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PP1

Why Might Plants Prefer Smart Herbivores?

Plants survive by, among other things, not being eaten. Toward this end, plants invest in a variety of defenses, from secondary metabolites to physical barriers. These protections can also shield their neighbors, a trait called associational resistance. The effectiveness of associational resistance depends on herbivore behavior. To study this phenomenon, we build a model where sets of defended and undefended plants are mixed in heterogeneous patches. Herbivores choose how long to feed on each plant, as well as when to leave a patch entirely to search for another. We study herbivores that range from completely random to optimal foragers, where optimal behavior is found by extending the marginal value theorem to a hierarchical spatial arrangement. We show that for plants to exhibit associational resistance, the driving mechanism must include intelligent herbivores. We also find conditions for herbivore behavior and plant communities under which defended or undefended plants benefit the most.

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PP1

Stochastic Nucleation via Autocatalytic Reactions

The Min system (critical for cell division in E-coli) has been demonstrated to produce a variety of patterns when purified and allowed to react in a artificial environment (Vecchiarelli 2016). In particular, for certain concentrations it produces previously unexplored 'burst' and 'mushroom' patterns. Here we explore the types of instability required to generate burst patterns in a PDE, using a mixture of analytic and numerical techniques.

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PP1

A Mathematical Model of Thrombin-fibrin Interactions

To form a blood clot, either pathologically or in response to an injury, a complex network of coagulation reactions take place and culminate in the production of the enzyme thrombin. Thrombin plays many roles in the clotting process; it is associated with multiple positive and negative feedback loops and cleaves fibrinogen into fibrin, which polymerizes to form a stabilizing gel matrix in and around the clot. Another important role for thrombin is its binding to the fibrin gel matrix, but it is not yet understood whether this role has beneficial or pathological consequences; both have been hypothesized. Thrombin is sequestered by fibrin through two binding events typically described as either high- or low-affinity. It has been shown experimentally that thrombin incorporated into a preformed fibrin matrix stays bound for long periods of time and is resistant to removal by flow and chemical inhibitors. However, the kinetic rates for these interactions found in the literature do not support these data. It has been shown that thrombin-fibrin interactions are bivalent, with binding occuring between multiple sites on thrombin and on fibrin. Here we present a mathematical model that tracks a mobile thrombin species, able to diffuse and advect, in the presence of a static fibrin matrix that includes bivalent interactions. Preliminary results suggest that the bivalent interactions aid in long-term residency of thrombin bound to fibrin.

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PP1

Mathematical Models of Cytoneme-based Morphogen Gradient Formation

Morphogen gradients play an important role in the spa-

tial regulation of patterning during embryonic development. The most commonly accepted mechanism for gradient formation is diffusion from a source combined with degradation. Recently, there has been growing interest in an alternative mechanism, which is based on the direct delivery of morphogens along thin, actin-rich cellular extensions known as cytonemes. In this poster, we develop several different possible transport models based on mechanisms that have been suggested by experimental studies. First, we build an advection-diffusion transport model for active motor-based mechanism along a fixed length cytoneme imposing absorbing, synaptic and stochastically-gated boundary conditions. Next, we revisit the Dogterom-Leibler model for an active transport of a cluster of morhpogens at the tip of a growing signaling cytonemes. By solving the steady-state transport equations, we show how a morphogen gradient can be established, and explore how the mean velocity of the transport affects properties of the morphogen gradient such as conductance of transport and accumulation time. We then investigate the effects of non-uniformly allocating morphogens to the various cytonemes projecting from a source cell. This competition for resources provides a potential regulatory control mechanism not available in diffusion-based models.

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PP1

Diffusion in an Age-structured Randomly Switching Environment

Age-structured processes are well known in population biology, where birth and death rates often depend on the age of the underlying population element. Recently, however, a different example of an age-structured process has been considered in the context of cell motility or certain types of ion channels, where the state of the system is determined by a switching process with transition rates dependent on some combination of density and the residence time in the current state. We look at an extension of work previously done by Lawley and Bressloff with switching boundary conditions, in the case with purely time-dependent switching rates. We show that the expected spatial distribution of the diffusion equation under these conditions satisfies a certain class of differential equations. In particular, the long-time behavior of the moments can be determined even when the boundary switches between Neumann and Dirichlet boundary conditions.

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PP1

Silencing Hub Cells in the Pancreatic Islets

Characterized by elevated blood sugar levels, diabetes jeopardizes the health of many people worldwide. Cells absorb glucose as a primary source of energy with the assistance of insulin secreted from pancreatic β cells. In non-diabetic patients, insulin secretion is pulsatile, but this is often lost in diabetic patients. In the pancreas, β cells are organized in clusters of electrically coupled cells called the islets of Langerhans. Recently the democratic paradigm of islet secretion with more or less equal input from each β cell has been called into question with the discovery of more functionally connected hub cells. We have begun to test the hub hypothesis using network analysis on hexagonal-close-packed-lattices with a model representing the electrical and calcium dynamics of β cells during secretion. Utilizing methods from graph theory on a map constructed from functional connectivity, small worldness was observed in the networks for certain coupling strengths, confirming results in published experimental and computational work. It has also been shown experimentally that silencing cells with the most functional connections can disrupt the synchrony of the islet's activity. Through constructing networks with certain specifications, we have been able to computationally replicate the reduction of synchronous behavior. This work was initiated as part of the NSF-REU (#1460652) with Elise Falgout, Destiny Frett, Lorenzo Neil, and Ryan Schumm.

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PP1

Modeling Waves in Early Embryonic Drosophila Cells

Cells within multinucleate Drosophila embryos early in their development display dynamically interesting behavior. Throughout the first thirteen cell divisions, desynchronization occurs amongst the cells resulting in the propagation of waves through the embryo. We model the cell cycle with a Response-Signalling model with one signalling and two response regions to account for both positive and negative feedback in cell interactions. We construct a return map for finite numbers of cells and use it to analyze the dynamics of the system. We show that the observed waves can be accurately modeled and are directly related to the spatial configuration of a Drosophila embryo early in development.

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PP1

Stochastic Modeling of Viral Coinfection in the Human Respiratory Tract

Respiratory coinfections are commonly found in patients hospitalized with influenza-like illness, but it is not clear whether these infections are more severe than single infec-

tions. Mathematical models can be used to help understand the dynamics of respiratory viral coinfections and their impact on the severity of the illness. Most models of viral infections use ordinary differential equations (ODEs) which reproduce the average behavior of the infection, however, they might be inaccurate in predicting certain events because of the stochastic nature of the viral replication cycle. Stochastic simulations of single virus infections have shown that there is an extinction probability that depends on the size of the initial viral inoculum and parameters that describe virus-cell interactions. Thus the coexistence of viruses predicted by the ODEs might be difficult to observe in reality. In this work we develop a stochastic numerical implementation of the deterministic coinfection model using the Gillespie algorithm. Stochastic extinction probabilities for each viruses are calculated analytically and will be verified by stochastic simulations. Preliminary analyses of the model have showed that even if the two viruses are given the same initial growth rates, one virus can have higher probability of extinction than the other, namely competitive exclusion, opposing the coexistence cases predicted by the deterministic model.

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PP1

Simulating Animal Movement on Landscapes with Barriers

Spatial ecological models are widely used to study wildlife disease spread, habitat use, or population dynamics. Ecological diffusion models connect animal movement with landscape heterogeneity through motility parameters. We use motility estimation techniques to parameterize models for animal dispersal on landscapes with movement constraints such as rivers, coastlines, and highways. We test these techniques for simulated animal trajectories on simulated landscapes before applying them to elk and deer GPS location data.

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PP1

Various Spatiotemporal Neural Activity Patterns in Mouse Hippocampal Slices Measured by Multi-electrode Array System and Laser Confocal Calcium Imaging

Synchronous neural activities are important for information processing in neural circuits. In the present study, we measured spatiotemporal neural activities in mouse hippocampal slices using multi-electrode array (MEA) system and laser confocal calcium imaging, and analyzed them by cluster analysis. The slices (350 m) were prepared from 1-week-old male ddY mouse. The slice preparation was stained with a calcium indicator dye, Cal-520. The stained preparation was placed on a MEA glass chip comprising 64 electrodes (5050 m) with 150 m spacing in an 88 grid arrangement (MED-P5155, Alpha MED Science). The MEA chip was placed on the stage of a microscope (E600-FN, Nikon). The stained slice was illuminated by a solid-state laser (488 nm; 85-BCD-050-100, Melles Griot), and the 520 nm fluorescence images were acquired through a Nipkow confocal unit (CSU-10, Yokogawa) and a CCD camera (iXon X3 897, Andor). By this experimental apparatus, we can simultaneously measure the electric and calcium signals of spontaneous neural activities that sometimes occur without any stimuli. Additionally, we can use each MEA electrode as a stimulus electrode and measure the induced electric and calcium signals. To analyze such signals, we obtained raster plots from the peaks of the measured signals. Then we classified the obtained spatiotemporal activity patterns by cluster analysis. As a result, the classified activity patterns differed from one another depending on the stimulated positions.

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PP1

Controlling Period-2 Electrical Activity in a Cardiac Cell Model

This study focused on the control of a dynamic behavior called alternans, exhibited by cells responding to stimuli. Electrical alternans, the beat-to-beat alternations of cellular action potentials and/or intracellular calcium concentration, is a state that precedes life-threatening arrhythmia. Arrhythmia is characterized by irregular propagation of electrical waves and is the leading cause of sudden cardiac death. Previous efforts at alternans control have utilized mathematical models that primarily exhibited voltage-driven alternans; we considered the impact of intracellular calcium mechanisms. We used the Shiferaw-Fox et al. cardiac action potential model [Coupled dynamics of voltage and calcium in paced cardiac cells], which is capable of both voltage- and calcium-driven alternans, for single cells (0D) and cables of cells (1D). Control schemes were applied to four different combinations of driving mechanisms. The control schemes include a constant-diastolic-interval(DI) method, a voltage-feedback method, a calcium-feedback method, and an early-stimulus method. The results showed differences depending on the alternans mechanism; calcium-driven alternans were more difficult to control. In 0d, the calcium-feedback method eliminated alternans regardless of driving mechanism. In 1D, the voltage-feedback and constant-DI methods showed the most promise. The results indicate that the success of control of cardiac alternans may depend on the underlying alternans mechanism.

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PP1

Eco-evolutionary Dynamics of Cooperation in Temporally Varying Environments

An organism's phenotype is defined as the expression of its genetic material. This expression may change under different environmental conditions. The ability to alter one's phenotype by turning on or off specific genes in response to changes in one's environment is known as phenotypic plasticity. Cooperation in certain microbial species is an example of phenotypic plasticity whereby some individuals express particular genetic machinery to produce a resource available to the entire population while others fail to express that same machinery but benefit from consumption of the resource without the cost of its production. Depending on the availability of the resource in its environment, an individual may switch from an expressing to a non-expressing state or vice versa. We develop a mechanistic model to explore the ecological and evolutionary dynamics of cooperation and phenotypic plasticity in social microbes under fluctuating environmental conditions. Using an adaptive dynamics approach, we examine whether there exists an evolutionarily stable switching strategy between states.

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PP1

A Mathematical Model of Flagellar Gene Regulation in *Salmonella Enterica*

Millions of human cases of salmonellosis, a foodborne illness caused by *Salmonella enterica* (*S. enterica*), occur world-wide every year. A key component to *S. enterica* pathogenesis is the flagella, a complex motor the bacteria uses to move through the environment. Interestingly, populations of genetically identical bacteria exhibit phenotypic heterogeneity in the quantity of flagella. To understand this heterogeneity, we propose a mathematical model of the gene network that regulates construction of flagella. Flagellar assembly is controlled by a complex regulatory network involving more than 60 genes. The most important member of the network is the master operon, *flhDC*, which encodes the $FlhD_4C_2$ protein. $FlhD_4C_2$ is responsible for initiating the production of the flagella, and it is tightly regulated at both the transcriptional and protein levels. Further, expression of *flhDC* is bistable across populations of genetically identical cells, which could explain variability in the number of flagella. The flagellar regulatory network is also involved in cross-talk with virulence networks, and this cross-talk could be important to host invasion and infection processes. Analysis of our model of the regulatory network suggests that a combination of feedback loops at the protein and transcriptional levels induce the bistable *flhDC* transcription and phenotypic heterogeneity observed experimentally.

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PP1

Neurotransmitter-induced Synchronization of Pancreatic Islet Oscillators

Pancreatic islets of Langerhans are responsible for pulsatile insulin release, with period of approximately 5 min. This pulsatility facilitates the uptake of glucose by target tissues such as liver and muscle, and is disorganized in patients with type II diabetes. To achieve oscillatory blood insulin levels, the hundreds of thousands of islet oscillators in the pancreas must be synchronized. What is the synchronization mechanism? Data show that islets are innervated by neurons that are present in pancreatic ganglia, and that these neurons release the neurotransmitter acetylcholine when stimulated. To replicated this in the lab, we have developed a microfluidic platform for applying pulses of carbachol (CCH), a cholinergic agonist. To investigate the mechanism of action of the neurotransmitter we employ mathematical modeling, making use of the Integrated Oscillator Model for islet activity. The data and the model demonstrate that CCH pulses can synchronize islets, even if the pulses are given at random times. We show both experimental and modeling data, and describe why CCH is able to reset the phase of islet oscillators, whose oscillation mechanism relies on glucose metabolism.

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PP1

Advection and Autocatalysis in Banded Vegetation Patterns

We motivate and analyze a simple model for the formation of banded vegetation patterns. The model incorporates a minimal number of ingredients for vegetation growth in semi-arid landscapes. It allows for comprehensive analysis and sheds new light onto phenomena such as the migration

of vegetation bands, their alignment with contour lines, and the interplay between their upper and lower edges. Stability analysis gives insights into how these bands interact with natural and human-made disturbances.

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PP1

A Multi-scale, Data-based Network Model: Structure and Dynamics

In this study, we investigate a multiscale model for neuronal networks. Each node in the network represents a functional unit (such as an olfactory bulb glomerulus or a cortical column) comprised of many neurons. We specify probabilistic wiring rules for outgoing connections of individual cells, based on tracing data from the mouse olfactory bulb, and study the emergent properties of the resulting network of nodes. An important parameter in the wiring rules, unknown from experiments, is connection selectivity. It is determined by the size of each nodes target set a set of nodes where all outgoing connections have to land. We investigate graph theoretic properties of these networks such as weighted degree distributions, clustering coefficients, centrality etc. We find that these properties differ significantly from well-studied network models (random, small-world, scale-free, etc). Finally, we add nonlinear firing rate dynamics to the networks to study the effect of network structure on the processing of sensory data. Using both experimentally-derived and artificial stimuli, we find that in these networks, regardless of connection selectivity, lateral inhibition mediates sparsening of neural code and the decorrelation of representations of similar stimuli.

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PP1

The Influence of Molecular Reach and Diffusivity on the Effectiveness of Membrane-confined Reactions

Tethered enzymatic reactions are a key component in signaling transduction pathways. It is found that many surface receptors rely on the tethering of cytoplasmic kinase to initiate and integrate signaling. A key factor to such reaction is the molecular reach; however, the role of it is incompletely understood. To date, A large number of compartment-based ODE and stochastic models have been developed to study this problem. In recent years, spatial-stochastic models have emerged as a more realistic representation for such processes, among which lattice-based stochastic reaction-diffusion models are a popular approach for studying complex spatio-temporal processes inside cells. To understand the role of molecular reach in tethered signaling, we employed an accurate and convergent lattice-based stochastic reaction-diffusion model (CRDME). We find that the molecular reach can increase or decrease biochemical reactions depending on the diffusion coefficient in 2D membrane but not in 3D cytosol.

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